World Psychiatry

OFFICIAL JOURNAL OF THE WORLD PSYCHIATRIC ASSOCIATION (WPA)

Volume 25, Number 1 *February 2026*

EDITORIALS

SPECIAL ARTICLES

PERSPECTIVES

FORUM – *SOCIAL INCLUSION OF PEOPLE WITH SEVERE MENTAL ILLNESS: PRACTICES, CHALLENGES AND TRENDS*

Commentaries

RESEARCH REPORTS

INSIGHTS

WILEY

NO. 1 OF PSYCHIATRIC JOURNALS FOR IMPACT FACTOR

ISSN 1723-8617

The World Psychiatric Association (WPA)

The WPA is an association of national psychiatric societies aimed to increase knowledge and skills necessary for work in the field of mental health and the care for the mentally ill. Its member societies are presently 147, spanning 123 different countries and representing more than 250,000 psychiatrists.

The WPA organizes the World Congress of Psychiatry every year. It also organizes international and regional congresses and meetings, and thematic conferences. It has 66 scientific sections, aimed to disseminate information and promote collaborative work in specific domains of psychiatry. It has produced several educational programmes and series of books. It has developed ethical guidelines for psychiatric practice, including the Madrid Declaration (1996).

Further information on the WPA can be found on the website www.wpanet.org.

WPA Secretariat
Geneva University Psychiatric Hospital, 2 Chemin du Petit Bel-Air, 1226 Thônex, Geneva, Switzerland. Phone: +41223055737; Fax: +41223055735; E-mail: wpasecretariat@wpanet.org.

World Psychiatry

World Psychiatry is the official journal of the World Psychiatric Association. It is published in three issues per year and is sent free of charge to psychiatrists whose names and addresses are provided by WPA member societies and sections.

Research Reports containing unpublished data are welcome for submission to the journal. They should be subdivided into four sections (Introduction, Methods, Results, Discussion). References should be numbered consecutively in the text and listed at the end according to the following style:

1. Cuijpers P, Sijbrandij M, Koole SL et al. Adding psychotherapy to antidepressant medication in depression and anxiety disorders: a meta-analysis. World Psychiatry 2014;13: 56-67.
2. McRae TW. The impact of computers on accounting. London: Wiley, 1964.
3. Fraeijs de Veubeke B. Displacement and equilibrium models in the finite element method. In: Zienkiewicz OC, Hollister GS (eds). Stress analysis. London: Wiley, 1965:145-97.

All submissions should be sent to the office of the Editor.

Office of the Editor – Department of Psychiatry, University of Campania "L. Vanvitelli", Largo Madonna delle Grazie, 80138 Naples, Italy. Phone: +390815666502; Fax: +390815666523; E-mail: mario.maj@unicampania.it.

***World Psychiatry* is indexed in PubMed, Current Contents/Clinical Medicine, Current Contents/Social and Behavioral Sciences, Science Citation Index, and EMBASE.**
All back issues of *World Psychiatry* can be downloaded free of charge from the WPA website (https://www.wpanet.org/world-psychiatry-volumes/?language=english).

The causal structure of psychopathology and why it matters

Psychiatry is blessed or cursed with theoretical questions that never go away. They mostly take the form of dichotomous oppositions. Nature *versus* nurture is the most familiar[1], but there is also mind *versus* brain, medication *versus* talk therapy, conscious *versus* unconscious, diseases *versus* problems in living, and categorical *versus* continuous. These chestnuts have been around so long and debated so many times that by now they are usually dismissed as either settled or irresolvable, yet to everyone's frustration they refuse to go away. This essay proposes that they are tied together, and could eventually be resolved by consideration of the ways in which behavioral entities are recognized, defined and caused.

The universe is organized hierarchically, with big things made out of little ones. Organisms – to which I will limit myself here – are no different. Atoms make molecules, molecules make chemical processes, which make cells, organs, and eventually individuals. Individuals go on to make families, groups and societies. As a hierarchically organized entity changes – that is as it behaves – the changes are manifest at all levels. The tiniest gears turn as a clock tells time, and the hands of the clock move along with motion in the gears. The whole thing churns together. Once again, organisms – now limiting myself further to people – are no different. An individual lapsing into a depressive episode is churning in the cells and genes and neurons, in a marriage and on a therapeutic couch, as part of a history that is personal, cultural and evolutionary.

An observer of this multi-level developmental churning is faced with a vastly complex, chaotic system that does not come with ready-made edges to make sense of it. Human observers of human behavior have evolved the ability to create linguistic categories that impose edges on the chaos. Entities created by language regularize developmental chaos by simplifying it. By regularizing it, they make it possible to talk about behavior in systematic ways. Geneticists, neuroscientists, psychiatrists and sociologists create entities at different scales. The parable about the blind men and the elephant misses the point: it is not one scientist holding the trunk and another the tail; it is one with a microscope and another with an aerial camera.

Any entity that is created by human observers depends on characteristics that exist at some scale. If we say that an individual is suffering from anaclitic depression, we are referring to edges that are imposed on behavior in personal relationships and in therapy. Observing that a person is a non-responder to selective serotonin reuptake inhibitors (SSRIs) finds edges in pharmacological metabolism and responses on the Beck Depression Inventory. Observing that a person is in a high-risk group based on a polygenic score for depression does not refer to behavior, but rather to the DNA that he/she has inherited. These different entities are to some extent independent of each other, but it is not the case that an entity specified at one scale does not exist at another: it is just less well defined. It becomes blurry[2]. People diagnosed by their analyst with anaclitic depression may have detectable differences in their SSRI responses or polygenic scores, but psychoanalysts cannot predict drug response, and one cannot identify anaclitic depression in the genes.

Except that, sometimes, one can. It occasionally turns out that what appears to be an entity defined at one scale is actually a blurry version of another entity more sharply defined at a different, usually smaller, scale. *Chorea* is a term from descriptive neurology that refers to a variety of abnormal movements that occur for many different reasons, including phenomena such as hysterical contagion among groups of young people at a school. But in 1872 (i.e., before Mendel), G. Huntington[3] noticed that a subset of choreiform movements appeared in families in a structured way, along with a variety of other devastating symptoms. The now eponymous chorea that Huntington called "hereditary" is a large-scale manifestation of a crisply defined entity on a genetic scale. This kind of cross-level reduction is powerful when it occurs, but it must be remembered that it is not inevitable. You could study bankruptcy for the rest of time and never discover a sub-syndrome that is crisply explained by its relation to genetic or neurological processes, despite the fact that bankrupt individuals certainly show blurry genetic and neurological differences from the financially solvent.

Behavioral entities are *composed* of molecules, neurons and genes, but they are *caused* by other behavioral entities defined on the same scale. This is true even for Huntington's disease. It is tempting to say that the choreiform movements of the patient with Huntington's disease are caused by the HTT gene on chromosome 4, but doing so risks explaining the cause of an entity's behavior with its own structure on a different scale. The turning of gears in a clock does not cause it to tell time: it is the clock telling time. Although it does not much matter in something as well-understood as Huntington's disease, it is better to say that the cause of the disease is the inheritance of the HTT gene from an exogenous parent; the motor and cognitive symptoms that ensue are a larger-scale representation of the smaller-scale biological consequences of carrying the gene.

The distinction between causal and compositional explanation is more important in entities that lack the well-understood structure of Huntington's disease. Let's say that an individual's bankruptcy is caused by redlining practices in the local real estate market. The physical and behavioral entities that might make someone a target of redlining, such as socially defined race, economic class, and personal budget practices, all have blurry representations at smaller scales. So when redlining ⇒ bankruptcy, the whole blurry structure of the neurology of home ownership gets crossed with the equally blurry genetics of savings plans. That guarantees that the geneticist who conducts a genome-wide association study (GWAS) of bankruptcy will find *something*, but what is found will not be causal, and it will not explain anything. It will just be a blurry genetic representation of a process that can only be meaningfully analyzed at a larger scale.

These examples illustrate why psychiatry's old dichotomies are so persistent: they are not merely empirical puzzles waiting for better data, but reflections of the difficulty of drawing stable, meaningful boundaries around behavioral entities across multiple explanatory scales. Understanding the causal structure of complex behavioral entities requires a different skillset than the technical tools that are applied under the assumption that everything will eventually yield to biogenetic reduction. It requires philosophical discourse (this essay owes much to the philosopher of science W. Wimsatt[4]), advanced statistical methods (the clinical psychologist and philosopher P. Meehl devoted the second half of his career to the problem[5]), and (hardest of all), if recent history is any guide, attention to the null hypothesis. One must ask questions such as: "Are candidate gene studies of depression working, and what does it mean if they are not?"[6]. What it means is that the causal structure of depression may be more like the causal structure of bankruptcy than it is like Huntington's disease.

If that turns out to be the case, depression will fall more in the domain of clinical and social science as opposed to GWAS and brain imaging. The so-called biopsychosocial model is tautologically true in a hierarchical universe, but it obscures something important: entities are better defined, discussed and explained at some scales than they are at others. Determination of that optimal scale is prior to specification of causes. It must be understood what depression *is* before it can be understood what causes it. When we debate nature *versus* nurture, or mind *versus* brain, we are really debating how best to impose conceptual order on a system that resists tidy partitions. There may be no final resolution to these tensions, but there can be progress if we remain vigilant about the scales at which explanations operate, and maintain a distinction between genuine explanatory reduction, which is rare but powerful when it occurs, and simple compositional analysis, which is universally possible but generally uninformative.

Eric Turkheimer
Department of Psychology, University of Virginia, Charlottesville, VA, USA

1. Turkheimer E. Understanding the nature-nurture debate. Cambridge: Cambridge University Press, 2024.
2. Turkheimer E. In: Kendler KS, Parnas J, Zachar P (eds). Levels of analysis in psychopathology, 1st ed. Cambridge: Cambridge University Press, 2020:521-44.
3. Huntington G. Med Surg Rep 1872;6:317-21.
4. Wimsatt WC. Re-engineering philosophy for limited beings: piecewise approximations to reality. Cambridge: Harvard University Press, 2007.
5. Meehl PE. J Pers 1992;60:117-74.
6. Border R, Johnson EC, Evans LM et al. Am J Psychiatry 2019;176:376-87.

DOI:10.1002/wps.70000

Stigma is on the rise

Over the last 30 years, stigma research – particularly research addressing mental illness stigma – has been quite successful in shedding light on mechanisms and circumstances of stigma, and how it affects people at multiple levels, from societal structures to internalization in self-stigma.

However, to our astonishment, many of the features of stigma that we identified as targets to eliminate are now being used purposefully in populist rhetoric against marginalized groups. This rhetoric applies an "us" vs. "them" assignment to other vulnerable groups, openly labeling, stereotyping and devaluing them in an effort to control and exclude "them". It thus follows the stigma process laid out by Link and Phelan in 2001[1] as if it was a playbook, rather than something we need to overcome. A massive societal change seems to unfold, where devaluation and discrimination of entire groups are no longer taboo. As stigma researchers, we cannot help but wonder what the consequences of these changes for people with mental illness will be.

At first glance, we look back at palpable improvements. The stigma concept has helped developing and evaluating successful interventions to reduce discrimination[2]. Mental health problems have to some extent been normalized, and attitudes toward people with mental health problems in general, and with depression in particular, have softened[3,4].

However, these past positive trends do not show the entire picture. People with schizophrenia, for example, have not seen any reduction in stigma. On the contrary, over the last 30 years, perceived differentness of people with schizophrenia has increased[5], willingness to help these people has declined[6], and several studies show a long-term trend of increasing desire for social distance toward these people[4,6]. The severe stigma toward substance use disorders has proven remarkably stable[4]. So, while common mental health problems, including depression, are now more often recognized and normalized, mental disorders that appear to be disturbing, strange or unpredictable such as psychosis, or morally loaded such as substance use disorders[7], are subject to constant or even rising stigma.

On a broader political stage, stigma is clearly on the rise. People at the intersection of race/ethnic discrimination and mental illness stigma are at particular danger of being targeted, as shown for example by political campaigns in Germany. Following deadly attacks committed by people with both a migration background and psychotic mental illness, there were general demands of "shutting the borders" and "creating registers for people with mental illness".

Groups that have made progress in their legal and societal emancipation, such as People of Color, or members of the lesbian, gay, bisexual and transgender community, have reason to fear that any achievements they fought for are being taken away. Election campaigns by populist parties in Europe and the US encourage openly hostile and hateful messages that now resonate with a growing proportion of the population. Stigma research consistently shows that authoritarian values are associated with more stigma towards people with mental disorders[8].

While a focus on single stigmatized conditions is important and informative, it also carries the risk of missing the "big picture", since broader trends affect more than one vulnerable group. If race/ethnic discrimination and mental illness stigma converge, we need to examine the overarching mechanisms that are pushing these linked processes forward, to arrive at useful interventions at multiple levels.

It has been hypothesized, for example, that economic competition and growing inequality foster a climate of violence, exclusion and toxic masculinity within society, all to the disadvantage of vulnerable groups[9]. These trends could also endanger any progress that has been made with regard to attitudes towards depression and other common mental disorders.

Both as psychiatrists and as stigma researchers, we cannot ignore these developments. To keep up with our understanding of a changing situation for people with mental illness in a changing societal context, we need to re-enforce the traditionally strong ties between psychiatry and social sciences. This seems even more urgent since the funding of science itself, and social science in particular, has also become a contested political battlefield in some countries.

The question arises of how the current societal developments are affecting the stigma experienced by people with mental illness. Does an overall sense of insecurity and crisis increase the readiness to discriminate against perceived outgroups, including people with severe mental illness? Questions like this need sound scientific answers to inform both psychiatry and the political sphere.

We believe that, in order to answer these questions, we need alliances. We need to connect across countries to see similarities and differences in societal trends that affect people with mental illness. Notably, trend studies on public attitudes are mostly conducted in few high-income countries, and the trends we see might be different in other countries. We also need to broaden our perspective by looking at more than one vulnerable group, since overarching trends likely shape stigma experiences. Finally, and probably most importantly, we need to work more closely with people with lived experience. This reflects the advocate's research imperative: stigma research is valued to the extent that it informs and activates efforts to reduce stigma.

Georg Schomerus[1], Sven Speerforck[1], Matthias C. Angermeyer[2], Patrick W. Corrigan[3], Bruce G. Link[4]

[1]Department of Psychiatry, Leipzig University Medical Center, Leipzig, Germany; [2]Center for Public Mental Health, Gösing am Wagram, Austria; [3]Center for Health Equity, Education, and Research, Illinois Institute of Technology, Chicago, IL, USA; [4]Department of Sociology, University of California Riverside, Riverside, CA, USA

1. Link BG, Phelan JC. Annu Rev Sociol 2001;27:363-85.
2. Morgan AJ, Reavley NJ, Ross A et al. J Psychiatr Res 2018;103:120-33.
3. Henderson C, Potts L, Robinson EJ. Eur J Public Health 2020;30:526-32.
4. Pescosolido BA, Halpern-Manners A, Luo L et al. JAMA Netw Open 2021;4: e2140202.
5. Schomerus G, Schindler S, Baumann E et al. Soc Psychiatry Psychiatr Epidemiol 2023;58:17-23.
6. Schomerus G, Schindler S, Sander C et al. Eur Psychiatry 2022;65:e78.
7. Corrigan P, Schomerus G, Smelson D. Br J Psychiatry 2017;210:180-1.
8. Spahlholz J, Baumann E, Speerforck S et al. Front Psychiatry 2024;15:1501194.
9. Heitmeyer W. Authoritarian temptations and right-wing threat alliance. Cham: Springer, 2024.

DOI:10.1002/wps.70001

Innovations to improve outcomes and uptake of psychotherapies for mental disorders: a state-of-the-art review

Pim Cuijpers[1,2], Mathias Harrer[1], Toshi A. Furukawa[3]

[1]Department of Clinical, Neuro and Developmental Psychology, Amsterdam Public Health Research Institute, WHO Collaborating Center for Research and Dissemination of Psychological Interventions, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; [2]International Institute for Psychotherapy, Babeș-Bolyai University, Cluj-Napoca, Romania; [3]Kyoto University Office of Institutional Advancement and Communications, Kyoto, Japan

Psychotherapies have been found effective in the treatment of most mental disorders. However, substantial improvements are still much needed, and many innovations of therapies are currently being developed. We review the current status of promising innovations to improve the outcomes and uptake of psychotherapies for mental disorders, discussing the largest and most recent meta-analyses. Innovations are categorized into four domains: a) the digital field (including Internet-based interventions in general; mobile interventions; serious games; virtual and augmented reality; prescription digital therapeutics; blended therapy; avatar therapy; and chatbots/artificial intelligence-generated conversational agents); b) personalized treatments (research on predictors and moderators in large randomized controlled trials; use of individual patient data meta-analyses in personalization; machine learning approaches; personalized and modular therapies; and matching therapists to patients); c) new and improved therapies (cognitive bias modification; cognitive remediation; psychedelic-assisted psychotherapies; transdiagnostic therapies; research on effective components through factorial trials and component network meta-analyses; innovations in the understanding of the processes involved in psychotherapies, including research on common factors and the therapeutic alliance, and on the fidelity vs. flexibility question; research on prevention of adverse effects of therapies, the impact of increased session frequency or progress feedback on outcomes, and methodological innovations in trial designs); and d) dissemination and simplification of therapies (task sharing, digital interventions in low- and middle-income countries; and single-session interventions). These innovations vary in their maturity, from dozens of supporting trials to few or none. Methods to assess the strength of innovations suggest that no innovation will be a paradigm-shifting "silver bullet" that dramatically increases treatment outcomes, but that progress will only be possible through multiple, incremental improvements.

Key words: Psychotherapies, innovations, digital interventions, personalized treatments, cognitive bias modification, cognitive remediation, psychedelic-assisted psychotherapies, transdiagnostic therapies, factorial trials, therapeutic alliance, adverse effects, task sharing

(World Psychiatry 2026;25:4-33)

Almost one billion people suffer from a mental health condition worldwide[1]. Although evidence-based treatments are available for most disorders, the burden of disease, economic costs, and personal suffering caused by mental disorders are still enormous.

Psychotherapy is a first-line treatment for most mental disorders, and is one of the main instruments to treat these disorders. Hundreds of randomized trials and meta-analyses have shown that various psychotherapies are effective across a broad range of mental disorders, including major depressive disorder[2,3], anxiety disorders[4-8], post-traumatic stress disorder (PTSD)[9,10], obsessive-compulsive disorder (OCD)[11,12]; insomnia[13], borderline personality disorder[14,15], psychotic disorders[16], and bipolar disorder[17,18].

Effect sizes of treatments of mental disorders (including psychotherapies) have been found to be comparable to those found in general medical care[19]. Moreover, in the past few decades, evidence-based treatments (including psychotherapies) have become available for large populations, especially in high-income countries, and are often included in national health services at no or relatively low costs.

Yet, significant improvements are still needed. It has been estimated that current treatments can only reduce by 40% the disease burden of mental disorders in populations under optimal conditions in which all patients with a disorder receive an evidence-based treatment[20]. Furthermore, the actual number of patients who recover under treatment is modest. We found that the response rates (defined as 50% symptom reductions) for psychotherapies were 42% for major depressive disorder, 38% for PTSD and OCD, between 32% and 38% for anxiety disorders, and 24% for borderline personality disorder[21]. This means that a large group of patients – according to our estimates, even more than half – do not respond to psychotherapies. There are also indications that mental health care has not improved over the past decades[22]. We recently found, for example, that the outcomes of mental health care for depression have been stable since the 1990s, without any improvement despite the availability of more effective treatments[23].

Treatment uptake remains limited. Even in high-income countries, only a minority of patients receive adequate care[24]. Fewer than 40% of individuals with depression, anxiety, or substance use disorders receive any form of treatment[25], and, among those who do, less than half receive care that meets minimal quality standards[26]. Uptake is even lower in specific age and target groups in high-income countries, such as adolescents, young adults, older adults, minority groups, and groups with lower socioeconomic status[27-30].

It has also been estimated that more than 80% of the almost one billion people with mental health conditions live in low- and middle-income countries (LMICs), where evidence-based treatments are only sporadically available[1]. For example, only one in 27 people with depression receives adequate treatments in LMICs[26]. In many LMICs, there is less than one psychiatrist for every 100,000 individuals[31].

Thus, the need for more effective and widely accessible treatments is urgent. Fortunately, many innovative psychotherapies are currently being developed and tested. In this paper, we focus on these advancements, broadly defining innovations as "new ideas, methods or devices"[32,33]. Specifically, we examine innovations in psychotherapies that aim to enhance effectiveness, improve efficiency, or increase uptake. We do not address innovations in prevention, diagnostics, or the fundamental understanding of mental disorders.

Psychotherapy can be defined as "the informed and intentional application of clinical methods and interpersonal stances derived from established psychological principles for the purpose of assisting people to modify their behaviors, cognitions, emotions, and/or other personal characteristics in directions that the participants deem desirable"[34]. We do not use this definition in a very strict way and include also psychological treatments in general, for example unguided digital interventions.

This paper is divided in four sections, each of which describes a broad category of innovations: advances in the digital field, stratification and personalized psychotherapy, new and improved therapies, and dissemination and simplification of therapies. These four categories are not mutually exclusive, and some innovations could be positioned in more than one category.

For each of the innovations, we present an overview of what the innovation is, and a summary of what the evidence tells us about the effects (if possible, based on core meta-analyses).

INNOVATIONS IN THE DIGITAL FIELD

Internet-based interventions

One area in which many promising innovations of psychological treatments take place is the digital field. Research on Internet-based interventions for mental health problems started in the early 2000s[35-38], but most trials have been conducted in the last decade. These studies build on the earlier literature on (guided) self-help that already started several decades earlier[39], with clinical trials on anxiety beginning in the 1960s and 1970s[40,41], on problem drinking in the 1970s[42], and on depression in the 1980s[43,44].

A self-help intervention can be defined as a psychological treatment in which the patient works through a standardized protocol more or less independently[45]. The treatment protocol can be provided in a book, as an audio file, or in a digital format through the Internet. Self-help can be unguided, when the patient works through the protocol without any support, or guided, when a human supports the patient to work through the protocol. Internet-based interventions can be considered as (guided) self-help interventions which are administered through the Internet.

Most Internet-based interventions examined in randomized trials in the last twenty years draw on existing psychotherapies, usually cognitive behavioral therapy (CBT), which are then transformed into digital platforms. The platforms are not fundamentally different from books or other media, although they are usually complemented with automated tests, brief videos, or some other multimedia content.

There is considerable evidence that these Internet-based interventions are effective in the treatment of several mental disorders, although many of the trials and meta-analyses suffer from several types of bias[46]. In Table 1, we provide the effect sizes for Internet interventions compared to control conditions in major mental disorders, based on recent meta-analyses[12,47-53]. As can be seen from this table, most of the trials have been conducted in depression, but there are also many trials in anxiety disorders, PTSD, OCD, substance use disorders and suicidal ideation, and some trials in borderline personality disorder. There is also evidence that Internet-based interventions for depression and anxiety are acceptable and effective in routine care[54].

It is well established that there are no important differences between Internet-based and face-to-face treatments of mental disorders. Meta-analytic research has consistently shown that randomized trials across multiple mental health conditions directly comparing these two formats do not result in significant differences between them[55,56]. In addition, there are several network meta-analyses showing that there is no significant difference between individual therapy, group therapy and (digital) guided self-help. Such network meta-analyses have been conducted on CBT for depression[57], panic disorder[5], eating disorders[58], and OCD[59].

Table 1 Core meta-analyses of randomized trials examining the effects of Internet-based interventions compared to control conditions in adult mental disorders

	n	N	SMD	95% CI	I^2	95% CI
Depression[47]	125	32,733	0.43	NR	NR	NR
GAD[48]	9	1,203	0.62	0.31-0.93	81	61-88
Panic disorder with or without agoraphobia[48]	15	837	1.08	0.77-1.39	76	57-84
SAD[48]	20	1,960	0.76	0.62-0.91	53	11-71
PTSD[49]	27	5,421	0.36	0.19-53	82	NR
OCD[12]	12	769	0.42	0.14-0.69	59	23-78
Suicidal ideation[50]	8	NR	0.23	0.11-0.35	18	0-59
Substance use disorder[51]	18	NR	0.24	0.13-0.35	27	NR
Gambling disorder[52]	13	2,183	0.73	0.43-1.03	94	NR
Borderline personality disorder[53]	3	NR	0.17	-0.10 to 42	0	0-90

SMD – standardized mean difference, GAD – generalized anxiety disorder, SAD – social anxiety disorder, PTSD – post-traumatic stress disorder, OCD – obsessive-compulsive disorder, NR – not reported

Most research suggests that Internet interventions with human support are more effective than those without any support[5,57,59,60]. However, the superiority of guided over unguided interventions is likely more nuanced, due to several factors. First, comparisons between "guided" vs. "unguided" interventions could be confounded by other factors, if the former tend to spend more time on complex and possibly effective skills such as cognitive restructuring, while the latter tend to include simple but ineffective skills such as relaxation, or if the former tend to be compared more often to waitlist than the latter. Second, guidance comes in various levels. Some guidance may mean 15 min per week by telephone from clinical psychologists, while other may mean e-mails from trained but lay coaches. When additional support was decomposed into "automated encouragement", "human encouragement" and "therapeutic guidance", there was evidence that only the first two could contribute to effectiveness and adherence, while the last was not necessary[61].

A recent meta-analysis of 23 trials on depression in LMICs found comparable effect sizes (0.90 and 0.87) and no significant difference (p=0.88) between guided and unguided Internet interventions[62]. This suggests that the difference may not be true in all contexts or populations. Another recent meta-analysis of 154 controlled trials examining the long-term effects of Internet-delivered CBT in depression, anxiety, PTSD and OCD did not find a significant difference between guided and unguided interventions at 12-month follow-up[63]. In an individual patient data network meta-analysis of 39 trials comparing guided and unguided digital interventions for depression with control groups or with each other, it was found that both interventions were effective compared to controls[60]. Guided interventions were more effective than unguided ones, but not at follow-up. Baseline severity was the most important predictor of outcome: in mild depression, there was no difference between guided and unguided interventions; guided interventions were only more effective than unguided ones in more severe depression.

One important element of digital interventions is the level of support that needs to be provided[64]. It is clear that the support in guided self-help interventions can be provided by people who do not need to have an extensive clinical training. In the Improving Access to Psychological Therapies (IAPT) program in the UK[65], guided self-help (digital or otherwise) is part of a stepped care approach, and the first step (guided self-help) is provided by "psychological well-being practitioners", who received a relatively brief training and do not have extensive clinical experience or training. This relatively low level of training required is an important element that may help to disseminate evidence-based treatments of mental disorders across populations who currently have no or only limited access to such treatments.

Most Internet-based interventions are based on CBT or third-wave therapies, because it is relatively easy to transform these interventions into self-help materials, and there is a strong empirical basis of the effects of CBT across mental disorders. However, digital interventions based on other therapeutical approaches have also been found to be effective. For example, there are several randomized trials showing that psychodynamic interventions[66,67], and interventions based on interpersonal psychotherapy (IPT)[68-70] are also effective.

The mobile revolution

Internet-based interventions were originally designed for patients using a computer, completing weekly sessions and homework assignments. However, Internet usage has changed in recent years. Most people now rely on smartphones or, when necessary, tablets. Phones are not ideal for reading long texts or completing assignments. Instead of setting aside dedicated time, users check their phones briefly throughout the day[71]. As a result, conventional self-help materials, which require extensive reading and structured homework, are often unsuited for smartphones.

It is not surprising that more and more research has shifted from "conventional" Internet interventions towards smartphone apps. A recent meta-analysis including 176 randomized trials examined the effects of smartphone interventions for depression and anxiety, of which more than two-thirds (67%) were conducted between 2020 and 2023[72]. The rapid increase in number of randomized trials may be further enhanced by the development of prescription digital therapeutics and investments from the industry[73]. Overall, the effects of smartphone apps are somewhat smaller than what is usually found for face-to-face treatments or conventional Internet interventions: the standardized mean difference (SMD) is 0.28 for depression and 0.26 for generalized anxiety[72]. While trials of smartphone apps are increasing, only a small fraction of the thousands of mental health apps available today has been tested in randomized trials.

Smartphones are different from conventional digital devices not only because they are used in a very different way, but also in that they make it possible to measure human behavior from sensors, keyboard interaction, and various features of voice and speech[74]. Sensors in smartphones that are often used for this purpose include GPS, bluetooth, accelerometer, microphone, illuminance, gyroscope, and Wi-Fi[75,76]. In addition to these passive measures, smartphones also allow the use of "ecological momentary assessment" (EMA), which is a self-report method that involves intensive longitudinal assessment of behavior and environmental conditions during everyday activities[77]. EMA has been used extensively in mental health research to investigate a variety of health behaviors, including substance use, eating, medication adherence, sleep, and physical activity.

What are the consequences of this different use of smartphones and of these additional possibilities of measuring behavior? The hope is that "digital phenotyping" will contribute to measurement-based care, allowing care managers to monitor remission and relapse[74], and to develop better precision treatments. However, this is not yet the reality, and research in these areas is still in its early stages.

More direct applications of the potential of smartphones and other mobile devices include "ecological momentary interventions" (EMIs) and "just-in-time adaptive interventions" (JITAIs). EMIs can be defined as treatments that are provided to people during their everyday lives and in natural settings, and are delivered using mobile technology[78,79]. They can be implemented as standalone interventions or as a supplement to existing treatments. These interventions have also been described as “therapist in your pocket” approaches, and have been claimed to have the potential to revolutionize clinical treatment[78,80].

Many EMIs are also JITAIs. These latter interventions are aimed at providing the right type and amount of support, at the right time, by adapting to an individual’s changing internal and contextual state[81]. Because of the availability of increasingly powerful mobile and sensing technologies, the expectations for such interventions are high[81].

Although there is broad agreement on the potential of EMIs and JITAIs to improve treatments – including in the fields of suicide prevention[82-84], depression[85], and substance use problems[86] – there are not yet many randomized trials testing their effects on mental health problems. A recent systematic review of JITAIs identified only six randomized trials aimed at different mental health problems[87]. Because of the differences in target groups, methods and outcomes in these trials, it is not yet possible to estimate the actual clinical utility of these approaches. In contrast to many physical conditions (e.g., diabetes mellitus), most mental disorders are not associated with one clearly identifiable disease mechanism. In addition, the outcome in JITAIs needs to be obtainable in short intervals (e.g., steps taken within 2 hours) for the interventions to be properly adapted. By contrast, the outcomes of interest in mental disorders tend to be assessable on longer terms. Thus, the potential of JITAIs in mental health care could be inherently limited.

Serious games for the treatment of mental disorders

Another significant development is represented by serious games. These are games devised with a primary purpose other than just recreation, which are applied in health care, but also in education, engineering and defense[88-90]. An important point in this area is the potential to enhance people’s motivation to engage in interventions[88]. Although there are worries that serious games may encourage excessive gaming and gaming disorder[91], it is important to examine whether these games may be beneficial in increasing uptake, improving outcomes and reducing dropout from mental health treatments.

A considerable number of randomized trials has focused on the effects of serious gaming on physical health and mental health promotion and prevention[92]. However, the number of randomized trials aimed at people with existing health problems is limited. In a recent meta-analysis of randomized and open trials of gamified interventions, only six of 42 studies were randomized trials in people with mental health problems[92]. In another meta-analytic review of randomized controlled trials (RCTs) of serious games with depression as an outcome, only four (out of 22) trials were explicitly aimed at people with depression at baseline[93]. In another meta-analysis examining the effects of serious games with anxiety as an outcome, only five trials (out of 22) were aimed at generalized anxiety, one at social phobia and two at specific phobias[94]. In a meta-analysis of the effects of serious games on depression in older adults, only one of the 17 included trials was actually aimed at older people with depression[95].

There are indications that serious games can have effects on depression and anxiety[93,94], when compared to inactive controls. However, there is too little research in clinical populations to state whether they are effective in these groups. It is also not yet clear whether these interventions really improve uptake and reduce dropout.

Virtual and augmented reality

Immersive virtual reality (VR) can be defined as a three-dimensional interactive computer-generated environment, which allows the user to experience real-time sensory and auditory perceptions and helps create the sensation of being present in that environment[96].

The first trials examining the effects of VR-based treatments were already conducted more than 25 years ago[97,98], and since then dozens of RCTs have shown that VR interventions are effective in the treatment of specific phobias, social anxiety disorder, and panic disorder with agoraphobia, when compared with passive control conditions such as waitlist, with effect sizes that are comparable to those of face-to-face treatments[99]. There is also some support for the effects of VR in the treatment of PTSD when compared to passive controls[100,101], and there are promising results in the treatment of eating disorders, substance use disorders, schizophrenia, and attention-deficit/hyperactivity disorder (ADHD)[99,102].

Most meta-analyses show that, when VR-based treatments of mental health conditions are compared with regular face-to-face interventions, there are no significant differences[102,103]. This means that the additional clinical benefit of VR-based treatments for mental health conditions is probably limited.

There are some promising new applications in the VR field that may have additional clinical value. One trial examined a self-guided intervention for acrophobia, enhanced with VR through the smartphone, and found considerable effects[104]. The self-guided nature of this approach may increase the uptake of evidence-based treatments for acrophobia and possibly other mental disorders.

Another interesting development is represented by multi-modal motion-assisted memory desensitization and reconsolidation (3MDR), a novel VR and motion-assisted exposure therapy which provides treatment in an immersive, personalized and activating context. This intervention has been tested in veterans with PTSD with a history of unsuccessful treatments[105], showing significant and large effects when compared to a non-trauma-focused treatment addressing daily stressors and symptoms. More research is needed to verify whether this treatment has additional benefits compared to a full conventional treatment of PTSD.

Another relatively new development is the use of “augmented reality” in intervention research. This is a technology that blends virtual and physical environments, enhancing one’s perception of reality[106-108]. Most research has been done in anxiety and phobias, as well as in neurodevelopmental disorders. Although a few RCTs have been conducted[107], it is too early to say whether augmented reality can contribute to better treatments or an increased uptake of evidence-based treatments.

More emerging trends in digital interventions

There are several more important emerging trends in the field of digital interventions. One important emerging development with considerable potential are so-called "prescription digital therapeutics"[109-112]. These are digital interventions which are rigorously evaluated for safety and effectiveness and are authorized by national regulatory agencies, such as the US Food and Drug Administration (FDA). They can be prescribed by health professionals to people with mental disorders.

There are several prescription digital therapeutics that have been approved by the FDA, including apps for ADHD, PTSD and substance use disorders[109], but also for depression, anxiety and insomnia. It is possible that an extension of regulatory pathways for prescription digital therapeutics could lead to an increase in industry-sponsored trials and further speed up research in this area[113].

There is also more and more research on "blended therapy", which combines digital with face-to-face psychological interventions. The face-to-face component is delivered by a mental health professional, such as a psychologist, while the digital component is patient driven[114]. Although the effects of Internet interventions have been well established, the uptake and adherence are low, especially when they are delivered in routine care[115,116]. Furthermore, many patients prefer face-to-face therapies[114,117], and clinicians often raise concerns about the use of digital therapies alone, feeling that patients are not suitable due to symptom severity, lack of digital access and literacy, and perception of digital treatment as less engaging than face-to-face treatments[113]. From this perspective, blended therapy can be seen as a midpoint option between digital and face-to-face therapy[114,118].

A recent meta-analysis of 29 randomized trials showed that most trials of blended therapy were conducted in depression and anxiety, almost all were based on CBT, and blended treatments were more effective or non-inferior to treatment as usual[114]. Whether blended therapy indeed results in higher levels of uptake and/or higher efficiency is not yet well established.

Another interesting development is the Avatar therapy for reducing severity and frequency of auditory hallucinations in people with psychotic disorders[119]. In this therapy, patients create an avatar with the help of a therapist. The avatar is an audio-visual entity created with a computer program. Participants give a face to their auditory verbal hallucinations, and the therapist gradually gives control over the avatar to the patient. A growing number of RCTs shows that this is indeed an effective intervention for reducing the severity of persistent verbal auditory hallucinations[119-122].

With the recent rise of large language models (LLMs), such as ChatGPT or OpenLLaMA, many new studies have focused on chatbots and conversational agents, introducing LLM programs for people seeking mental health support. For example, platforms have been developed as personal digital companions, on-demand online counseling, and to provide emotional support[113,123]. Although the number of publications in this field has increased rapidly, recent systematic reviews have identified only few RCTs examining the effect of these interventions or comparing them to face-to-face therapies[123-126].

One meta-analysis of trials on artificial intelligence (AI)-based conversational agents for promoting mental health and well-being included 15 randomized trials[127], but most were aimed at non-clinical populations or groups with subclinical symptoms, and only one trial was aimed at adolescents with a diagnosis of depression or anxiety[128]. It can be expected, however, that this area will develop into a large new research field soon.

STRATIFICATION AND PERSONALIZED PSYCHOTHERAPY

Who benefits from which psychotherapy?

In the field of psychotherapy, it has been recognized for a long time that outcome research should not only focus on the effects of treatments, but also on "which treatment, by whom, is most effective for this individual with that specific problem, and under which set of circumstances"[129]. Most research on psychological treatments in the past five decades has focused on whether therapies are effective on average. RCTs comparing a psychological intervention to a control condition in a group of patients with a mental health condition can show if this intervention is effective in that population of patients. This approach has resulted in many hundreds of such trials, and we know quite a lot on the average effects of psychotherapies on most mental health problems.

Personalized medicine, including personalized psychotherapy, promises to move beyond data regarding the average effectiveness of treatments, to determine the best treatment for each individual[130-132]. This approach aims to identify subgroups of individuals within a heterogenous population, based upon unique characteristics such as underlying mechanisms, risk factors, course of disease, or treatment responses. There is not, however, one single research strategy that can directly lead to evidence on who benefits more from one treatment compared to another.

One approach to personalized psychotherapy is to identify and test potential predictors and moderators. Predictors, sometimes referred to as "prognostic factors", can be defined as characteristics that predict the overall course of a condition regardless of treatments. Moderators, also known as "effect modifiers" or "prescriptive factors", can be defined as characteristics that predict differential response to alternative treatments.

Early research to identify moderators of outcome

Much research in this area has focused on treatment of depression, probably because this is such a heterogeneous condition[133]. In an earlier systematic review, fifteen models for subtyping depression were identified[134]. These were divided into five categories: a) symptom-based subtypes, such as melancholia, psychotic depression, atypical depression, and anxious depression; b) etiology-based subtypes, exemplified by adjustment disorders, early trauma depression, perinatal depression, organic depression, and drug-induced depression; c) time of onset-based subtypes, as illustrated by early and late onset depression, as well as seasonal affective disorder; d) gender-based (e.g., female) depression; and e) treatment-resistant depression[134]. The authors concluded that none of these subtypes is absolutely distinct from the others, with substantial overlaps across symptoms, etiologies and time of onset, and that there is no strong evidence for treatments resulting in better outcomes in specific subtypes.

However, it is currently generally accepted that bipolar and psychotic depression are two subtypes that do need specific treatments. For seasonal depression, specific treatments have been developed[135]. It is also generally accepted that psychotherapy is the preferred treatment in mild depression, while severe depression may be treated with psychotherapy and/or pharmacotherapy.

A more recent and comprehensive review identified the key domains that should be considered when developing personalized treatments of depression[136]. These domains include clinical subtypes of depression, symptom profiles, severity, neurocognition, clinical staging, personality traits, comorbidities, family history, early childhood trauma, recent environmental exposures, resilience, and dysfunctional cognitive schemas. In this extensive review, only a few indications were found for specific effects of treatments in some of these domains. For instance, some preliminary evidence from an individual patient data meta-analysis was found that some specific symptoms of depression (i.e., depressed mood, feelings of guilt, suicidal thoughts, psychic anxiety, and general somatic symptoms) improve more with antidepressant medication compared to CBT[137].

An earlier suggestion that patients with melancholic depression respond less well to psychotherapy[138] was not confirmed in an individual patient data meta-analysis[139]. There is also not strong evidence that baseline severity moderates the effects of psychotherapies[140], or their effects compared to antidepressants[141]. It has been suggested that combined treatment is more effective than pharmacotherapy alone in people with depression and a comorbid personality disorder[142], but that is based on limited research. Furthermore, combined treatment is also superior to pharmacotherapy alone in the general group of people with depression.

A somewhat different and more pragmatic approach[143] was aimed at identifying moderators of differential treatment response in the literature. These moderators – i.e., symptoms and other easily assessed clinical features – could then be used to develop multivariate prediction equations of treatment outcomes. Again, very few significant moderators were found that could help to identify who would benefit more from one treatment compared to another. Three studies found that CBT is more effective than IPT in people with comorbid personality disorders[144-146]. One study reported that behavioral activation treatment is more effective than CBT when depression is more severe[147]. Another study found that CBT is more effective than IPT in the presence of a non-secure attachment style[148]. One more study reported that IPT is more effective than CBT in more severe depression[149], while another found the opposite[150]. Individual studies reported that CBT is more effective than pharmacotherapy in people who are not full-time employed, in married people, in the presence of high levels of stress[151], and in patients with a history of childhood trauma[152]. Further individual studies found that selective serotonin reuptake inhibitors (SSRIs) are more effective than CBT in depression with comorbid personality disorders[153], and when levels of negative affect and neuroticism are high[154]; that SSRIs are more effective than IPT when psychomotor symptoms are pronounced[155]; and that IPT is more effective than SSRIs in the presence of high somatic anxiety[155].

Based on the above three extensive reviews, we can conclude that until now there is very little knowledge on personalizing psychotherapies for depression. These therapies work on average, but knowledge on who benefits from which treatments is almost completely absent.

The major problem with earlier studies summarized in the above three reviews is that they did not have sufficient statistical power and focused on single variables. RCTs are typically designed to show that an intervention works, and that its average effect is significantly larger than the control or comparison condition. However, in order to establish a significant moderating variable, the number of included patients has to be increased considerably compared to establishing whether an intervention is effective[156]. According to a simulation study[157], the required sample size increases by four-fold to find an interaction of the same magnitude as the main effect, and exponentially to a factor of more than 100 for more subtle interactions of <20% of the overall effect. This means that a single trial should include hundreds of participants per arm to be able to identify a predictor or moderator. Such trials have hardly been carried out in the field of psychotherapy. For example, in a recent meta-analysis of randomized trials comparing psychotherapies for depression with control conditions, we included 669 comparisons, with an average of only 50 participants per condition[158].

Some larger trials with substantial numbers of participants have been conducted in the past decades, for example on CBT for depression in mothers in Pakistan (N=903)[159], and on collaborative care for depression and anxiety in India (N=2,796)[160]. However, these trials were not designed to identify predictors or moderators. In recent years, some large trials have been conducted that were aimed at developing personalized treatments, and others are planned.

For example, one trial examined the effects of guided and unguided Internet-based CBT for depression and anxiety in 1,319 university students in Colombia and Mexico[161,162], and included a substantial number of potential predictors and moderators of outcome. Overall, it was found that guided CBT was optimal in terms of remission from depression and anxiety for 81% of all participants, self-guided CBT for another 8%, and treatment as usual for the remaining 11%. The most important predictors of outcome were physical health, comorbid mental disorders, and exposure to recent and lifetime stressors. In another trial of unguided Internet-based CBT for subthreshold depression among Japanese university students (N=1,093), it was found that higher baseline severity was associated with better outcomes, and that several other predictors and moderators were potentially associated with the outcomes, including for example age[163].

New approaches: individual patient data (network) meta-analyses

One innovative approach to identify moderators and predictors is represented by individual patient data meta-analyses. In these meta-analyses, the primary data of multiple trials are collected, combined into a large, merged dataset, and subsequently analyzed jointly[156,164]. This integrated dataset can be used to examine whether baseline patient characteristics are associated with the outcomes of therapies. Because data from multiple trials are combined, the statistical power to examine predictors and moderators of outcome is substantially increased.

An overview of recently published individual patient data meta-analyses[141,165-180] is presented in Table 2. As can be seen, most meta-analyses of psychological treatments have been conducted in depression. Several studies found that higher baseline severity is associated with worse outcomes as prognostic factor and greater impact as effect modifier[165,167,169,170,172,174], but that was not confirmed in all studies, although they did have considerable statistical power to find such an association. Two studies found that older age was associated with greater effects[167,170]. Other meta-analyses identified some other predictors and moderators, but none was consistent across studies.

Most individual patient data meta-analyses on depression summarized in Table 2 included trials comparing psychological treatments with control conditions. These studies do not indicate whether one treatment is better than another in a specific group of patients. Only one meta-analysis compared two active treatments, CBT and pharmacotherapy for depression[141]. In this meta-analysis, no significant moderators were found indicating which patients benefit more from one of the two treatments, including baseline severity.

A different approach is represented by individual patient data network meta-analyses (not included in Table 2). In these studies, in contrast to "conventional" individual patient data meta-analyses, more than one active treatment is compared to control conditions. This makes it possible to identify characteristics of participants who benefit more from one treatment compared to one or more other treatments or control conditions.

In one individual patient data network meta-analysis of 39 RCTs (9,751 participants) on digital CBT for depression, several important variables were found to be associated with differential outcomes, including gender, relationship status, and employment status[60]. However, the most important moderator was baseline severity of depression. Both guided and unguided interventions had better outcomes than the control conditions, but no significant difference between these interventions was found among participants with mild depression, while guided CBT was superior to unguided CBT among participants with more severe depression. In another meta-analysis, data from three trials comparing cognitive-behavioral analysis system of psychotherapy (CBASP) with pharmacotherapy and combined treatment for depression were integrated (1,036 participants)[181]. It was found that baseline depression, anxiety, prior pharmacotherapy, age, and depression subtypes moderated the relative efficacy of the three treatments. Both the above meta-analyses generated web-based apps that allow to predict the outcome of each treatment for a specific individual with specific characteristics.

Although individual patient data meta-analyses are relatively new in the field of psychotherapies for mental health conditions, several have been conducted in recent years in areas other than depression. Some studies have focused on PTSD[175-177] (see Table 2), but only few significant and consistent predictors and moderators were identified. The same was true for meta-analyses on Internet interventions for alcohol problems[178] and for suicidal ideation[179], and on VR for anxiety[180].

When reviewing this area of research, it becomes clear that individual patient data meta-analyses have shown some evidence that treatment outcomes are linked to specific patient characteristics. Individual patient data network meta-analyses, in particular, show great promise in identifying which patients benefit from which treatments. However, despite the growing number of meta-analyses, little knowledge is yet available that can be directly applied in clinical practice. A general limitation is that only a small number of variables are typically available as potential predictors or moderators[156]. Included trials often assess different predictors and moderators, making it difficult to analyze a broad set of common variables. Paradoxically, the more trials are included, the fewer shared covariates can be examined. Establishing a consensus on core outcome sets[182], as well as standard predictors and moderators, for all new randomized trials would greatly enhance the value of these meta-analyses. Until then, their contribution will remain valuable but constrained.

Another important limitation of individual patient data (network) meta-analyses in the development of personalized treatments is that they can only generate correlational and not causal evidence, because patients are not randomized according to baseline characteristics. Whether the data come from large RCTs or from individual patient data meta-analyses, the constructed personalization algorithms are in essence prediction models. That means that, when a significant predictor or moderator is identified, a new randomized trial is needed to confirm that this predictor or moderator or their combinations can indeed improve outcomes for a specific group of patients. Such randomized trials should assign patients to an intervention according to the constructed model, which is then compared with a group of patients who are assigned to a certain intervention without using the model[156].

Machine learning approaches to personalized psychotherapies

One important innovative methodological approach is machine learning (ML). Broadly speaking, ML involves the use of

Table 2 Significant predictors and moderators of outcomes identified in individual patient data meta-analyses of randomized trials comparing psychotherapies for mental disorders with control conditions

	Comparison	n (N)	Predictors/moderators
Depression			
Bower et al[165]	Low intensity CBT vs. controls	16 (2,470)	Better outcomes associated with higher baseline severity
Weitz et al[141]	CBT vs. antidepressants	16 (1,700)	None
Furukawa et al[166]	CBT vs. pill placebo	5 (509)	None
Karyotaki et al[167]	Guided iCBT vs. controls	24 (4,889)	Better outcomes associated with older age, higher baseline severity, and being native-born
Karyotaki et al[168]	Unguided iCBT vs. controls	13 (3,876)	None
Kuyken et al[169]	Mindfulness-based CBT vs. controls	9 (1,258)	Better outcomes associated with higher baseline severity
Reins et al[170]	Digital interventions for subclinical depression vs. controls	7 (2,186)	Better outcomes associated with older age and higher baseline severity
Wienicke et al[171]	Psychodynamic therapy vs. controls	11 (771)	Larger effect associated with longer current episode duration and earlier onset
Driessen et al[172]	Combined psychodynamic therapy + antidepressants vs. antidepressants alone	7 (482)	Effects for combined therapy associated with higher baseline severity and longer episode duration
Karyotaki et al[173]	Task-sharing interventions for depression vs. controls	11 (4,145)	Better outcomes associated with presence of psychomotor symptoms
Buntrock et al[174]	Any intervention in subthreshold depression vs. controls	30 (7,201)	Better effects in people who never had treatment before; better outcomes associated with higher baseline severity
PTSD			
Wright et al[175]	EMDR vs. other therapies for PTSD	8 (346)	Worse outcomes for EMDR in unemployed people; males dropped out of EMDR more often
De Haan et al[176]	CBT with trauma focus in young people vs. controls	25 (1,686)	Larger effects associated with more severe symptoms at baseline
Hien et al[177]	Behavioral and pharmacological therapies for PTSD + substance use vs. controls	34 (3,938)	None
Other disorders			
Riper et al[178]	Internet interventions for alcohol problems vs. controls	19 (14,198)	Higher response in people >55 years of age
Sander et al[179]	Internet interventions for suicidal ideation vs. controls	8 (1,980)	None
Fernández-Alvarez et al[180]	VR for anxiety vs. controls	15 (810)	Married people had lower chance of deterioration

CBT – cognitive behavioral therapy, iCBT – Internet-based CBT, PTSD – post-traumatic stress disorder, EMDR – eye movement desensitization and reprocessing, VR – virtual reality

advanced statistical and probabilistic techniques to construct systems with an ability to automatically learn from data[183,184]. ML techniques include various non- and semi-parametric algorithms that can "learn" complex multivariate interactions from datasets, while conventional (parametric) models are more restricted in the number and complexity of patterns they can capture.

Although there are many potential pitfalls when applying these techniques, they do afford many opportunities for psychiatric research when applied correctly[185,186]. The use of ML techniques is increasing rapidly in mental health research, not only in predicting and improving treatment outcomes, but also for example in detection and diagnosis[183,187], and clinical administration[183].

Several of the studies previously discussed in this paper used ML techniques. For example, EMIs and JITAIs often use ML, as do prediction models built from large trials[161,162], and individual patient data (network) meta-analyses[60,188]. However, there is also a growing body of research specifically aimed at the development of algorithms to predict who benefits from treatments in RCTs. Although most of this research has been conducted in pharmacotherapy and neurobiological treatments[185], there are also several studies in psychotherapy.

One influential method, called the "personalized advantage index" (PAI), has been used extensively in psychotherapy research[189-191]. The first demonstration study on PAI used data from an RCT comparing psychotherapy with pharmacotherapy for depression[191]. Five baseline characteristics of patients were found to predict differential response (marital status, employment status, life events, comorbid personality disorder, prior medication). These characteristics were used to calculate the PAI for each patient. For 60% of the participants, a clinically meaningful advantage was predicted for one of the treatments relative to the other. When these patients were divided into those randomly assigned to their optimal treatment and those receiving the other treatment, outcomes in the former group were superior, with a moderate effect size (SMD=0.58). A recent systematic review identified 19 comparative outcome trials in which the PAI was examined[192]. The results suggested that the PAI has the potential to improve outcomes with an SMD of 0.32, although this may be an overestimation due to the considerable methodological problems with the studies, such as overfitting/model optimism.

It has also been argued that, in addition to large RCTs and individual patient data meta-analyses, large observational treatment samples – such as electronic health record databases – can be used to develop precision treatment rules[193,194]. For example, a proof-of-concept study, using electronic health records to develop an individualized treatment rule for veterans with major depressive disorder, found a considerable improvement in outcomes with minimal additional costs[195].

There are also several other types of studies using ML techniques to improve outcomes of psychotherapies. For example, some studies predict whether patients need high- or low-intensity therapies[196-198]. Others have developed personalized modular treatment plans on a person-by-person basis[199], or have developed a system for optimal treatment strategy selection and personalized adaptive recommendations during treatment[200], or have used natural language processing techniques to discover patterns of therapist-patient interactions that predict treatment response[201,202]. However, despite the quickly growing number of studies in the field, most ML approaches to predict responses to psychotherapies are still in the early stages of development and are not yet ready for implementation in routine care[185,203].

It is increasingly recognized that, regarding the prediction of therapy outcomes, ML techniques have limitations. Over the past decade, the development of ML-driven prediction models has surged across all fields of medicine, with statistical experts warning that most models are too unreliable, impractical, or both, to inform practice[204-206]. All prediction models face the so-called bias-variance trade-off[185], where a model's data adaptivity must be balanced against the risk of overfitting. ML techniques offer great flexibility in detecting complex interactions, but also increase the risk of identifying spurious associations – particularly in psychological treatment research, where even large trials (>1,000 patients) can be considered "small data".

A related issue is that training data are often restricted and noisy, resulting in an unfavorable signal-to-noise ratio[207]. Consistent with this, even in very large samples, simple regression models have not been outperformed by more complex ML approaches[208], including in the prediction of psychotherapy outcomes[209]. Psychological interventions also depend heavily on contextual and setting-specific factors, which further limits the generalizability of ML-based prediction models[210].

To demonstrate that ML-driven treatment recommendations are effective in routine care, new randomized trials are needed, in which patients are assigned either to treatment based on the prediction model or to "ordinary" treatment (as we already noted for predictors and moderators found in individual patient data meta-analyses). Only if such trials show better outcomes for patients receiving model-based treatment, we can assume that these models truly improve patient care.

Matching therapists to patients

Up to now, we have discussed research using ML techniques to determine patient characteristics that could predict outcome. A different approach is to develop methods to match patients better with therapists. It is well established that the outcomes of treatments vary considerably across therapists[198,211]. It has been estimated that about 5 to 8% of outcome variance is attributable to systematic differences between therapists[212]. There are also several studies showing that some therapists are more effective in some problem domains than others, while almost all therapists are at least effective in one specific domain[213].

In a recent study with a large sample of patients, ML techniques were used to identify subgroups of therapists that were differentially effective for highly specific subgroups of patients[198]. This resulted in 17 classes of patient-to-therapist matches with varying outcomes per class, but the predicted outcome in patients was 60% higher if they had been matched with the therapist using this method.

This matching of patients to therapists is also supported by results from an RCT of 218 patients treated by 48 therapists[214]. Before the trial, therapists were classified as effective, neutral or ineffective across 12 problem domains, based on their historical cases. In the trial, patients were either randomized to a therapist who was effective in their problem domain (matched care), or pragmatically to any therapist (care as usual). The matched care was significantly more effective than care as usual in terms of symptom reduction and functional impairment (SMD=0.75), and global distress (SMD=0.50), with no adverse events. To the best of our knowledge, this is the only trial which examined matching of therapists to patients, but the approach is certainly promising and may improve outcomes of therapies substantially[215].

Randomized controlled trials of personalized and modular psychotherapies

There is a growing number of RCTs examining the effects of personalized psychotherapies. These studies go beyond predicting the outcomes of therapy. They have already developed a personalized treatment, and compare it to ordinary therapy. The personalized therapies are tailored to specific characteristics of patients.

Some personalized treatments are developed using ML techniques. For example, in one of these studies, patients received either ordinary stepped care, or stratified care in which they were assigned to low- or high-intensity CBT according to a ML algorithm[216]. It was found that stratified care was more effective than ordinary stepped care, although the costs were also somewhat higher.

Other personalized treatments tested in RCTs are based on clinical factors that are assumed to be associated with differential outcomes. For example, the Trier Treatment Navigator is a system that combines prediction and outcome tracking tools, providing feedback to clinicians and supporting them to apply targeted clinical problem-solving strategies when poor treatment response is likely[217]. A randomized trial comparing this system with ordinary therapy found significant effects of the former (SMD=0.30)[217].

One recent meta-analysis included nine RCTs comparing personalized psychotherapies with standard therapies[218]. This meta-analysis did find a small but significant effect of the personalized psychotherapies (SMD=0.22), although only one of the studies had a low risk of bias. Furthermore, few of the included personalized psychotherapies were based on empirically derived recommendations models, being instead only expert-opinion based. This meta-analysis cannot, therefore, be considered as strong evidence that personalized psychotherapies are indeed more effective than standard therapies.

A specific type of personalized therapy is represented by "modular psychotherapies". In these therapies, the clinicians are provided with an evidence-based toolbox, which includes treatment modules that can be used depending on the clinical problems of the patient at baseline, and decision tools that guide the selection of the different modules[219-221]. Probably the best-known modular therapy is MATCH (Modular Approach to Therapy for Children with Anxiety, Depression, or Conduct Problems)[221]. This contains treatment modules aimed at the treatment of depression, anxiety and conduct problems in youth, which form a menu for clinicians from which they can select modules for the treatment of an individual patient. MATCH is tailored to fit each youth's specific needs at intake. Decision flow charts guide the selection and sequencing of modules, with a default module sequence suggested, but changes in the sequence specified to address treatment difficulties[221].

There are several RCTs that have compared the effects of MATCH to standard care. Some of these trials have found that MATCH had superior results when compared to standard treatment of depression, anxiety and conduct problems in youth[221-223], but that was not confirmed in other trials[224-226]. Meta-analytic evidence integrating these results is not yet available.

Apart from MATCH, there are several other modular therapies that have been tested in RCTs. For example, in one study, it was found that modular CBT for children with autism-related symptoms was significantly more effective than standard treatment in reducing these symptoms[227]. Two other trials examined the effects of modular therapy in children with anxiety disorders, and found significant effects when compared with usual care[228] and waitlist[229].

Not all trials have found superior effects of modular psychotherapies. In one trial in adults with alcohol use disorders, patients were randomized to either usual care or a targeted modular treatment[230]. Patients in this latter arm were allocated to one of three treatment modules focusing on craving, positive expectancy, or impulsivity, based on an assessment at baseline. No significant difference was found between modular psychotherapy and usual care. Another study compared a standard CBT self-help program with a tailored program in which the content of the sessions differed depending on the anxiety symptoms at baseline[231]. Again, no significant difference at post-test or follow-up was found. An earlier trial on modular psychotherapy for anxiety in older primary care patients also did not find a significant benefit when compared with routine care[232].

In a recent proof-of-concept trial[220], patients with depression and psychiatric comorbidity were either randomized to standard CBT or to CBT plus transdiagnostic modules, depending on early trauma-related mechanisms. There was a non-significant superiority of the modular therapy over standard CBT, but patients randomized to the former were nearly three times as likely to experience remission at the end of therapy.

These results are conflicting and do not allow to state whether modular psychotherapies are more effective than standardized ordinary treatments. A meta-analysis or systematic review could shed some more light on this issue, but to the best of our knowledge no such review has yet integrated the results of trials in this specific field.

NEW AND IMPROVED PSYCHOTHERAPIES

The development of new psychotherapies

In the past decades, several hundreds of psychotherapies for mental health problems have been developed. The Wikipedia list of psychotherapies currently includes 218 separate therapies[233]. Although it is not clear how this list was composed, it is probably only a selection of all therapies that have been developed over the years. The development of new therapies is a continuing process[e.g., 234-238].

Many new therapies claim to have better outcomes than "conventional" psychotherapies or to be based on better theoretical or clinical frameworks. However, most research does not support these claims. Network meta-analyses are well-suited to examine the comparative effects of psychotherapies for specific mental disorders, because they include not only RCTs directly comparing different therapies, but also indirect comparisons. For example, when two therapies are not compared directly in RCTs, their effects can still be estimated when both therapies have been compared with a waitlist control group or a third therapy.

Most network meta-analyses do not indicate superior effects of one therapy over another. For example, a large network meta-analysis of 331 RCTs with more than 34,000 patients on eight types of psychotherapy for depression found no significant differences between the effects of these therapies[2]. Only non-directive supportive counseling was found to be less effective than other psychotherapies, but that was probably an artefact, because this therapy is also often used as control condition[239]. Other network meta-analyses for other disorders have also not found significant differences between the effects of psychotherapies. One network meta-analysis on generalized anxiety disorder found no significant difference between eight major types of psychotherapy[240], and another on seven types of therapy for PTSD also found no significant differences[241].

However, not all research supports the notion that all psychotherapies have comparable effects. A network meta-analysis examining the relative efficacy of therapies for social anxiety[242] found that most therapies had comparable effects, but also that individual CBT was more effective than psychodynamic therapy, while there was no significant difference between individual CBT, group CBT, and exposure and social skills. Another network meta-analysis examining eight psychotherapies for panic disorder found comparable effects for most therapies, but did find that behavioral therapy and CBT were more effective than third-wave CBT[4].

Conventional meta-analyses are also not consistent. In a review of 15 meta-analyses of RCTs directly comparing 23 psychotherapies for different disorders with other psychotherapies, only five found significant differences[243], and all significant differential effect sizes were small.

Thus, most evidence suggests that psychotherapies for mental disorders either have comparable effects, or in some cases can have small differential effects. This implies that many new psychotherapies are not so innovative, and may not contribute much to improving relevant outcomes. Therefore, it goes beyond the current overview to discuss all new psychotherapies that have been developed.

An important category of psychological interventions that is new is represented by the so-called “bottom-up” therapies[244]. Traditionally, almost all psychological interventions have been developed top-down, with clinicians designing treatments based on their experience and knowledge of the literature. Although the rationale of these therapies typically sounds intuitive and credible to patients, the methods to develop them are not systematic or reproducible, and the processes to select, combine and weigh the evidence are entirely subjective. These methods are also heavily influenced by the founder’s unique sociocultural background, values and perspectives, and the manuals are developed by the founder, based on subjective principles. As we saw earlier, many of these top-down therapies have been found to be effective in the treatment of mental disorders, but the exact mechanisms through which they work remain unclear and are based on clinical experience and selective reading of the literature.

Bottom-up interventions start with psychological theories of factors that cause or maintain symptoms of mental health problems[244]. Based on these theories, targets for experimental manipulation are selected, and interventions focusing on these targets are developed. Probably the best-known example of a bottom-up intervention is exposure, that goes back to the theoretical work on systematic desensitization in the 1950s[245]. Most therapies developed since then were top-down[244]. In the past years, however, several new bottom-up interventions have been developed and tested in RCTs.

We will discuss here the two most important categories of bottom-up therapies: cognitive bias modification (CBM) and cognitive remediation (CR). There are several other bottom-up interventions, such as consolidation/reconsolidation therapies[246], and memory specificity training[247,248], but these have been examined in only a few trials.

In this section, we will subsequently consider some other recent developments concerning new psychotherapies or new approaches aimed to improve the outcomes of psychotherapies.

Cognitive bias modification

CBM is based on a large body of research showing that biases in attention, interpretation and memory are associated with mental health problems and may contribute to them. This has been confirmed for depression[249-251], anxiety[251,252], eating disorders[253,254], substance use disorders[255,256], and psychotic experiences[257]. CBM is a psychological intervention aimed at correcting such biases. Participants engage in structured, computer-based repetitive tasks that train them to modify their automatic responses. These tasks can be gamified to maintain engagement, and immediate feedback is usually provided to reinforce the desired cognitive patterns[258].

CBM and related interventions – such as attention bias modification (ABM), interpretation bias modification, and “approach and avoidance” training – have been examined in dozens of RCTs and a considerable number of meta-analyses. Overall, these interventions seem to have a moderate and significant effect on the biases they are aimed at[259]. The effects on symptoms of mental health problems are less clear.

A large network meta-analysis of 75 trials on CBM for anxiety and depressive disorders[260] differentiated between four types of CBM: ABM; CBM aimed at interpretation bias (CBM-I); the combination of ABM and CBM-I; and approach and avoidance training. For anxiety, only CBM-I had a significant effect when compared with waitlist (SMD=–0.55) and sham training (SMD=–0.30). In depression, CBM-I also had a significant effect when compared with waitlist (SMD=–0.63).

A meta-analysis of 14 trials on CBM for alcohol and smoking addiction did not find a significant effect on substance use, but did find a significant effect on relapse[261]. A meta-analysis of 23 trials in children and adolescents with or without mental health problems found small and non-significant effects on mental health[262]. A meta-analysis of 29 RCTs in anger and aggression found small but significant effects on both variables[263].

Overall, the evidence suggests that CBM and related interventions can have an effect on cognitive biases, and some types may also have small effects on mental health problems. It is not clear, however, if such interventions can improve clinical practice. A meta-analysis of trials comparing the combination of CBM and CBT with CBT alone in people with anxiety disorders did not find that CBM significantly improved the outcome of CBT[264]. More research is therefore needed to examine if and how CBM can be used in routine care, and if it actually improves outcomes in real life settings.

Cognitive remediation

CR targets cognitive deficits (of attention, memory, executive function, social cognition, or metacognition) using scientific principles of learning, with the ultimate goal of improving functional outcomes[265]. Cognitive impairments have been well established in several mental disorders, including schizophrenia, bipolar disorder, depression, ADHD, PTSD and OCD[265,266]. CR can include many different techniques to improve these impairments, but should contain at least four core elements: facilitation by a therapist, cognitive exercises, procedures to develop problem-solving strategies, and procedures to facilitate transfer to real-world functioning[267].

The ideas underlying CR go back several decades[268,269]. However, in the last years the number of trials examining CR has increased exponentially, including a growing number of computerized CR interventions[270,271]. For example, in a recent meta-analysis of 67 randomized trials of CR in schizophrenia, it was found that more than 80% were conducted after 2010[272]. This increase in research on CR is undoubtedly also related to its growing use through digital technologies[273,274].

A recent meta-analysis of 67 trials on CR in schizophrenia found small but significant and durable effects on cognition (SMD=0.23) and global functioning (SMD=0.26)[272]. Another meta-analysis of 73 trials investigating more detailed outcomes[275] also found small-to-moderate size improvements in all domains of cognition studied (SMD range: 0.19 to 0.33), as well as a small significant effect on negative symptoms (SMD=0.16), but not positive symptoms or overall levels of symptomatology. A meta-analysis of 21 trials on CR in depression resulted in a small significant effect on depression (SMD=0.28) and daily functioning (SMD=0.22), and a moderate effect on cognitive functioning (SMD=0.60)[276]. This is comparable to the results of other meta-analyses of trials on CR in depression [277,278].

The outcomes of CR in other mental disorders are not consistent. A meta-analysis of seven trials in bipolar disorder resulted in small significant effects on working memory, planning and verbal learning, but not on functional outcomes[279]. Another meta-analysis of 11 trials on CR for adolescents with mixed mental disorders also showed small but significant effects on cognition, but not on clinical symptoms or social functioning[280]. In a small meta-analysis of eight trials on CR in anorexia nervosa, no significant effects were found on cognitive functioning or symptomatology[281]. These meta-analyses on CR in disorders other than schizophrenia or depression should be considered with caution, because the number of included trials was small, and results may not be significant because of low statistical power.

Overall, CR seems to have small but significant effects on negative symptoms in schizophrenia, and on symptoms of depression. Considering these outcomes, more research could be focused on how these interventions can be implemented in routine care, and if the effects are retained in real-life settings.

Psychedelic-assisted psychotherapies

An increasing number of studies is focusing on the effects of psychedelic-assisted psychotherapies in mental disorders[282,283]. Psychedelics are powerful psychoactive substances that alter perception and mood, and affect numerous cognitive processes[284]. Combining them with psychotherapies has the potential to enhance the effects of the latter.

Most research in this area has focused on the use of psychedelics – psilocybin, lysergic acid diethylamide (LSD) or ayahuasca – for depression[282], and to a lesser extent of methylene-dioxy-methamphetamine (MDMA) for PTSD[285,286]. There are also trials exploring the use of psychedelics in other disorders[282], including borderline personality disorder[287], body dysmorphic disorder[288], OCD[289], and alcohol use disorder[290].

Although the effects of psychedelic-assisted psychotherapies have been examined most extensively in depression, the number of trials is still small (the largest meta-analysis, focusing on psilocybin-assisted psychotherapy, includes nine RCTs[291]). It is also remarkable that the number of meta-analyses in this small area of research is almost as large as the number of primary trials. The above-mentioned meta-analysis[291] indicated a large effect size of psilocybin-assisted psychotherapy (SMD=0.78; N=596) when compared to placebo or waitlist control conditions.

MDMA-assisted psychotherapy for PTSD has also been examined in several trials and meta-analyses. The largest meta-analysis[285], including nine RCTs (N=297), found a large effect of MDMA-assisted therapy on symptoms of PTSD (SMD=-1.10), when compared with placebo or low-dose MDMA.

Although these effects seem rather positive, and these treatments have been claimed to represent a new paradigm for mental health care[292], the number of studies and of participants in these studies is too small to draw strong conclusions. The potential impact of conflicts of interests of researchers, and the potential selection bias in the trials[293] are further problems. Moreover, participants in the trials can be expected to be positive about the effects of psychedelic-assisted therapies. Many of them hope to be assigned to the treatment condition and will be disappointed when they end up in the control group[292,294]. Since it is not possible to mask participants, they are typically aware if they are in the treatment or control group, which may have an impact on the outcomes. Furthermore, psychedelics can be expected to have short-term effects, while from a clinical perspective it is much more important to achieve long-term effects, when the direct impact of psychedelics has passed. Unfortunately, hardly any research on the long-term effects of these therapies has been conducted.

Another important problem is that the psychotherapies that are actually implemented are not described clearly in the reports of the trials[295]. This means that psychedelic-assisted therapies consist of two components of which the effects are not clear: the psychedelic and the psychotherapy. It is unclear to what extent each of these components is responsible for the assumed effects of the therapies[293,296]. The conclusion is that psychedelic-assisted psychotherapies may have the potential to increase the effects of treatments of mental disorders, but this is still uncertain. The current evidence is insufficient to reach a final conclusion about their potential.

Transdiagnostic psychotherapies

Most psychotherapies focus on specific disorders, and RCTs examining the effects of these treatments usually focus on one specific disorder[21,297,298]. However, comorbidity between mental disorders is very high. For example, comorbidity between depression and anxiety has been estimated to be as high as 60% for case-level disorders[299], and is probably even higher when subthreshold cases are considered[300]. It has also been argued that depression and anxiety in fact constitute one cluster of internalizing disorders and share similar psychological and biological mechanisms[301]. Analogously, it has been suggested that the same underlying processes are involved in different eating disorders[302]. Psychological treatments of different mental disorders also often share the same core elements. For example, cognitive restructuring has been found to be effective in most major mental disorders[297].

Transdiagnostic psychotherapies are treatments that apply the same underlying principles across different mental disorders, without tailoring the protocol to specific diagnoses[303,304]. These approaches focus on identifying common and core maladaptive temperamental, psychological, cognitive, emotional, interpersonal and behavioral processes that can be targeted in treatment. People with different disorders can be treated with the same protocol, which makes it easier for them to access care without needing multiple, disorder-specific therapies, and has the potential to spare time and resources, without reducing the effects of therapies.

Transdiagnostic approaches have been claimed to offer more flexible, inclusive and effective treatment options[305]. Most of them have been developed for depression and anxiety disorders (sometimes also including PTSD, OCD and somatoform disorders), and are based on CBT principles[300,306-310]. However, transdiagnostic treatments have also been developed in the field of eating disorders. Enhanced CBT was specifically designed to target the underlying processes that are assumed to maintain different types of eating disorders[302].

Several dozens of RCTs have examined the effects of transdiagnostic psychotherapies, most of which were conducted after 2010. A handful of trials have examined enhanced CBT for eating disorders[311], but most research has focused on transdiagnostic treatments of various anxiety disorders or depression and anxiety. One large, recent meta-analysis of transdiagnostic treatments in emotional disorders included 53 trials and found that the treatments had considerable effects on depression (SMD=0.74) and anxiety (SMD=0.77)[309]. However, the nine comparisons between transdiagnostic and disease-specific treatments resulted in a small, non-significant difference (SMD=0.09).

The best example of a transdiagnostic psychotherapy is the unified protocol (UP) for emotional disorders[312], which was the first and is the most examined transdiagnostic treatment of depression and anxiety. One recent meta-analysis examining the effects of the UP included 19 randomized trials[313]. This study found moderate effects for depression and anxiety when compared to waitlist control conditions (SMD=0.59), but also small significant effects when compared to other active treatments (SMD=0.38).

Many transdiagnostic psychotherapies that are examined in RCTs are conducted through the Internet, and include guided and unguided versions. One recent meta-analysis included 57 trials and found moderate effects for depression (SMD=0.52) and anxiety (SMD=0.45) when compared to passive controls[307]. Only three trials compared transdiagnostic interventions with other treatments, so that a comparison of the relative effects is not yet possible.

Overall, this body of research shows that transdiagnostic psychotherapies are effective in the treatment of depression and anxiety, but it is unclear if they have better effects than disease-specific treatments. One could argue, however, that transdiagnostic treatments have several advantages when compared to disease-specific treatments, which makes them more useful even when the effects are comparable.

A new generation of dismantling studies

A considerable body of research within the psychotherapy field has focused on identifying the core elements or components of these treatments. This research can clarify how therapies work, remove inactive or irrelevant components, and potentially make therapies more effective and cost-effective[314,315]. Understanding how therapies work may also make it easier to train therapists and disseminate therapies more widely[314].

Traditionally, components of therapies are examined in RCTs in which a full therapy is compared with the same therapy with or without a specific component. Although many of such dismantling trials have been conducted, they rarely have enough statistical power to examine if adding or removing a component is related to larger or smaller effects of the intervention. The dismantling trials covered in systematic reviews and meta-analyses rarely included more than 100 participants, while much larger trials are needed to find differential effects[316-318]. For example, based on the assumption that a minimally clinically important difference for depression is SMD=0.24, a dismantling trial would need 274 participants in each condition[316].

There are two important new developments in this area of research that could generate more knowledge on effective components of psychotherapies. The first is the introduction of the so-called "factorial design"[314,315]. This design allows to examine multiple components in one study and to explore the main effects of these components as well as the interactions among them. The basic idea is that participants are randomized to any combination of components in the intervention. Because the number of potential experimental conditions increases exponentially as the number of components of the intervention increases, some studies make use of the so-called "fractional factorial design"[314]. This is a variation on the factorial design in which only a pre-specified selection of the possible conditions is examined to make the study more manageable.

Although (fractional) factorial designs have been used in other areas of the biomedical field[319-321], their use in psychotherapy research has started only recently[322]. Table 3 presents an overview of recent factorial trials on psychotherapies and the most important outcomes[71,322-327]. As can be seen, the results have been somewhat disappointing, but future research may help to shed more light on effective components for specific disorders.

The other recent important development that can help with the finding of effective components of psychotherapies is represented by component network meta-analyses. This is an extension of standard network meta-analyses that can be used to disentangle the associations with outcomes of different components of an intervention[328,329]. Several such meta-analyses have been carried out in recent years, including one conducted with the individual participant data of the included trials[61].

Table 4 gives an overview of the most important component network meta-analyses and a summary of their outcomes[13,17,61,330-332]. One interesting finding is that relaxation, often included in packages of CBT because it is considered to be easy to practice, has been found to be possibly harmful across several disorders, including panic disorder[331], depression[61] and insomnia[13]. Although the results of these studies certainly provide some directions for potentially effective and non-effective components, further research is needed to detect more clear outcomes.

Innovations in understanding processes involved in psychotherapies

Apart from dismantling studies, there are large research areas focusing on the processes involved in psychotherapies that can explain how they work. The hope is that this research will increase our understanding of psychotherapies and will make it possible to strengthen their effects or make them more efficient. Here we describe where this field currently is. We first explain why it is difficult to examine the change processes in psychotherapies. Then we focus on the current state of knowledge on three core topics: specific versus common factors in therapy, the therapeutic alliance, and fidelity versus flexibility.

Although RCTs provide an excellent design for examining *if* a

Table 3 Selected factorial trials aimed at examining components of psychotherapies for mental health problems

	Disorder	N	Intervention	Components	Main findings
Andersson et al[323]	Depression	197	Internet-based CBT	Self-tailored vs. clinician-tailored treatment; scheduled therapist support vs. support on demand; clients in supervision vs. not in supervision	Only self-tailored treatment was a little more effective than clinician-tailored treatment.
Bur et al[324]	Depression	316	Problem-solving therapy with CBT	Human support vs. not; diagnostic interview vs. not; motivational interviewing vs. not; automated e-mails vs. not	Human support resulted in better outcomes at post-test, but not at follow-up. The other three factors were not associated with better or worse outcomes.
Furukawa et al[71]	Depression	3,936	Unguided smartphone CBT	Behavioral activation; cognitive restructuring; problem solving; assertion training; behavior therapy for insomnia	All included skills and their combinations were superior to all control conditions.
Kelders et al[325]	Depression	239	Acceptance and commitment therapy	Human vs. automated feedback; text message coaching (present or absent); interaction (high or low); tailoring of success stories (high or low); personalization (high or low)	Human support was associated with better outcomes; no significant differences for any of the other components was found.
Sakata et al[322]	Depression	1,093	Unguided smartphone CBT	Self-monitoring; behavioral activation; cognitive restructuring; assertiveness training; problem solving	Depression reduction was not significantly associated with any component.
Sipka et al[326]	Social anxiety	464	Internet-based CBT	Psychoeducation; cognitive restructuring; attention training; exposure	All components were associated with improvement when compared to waitlist, but psychoeducation and exposure brought more improvement than the other two components.
Watkins et al[327]	Depression	767	Internet-based CBT	Activity scheduling; functional analysis; thought challenging; relaxation; concreteness training; absorption training; self-compassion training	None of the components was associated with better outcomes at post-test or 6-month follow-up, except for absorption training that had better outcomes at 6-month follow-up.

CBT – cognitive behavioral therapy

Table 4 Selected component network meta-analyses of psychotherapies for mental disorders

	Disorder	n	N	Intervention	Components	Main findings
Coventry et al[330]	PTSD	18	933	Psychological treatments	14 combinations of the following 11 components: active control; cognitive restructuring; imaginal exposure; in vivo exposure; mindfulness; multidimensional; psychoeducation; relaxation; support; virtual reality exposure; waitlist	Interventions that took a multicomponent approach were more effective than those that did not. None of the other individual components or examined combinations differed significantly from waitlist.
Furukawa et al[61]	Depression	48	11,704	Guided and unguided digital CBT	Waiting; conventional drug treatment; non-specific treatment effect; psychoeducation; cognitive restructuring; behavioral activation; interpersonal skills training; problem solving; relaxation; third-wave components; behavior therapy for insomnia; relapse prevention; homework required; initial face-to-face contact; automated encouragement; human encouragement; therapeutic guidance	There was suggestive evidence that behavioral activation might be beneficial and that relaxation might be harmful.
Furukawa et al[13]	Insomnia	241	31,452	CBT	Educational (sleep hygiene, sleep diary); cognitive (cognitive restructuring; third-wave components; constructive worry); behavioral (sleep restriction; stimulus control; relaxation; paradoxical intention; other (nonspecific treatment effect; waiting; conventional drug treatment); delivery (individual, group, in-person; online guidance; human encouragement; automated encouragement)	Cognitive restructuring, third-wave components, sleep restriction and stimulus control are critical components of CBT; sleep hygiene education was not essential and relaxation is potentially harmful; in-person therapist-led programs were most beneficial.
Miklowitz et al[17]	Bipolar disorder	39	3,863	Psychological treatments	Psychoeducation; psychoeducation including skills training; self-monitoring; self-management; cognitive restructuring; maintaining daily rhythms; behavioral activation; interpersonal problem solving; communication training; group format; family format; individual format	Cognitive restructuring and regulating daily rhythms were the most potent components for reducing severity of depression and manic symptoms; the least potent component was behavioral activation (and for depression also the individual therapy format).
Pompoli et al[331]	Panic disorder	72	4,064	CBT	Waiting; placebo effect; support; psychoeducation; breathing retraining; relaxation; cognitive restructuring; interoceptive exposure; in vivo exposure; virtual reality exposure, third-wave components; face-to-face setting	Interoceptive exposure and face-to-face setting were associated with better treatment outcomes. Muscle relaxation and virtual-reality exposure were associated with significantly lower efficacy.
Williams et al[332]	Early psychosis	37	4,599	Various early interventions	Pharmacotherapy; case management; psychological treatment; family intervention; social intervention	The addition of psychological interventions reduced negative psychotic symptoms at 3-month follow-up. No other significant finding at 3-month follow-up was found.

PTSD – post-traumatic stress disorder, CBT – cognitive behavioral therapy

treatment works and how large the effects are, they do not directly provide information on *how* treatments work. Much research has been done on mediators, but, when these are examined in trials, the findings are always correlational rather than causal[243,333]. This means that, when a mediator is significantly associated with the outcome of therapy in a trial, this can be explained in three different ways: a) the change in the mediator causes the outcome; b) the improvement in the outcome causes the improvement in the mediator; or c) a third variable causes the improvement in both the outcome and the mediator.

This issue of causality cannot be settled completely. But there are several factors that can help to make the causal relationship between a mediator and an outcome more plausible: a temporal relationship between mediator and outcome (change in the mediator comes before change in the outcome); a dose-response association; evidence that no third variable causes changes in the mediator and the outcome (usually by including many potential third variables in the study); supportive experimental research;

and a strong theoretical framework that can explain why the mediator is probably indeed a causal factor. There are also improvements in the methodology, such as the so-called "causal inference framework" that provide logical foundations for research in this area[334-336]. Working mechanisms, however, remain extremely difficult to examine.

This complexity of examining mechanisms of change in psychotherapies has resulted in many discussions about how they actually work. One important discussion is about common versus specific factors as key mechanisms of change[243]. The common factors model assumes that all therapies work through factors such as the alliance between therapist and patient, a rationale for causes of the problems and how to solve them, modeling, and catharsis, which are present in all therapies[211,337]. The specific factors model assumes that therapies work through specific mechanisms, such as changing maladaptive thoughts, changing actual behavior, or learning how to stop avoiding fearful situations.

Proponents of the common factors model often point to meta-analyses of outcome studies, which show that all therapies have comparable effects[243]. However, this does not necessarily prove that they work through common mechanisms. Component network meta-analyses can provide some insight on whether specific components have independent effects, which would support the specific factor model. Table 4 provides an overview of these meta-analyses, and several of them do suggest that some components contribute independently to the effects of therapies.

The most important common factor is undoubtedly the therapeutic alliance, i.e. the relationship between therapist and patient. This alliance has three components: the bond between the therapist and the patient, the agreement about the goals of therapy, and the agreement about the tasks of therapy[337]. The largest meta-analysis examining the association between the therapeutic alliance and outcome at one time point included almost 300 studies in adults[338]. There was a strong and significant association between the outcome and the alliance (correlation r=0.28, which corresponds to an SMD of 0.58), and this was true for face-to-face as well as for Internet-based therapies. A meta-analysis of studies in children and adolescents found a somewhat smaller, but still significant and substantial effect size (r=0.18, which corresponds to SMD=0.37).

As stated previously, an association between alliance and outcome cannot be considered as causal evidence showing that the alliance causes change. However, the above-mentioned meta-analysis in adults[338] also included a number of studies that examined the temporal association (change in the alliance precedes change in outcome), as well as an adjustment for baseline characteristics of patients that could explain the association. This supports the hypothesis that the alliance is a causal factor in generating change in patients, although the empirical evidence in this respect cannot be considered very strong[243].

Two different components of the alliance have been recently differentiated[339]. The "trait-like" component refers to the general ability of patients to form satisfying relationships with others, which also affects their capacity to form a satisfactory relationship with the therapist and to benefit from treatment. This trait-like component does not make alliance sufficient to generate change by itself, but can enable the use of other aspects of treatment that may induce change, such as effective techniques. The "state-like" component refers to changes in alliance that occur during treatment, which can be assumed to be the result of in-session work between patient and therapist. This component may contribute to trait-like changes in patients, which in turn enables the use of other aspects of treatment. This distinction between "trait-like" and "state-like" components of the alliance should be examined in more depth, but it does provide a new perspective, and may generate new knowledge on the mechanisms of change in therapy.

Another important issue in the process of therapy is the so-called "fidelity versus flexibility" question. This refers to whether a therapist should adhere strictly to the manual of a therapy, or can be more flexible in its application depending on the needs of the patient[340-342]. In RCTs, fidelity is an important element to strengthen the internal and external validity of the trial, and protocols with strong adherence of therapists are also those that are typically considered for implementation in routine care[341]. Fidelity also helps in limiting the number of sessions and facilitates training of therapists. In the IAPT program in the UK, aimed at increasing uptake of psychological treatments, fidelity to the protocols has been suggested to enhance efficacy considerably[65]. However, there are also several criticisms of treatment protocols. They have been called "cookbooks", they have been claimed to detract from the therapeutic alliance, and to be narrow and not broadly applicable[341]. It has been suggested that broader therapies, such as transdiagnostic approaches, offer more flexibility while retaining fidelity[340].

It remains unclear if more fidelity is associated with better outcomes. One earlier meta-analysis of 32 studies did not find that fidelity was significantly associated with outcome[343]. However, a more recent and extensive meta-analysis of 62 studies differentiated between adherence (prescribed methods are actually implemented in therapy), competence (knowledge, skills and appropriateness with which the methods are delivered), and integrity (that should include adherence, competence and treatment differentiation)[342]. This meta-analysis did find a significant association between integrity and outcome in two different groups of studies (r=0.15 and r=0.23).

It should be kept in mind that all this research is correlational, and cannot provide a definite answer to the "fidelity versus flexibility" question. To answer this question, new trials are needed in which patients are randomized to a fidelity or a flexibility condition, and to the best of our knowledge such trials have not been conducted. At this moment, it is not clear whether increasing or reducing fidelity can strengthen the outcomes of therapies.

Other innovations aimed to improve outcomes

One further innovation with the potential to improve outcomes of psychotherapies is the frequency of sessions. Meta-analytic research on psychotherapies for depression has suggested that, in individual therapy, the effects are not associated with the number of sessions, the contact time between patient and therapist, and the length of treatment[344,345]. However, meta-regression analyses did indicate that the frequency of sessions is significantly associated with the outcomes. Sessions twice per week are more efficacious than sessions once per week (SMD=0.60)[345].

Because meta-regression analyses do not provide causal, but only correlational evidence, more direct evidence is needed to confirm this finding. One RCT was conducted in which 200 outpatients with depression were randomized to once or twice weekly sessions of CBT or IPT[346]. It was found that those having sessions twice a week had better outcomes than those receiving sessions once a week (SMD at month 6: 0.55). Although these are preliminary findings that need to be confirmed in further research, this may be a promising innovation to improve the effects of psychotherapies.

Another innovation with the potential to improve outcomes is progress feedback. Outcome instruments are administered regularly throughout therapy[347] and monitored by the therapist. This allows the clinician to adjust treatment when there is too little progress, so that poor outcomes might be prevented[348-350]. The results of meta-analyses of RCTs that compare treatments with or without progress feedback have been mixed, with most of them finding small significant effects[351-353], but others finding no significant effects[354,355]. These meta-analyses, however, included subsets of studies aimed at specific target groups or using a specific feedback instrument, and all covered less than 20 trials. The largest meta-analysis in all target groups and any instrument included 58 trials[349], and found a small but significant overall effect of progress feedback (SMD=0.15). More research is needed to verify the effects of progress feedback, but this seems to be a promising method to improve outcomes.

Preventing and reducing adverse effects of psychotherapies

One important way to improve the outcomes of psychotherapies is to prevent or reduce their adverse effects. This is now widely recognized as a major priority for research and practice of psychotherapy[356-358].

For a long time, it has been assumed that adverse effects are not relevant in psychological interventions. The belief that psychotherapy, being "just talking", could not cause harm has led to patients rarely reporting these effects. Adverse effects are also not well reported in RCTs. For example, a meta-analysis of deterioration rates in psychotherapies for depression[359] found that only 6% of trials reported these rates.

One major problem in this area is the lack of consensus on what constitutes an adverse effect in psychotherapy. Clinically significant deterioration and suicide attempts are clearly important adverse effects. However, there is less clarity on what other events should be considered adverse effects. For instance, non-response and dropout could also be viewed as adverse outcomes, as they might prevent patients from receiving adequate care or experiencing spontaneous remission[360]. Other adverse effects that are often mentioned include treatment dissatisfaction, lack of therapeutic alliance, anxiety or rumination about therapy, emergence of new symptoms, stigmatization, and perceived negative effects of treatment on family/friends[356,357,361,362]. A systematic review of tools used to assess negative effects of psychotherapy included nine instruments[362]. They covered 17 domains of negative effects, but none of them covered all these domains.

One cluster of negative outcomes that has been examined extensively is represented by deterioration rates. Table 5 gives an overview of the results of meta-analyses providing data on deterioration rates in psychotherapies compared to control conditions[180,349,359,363-369]. Most research has been done in depression, but there are also some studies in anxiety disorders and PTSD. The deterioration rate in psychotherapies varied between 1 and 6%, while in the control conditions was between 5 and 17%. In almost all meta-analyses, the deterioration rate was significantly lower in psychotherapy compared to the control group.

Although there is now more attention to adverse effects of psychotherapies, and deterioration has been examined extensively in recent years, there is still a long way to go before methods to reduce adverse effects can improve clinical practice. More consensus on what adverse effects are is very much needed, and then more research should make clear how prevalent the different adverse effects are, and what methods can be used to prevent or reduce them.

Other methodological innovations in research on psychotherapies

In the past years, several new methodologies (in addition to those already described) have been developed that can help to speed up innovations in research on psychotherapies.

One important new design is the so-called "stepped wedge design", which is especially useful in research on the implementation of interventions in clinical practice[370]. This is a cluster-randomized trial in which all clusters (such as clinics or communities) start in the control condition. At regular intervals (the "steps"), a randomly selected subset of clusters moves from the control to the intervention condition. This continues until all clusters have received the intervention. This design makes it possible to examine the impact of the implementation of the intervention in routine care, and is increasingly used in mental health research[371-375].

Another important methodological innovation is represented by "platform trials"[376], which have transformed other areas of medicine, including oncology and infectivology, but are only now beginning to be used in mental health research[376,377]. In platform trials, an infrastructure with a master protocol is developed, allowing to compare multiple interventions against a single control group [378], to add new treatments as they become available, or to drop some when they turn out to be not useful.

Several platform trials on pharmacological interventions have been developed recently for PTSD, depression and psychosis[376]. In the field of psychological treatments, a recent study[71] tested the differential efficacy of five CBT skills (behavioral activation, cognitive restructuring, problem solving, assertion training, and behavior therapy for insomnia) on a smartphone app among people with

Table 5 Core meta-analyses examining reliable deterioration rates in psychotherapies versus control conditions

	Type of meta-analysis	Disorder	Type of psychotherapy	Control	n	N	Deterioration rate Psychotherapy	Deterioration rate Control	Relative outcome (95% CI)
Cuijpers et al[359]	Conventional MA	Depression in adults	Any therapy	Any	18	1,665	4%	11%	RR=0.39 (0.27-0.57)
Cuijpers et al[363]	MA imputed	Depression in adults	Any therapy	WL	101	NA	5%	13%	RR=0.27 (0.22-0.33)
Cuijpers et al[364]	MA imputed	Depression in youth	Any therapy	Any	38	NA	6%	13%	RR=0.40 (0.28-0.57)
De Jong et al[349]	Conventional MA	Any	Therapy with progress feedback	CAU	26	NA	5%	5%	OR=1.16 (0.99-1.35)
Fernández-Alvarez et al[180]	IPDMA	Anxiety disorders	VR interventions	WL	15	810	4%	15%	OR=4.87 (0.05-0.67)
Hoppen et al[365]	Conventional MA	PTSD	Any therapy	Passive	8	NA	1%	11%	RR=0.21 (0.15-0.28)
Karyotaki et al[366]	IPDMA	Depression	Self-guided digital interventions	Any	13	3,805	6%	9%	OR=0.62 (0.46-0.83)
Lofthouse et al[367]	MA imputed	PTSD in youth	Any therapy	Any	60	5,113	1%	13%	NA
Mather et al[368]	IPDMA	Depression in people with diabetes mellitus	Any therapy	Any	12	2,070	3%	7%	RD=-0.03 (-0.05 to -0.01)
Rozental et al[369]	IPDMA	Multiple disorders	Internet interventions	Any	29	2,866	6%	17%	OR=3.10 (2.21-4.34)

Some RRs and ORs are above 1 and others below, but they all indicate lower deterioration rates for psychotherapies compared to control condition (except for De Jong et al[349]). MA – meta-analysis, IPDMA – individual patient data meta-analysis, PTSD – post-traumatic stress disorder, VR – virtual reality, WL – waitlist, CAU – care as usual, NA – not available, RR – relative risk, OR – odds ratio, RD – risk difference.

subthreshold depression. The CBT skills were examined in four 2x2 factorial trials embedded in a large master protocol. This design, together with the digital infrastructure, enabled recruitment of 5,361 participants with or without subthreshold depression. The five skills were found to be differentially superior to three control conditions (delayed treatment, health information, and self-checks), not only on depression but also on anxiety, insomnia and well-being.

New methodologies are also being developed in the field of meta-analyses, such as the meta-analytic research domains (MARDs)[379]. These are living systematic reviews that cover a whole research domain, regardless of age, target group, or comparator, providing an overview of everything that can be known about the field from RCTs. MARDs have been developed for psychological treatments of depression[380], mental health problems in children and adolescents[381], suicidal behavior[382], and anxiety disorders[4]. They can be expected to bring meta-analytic research to a new level.

DISSEMINATION AND SIMPLIFICATION OF PSYCHOTHERAPIES

Conventional psychotherapies are in fact beneficial only to a tiny minority of those who could benefit from them[348,383-385], since more than 80% of the almost one billion people with mental disorders live in LMICs, with little access to them, and only a small proportion of patients in high-income countries receive these therapies. Here we focus on innovations in psychological interventions which can make them more scalable and easier to implement in large populations.

Task sharing

One major problem in the implementation of psychological treatments in LMICs is that the task force to deliver them does not or hardly exist. One solution to this problem is the so-called "task sharing", the delegation of tasks to community or primary care-based non-specialist workers with no formal degree or training in implementing mental health care[173,386]. Task sharing is indeed considered to be one of the main innovations to improve access to evidence-based psychological therapies in low-resource settings[383-386].

Task-sharing interventions have involved a wide variety of non-specialist health workers, such as community health workers, midwives, nurses, primary care providers, village health workers, complementary alternative health providers, teachers, religious and traditional healers, and community members[386]. Task sharing is firmly established in the delivery of care for maternal-child health and for human immunodeficiency virus (HIV) infection in low-income settings, but is also growing in global mental health care[383-386]. Although task-sharing interventions are especially important in low-resourced settings, they are also increasingly considered in higher-income contexts[387-389].

A considerable number of trials examining the effects of task-sharing interventions has been conducted. The largest meta-analysis was aimed at perinatal mental health[387]. It included 44 RCTs (18,101 participants), and found small but significant effects on depression (SMD=0.24) and anxiety (SMD=0.30). Some smaller meta-analyses estimated the effects of task sharing in LMICs compared to control groups, focusing on transdiagnostic behavioral activation interventions for common mental disorders (20 trials; SMD =0.59 for depression; SMD=0.61 for anxiety; SMD=0.38 for PTSD/trauma)[390], and for depression (11 trials, SMD=0.32)[173].

A systematic review of 19 trials on task-sharing interventions for substance use and substance use disorder in LMICs suggested positive effects, but, because no meta-analysis was conducted, this finding should be considered with caution[391].

Digital interventions in LMICs

Guided Internet-based interventions can be delivered by trained lay counsellors without extensive training. Self-guided interventions do not require any human contact with patients. These interventions have, therefore, much potential from the perspective of global mental health, especially since the majority of the world population now owns a smartphone and has access to the Internet[392].

The largest meta-analysis of digital interventions for depression and anxiety in LMICs included 80 randomized trials (12,070 participants), most of which were conducted in 2020 or later[393]. This meta-analysis was very liberal in its inclusion criteria (physical exercise interventions were also included, as well as studies in high-risk groups without depression or anxiety at baseline), but it did find substantial and significant effects for depression (SMD=0.61) and anxiety (SMD=0.73).

Another meta-analysis of RCTs in LMICs focused exclusively on digital psychological interventions for people with depression and/or anxiety, and included 21 trials (5,296 participants)[62]. The interventions resulted in substantial effects on depression (SMD=0.77) and anxiety (SMD=1.02), and small but significant effects on quality of life (SMD=0.32), when compared with control conditions. Over the longer term, the effects were smaller, but remained significant for all examined outcomes.

An important finding of this meta-analysis was that no significant difference (p=0.93) was found between interventions with human support (SMD=0.90 against controls; 15 studies) and unguided interventions (SMD=0.87 against controls; 8 studies). Most previous research suggested that interventions without human support have significantly smaller effects than those with support[57]. This may not be true, however, in LMICs, for example because usual care differs considerably from high-income countries. This is a highly important finding from a dissemination point of view, because delivery of unguided interventions is much cheaper than that of guided interventions.

Single-session interventions

Another method to make treatments more scalable and easier to implement is to make them shorter. Meta-analytic research on

Table 6 Summary of innovations in psychotherapies for mental disorders and their main supporting evidence

	Description of innovation	Core studies on outcomes
Innovations in the digital field		
Internet-based therapies	Guided and unguided self-help interventions applied digitally	>250 RCTs in multiple disorders and several meta-analyses have shown effects (see Table 1)
Smartphone apps	Apps on mobile phones	A meta-analysis of 176 RCTs[72] showed small significant effects for common mental disorders
Ecological momentary interventions	"Therapist in your pocket" approaches; use of sensors from smartphones/devices to intervene during everyday life	Potential to improve treatment for a broad range of problems, but too few RCTs available to make a final judgment; no meta-analysis yet available
Just-in-time adaptive interventions	Interventions providing the right type and amount of support, at the right time, by adapting to an individual's internal and contextual state	Potential to improve treatment for a broad range of problems, but too few RCTs available to make a final judgment; no meta-analysis yet available
Serious games	Games that are not devised just for recreation, but also to address mental health problems	Few RCTs in people with mental disorders; some potential effects on depression/anxiety[93,94]
Virtual reality	Three-dimensional interactive computer-generated environments creating the sensation of being present in the environment	>50 RCTs in multiple disorders; overall positive effects, but not more effective than ordinary treatments[102]
Augmented reality	Technology that blends virtual and physical environments, enhancing one's perception of reality	Too few RCTs available to assess if it has additional value over ordinary treatments[107,108]
Prescription digital therapeutics	Digital treatments rigorously evaluated for safety and effectiveness, and authorized by national regulatory agencies	Several treatments approved by FDA in ADHD, PTSD, depression, substance use[109]
Blended therapy	Combined face-to-face and digital treatments	Nine RCTs showed positive effects, but not yet clear if it results in better effects and/or uptake
Avatar therapy	Patients with psychosis create an avatar aimed at reducing auditory hallucinations	A growing number of RCTs shows effectiveness in reducing severity of persistent verbal auditory hallucinations[119,120]
Chatbots/conversational agents	Chatbots that operate through artificial intelligence	Only few RCTs; not yet possible to examine effects or compare with ordinary therapies[126,127]
Personalized treatments		
Predictors/moderators in large RCTs	Research on characteristics of people who respond better to specific treatments	Very large RCTs are needed to examine predictors/moderators; a few have been done, but no clear outcomes yet
Individual patient data (network) meta-analyses	Meta-analyses in which the primary data of RCTs are combined into one dataset	Growing number of published meta-analyses, especially in depression, but until now only limited evidence for significant predictors/moderators (see Table 2)
Machine learning approaches	Techniques allowing researchers to evaluate many predictors/moderators at the same time, in large datasets	Growing number of studies, but until now only limited evidence for significant predictors/moderators
Matching therapists to patients	Patients are assigned to therapists that have been shown to be effective for their problem area	This may increase outcomes, which is confirmed by a well-designed RCT[214]
Personalized/modular therapies	Personalized therapies are tailored to specific characteristics of patients; modular therapies are toolboxes from which the clinician selects modules that are relevant for a patient	Growing number of studies; no consensus yet on what relevant characteristics are; some studies are positive, other negative; MATCH is the best examined modular therapy for youth, but its outcomes are mixed
New and improved therapies		
Cognitive bias modification	Therapy aimed at changing cognitive biases through structured, computer-based training to modify automatic responses	Some types have small but significant effects on depression and anxiety; effects on alcohol problems are unclear[260,261]
Cognitive remediation	Therapy targeting cognitive deficits (attention, memory, executive function, social cognition, metacognition)	Effects on some cognitive deficits in schizophrenia[271]; small significant effects on negative symptoms in schizophrenia[275] and on symptoms of depression[276]
Psychedelic-assisted psychotherapy	Therapies in which psychedelics are used to augment psychotherapy effects	Small number of trials; effects are positive and strong[282], but there are many methodological problems
Transdiagnostic therapies	Treatments that apply the same underlying principles across disorders, without tailoring the protocol to specific diagnoses	A meta-analysis of 53 RCTs in emotional disorders found large effects on depression and anxiety[310]; unclear if they are more effective than disorder-specific therapies

Table 6 Summary of innovations in psychotherapies for mental disorders and their main supporting evidence *(continued)*

	Description of innovation	Core studies on outcomes
Factorial trials	Trials can examine the effects of multiple components of an intervention	Growing number of trials, but too little research yet to draw definite conclusions (see Table 3)
Component network meta-analyses	These can disentangle associations of components of interventions with outcomes	Growing number of meta-analyses, but too little research yet to draw definite conclusions (see Table 4)
Focus on common factors and therapeutic alliance	Unclear whether effects of therapy are mostly caused by common or specific factors; alliance is the most important common factor	A meta-analysis of 295 studies found a strong correlation between alliance and outcome[338]
Focus on adverse effects	It is not clear what adverse effects of psychotherapy exactly are, but deterioration rates are relatively well examined	Multiple meta-analyses show that clinical deterioration rates vary between 1 and 6% in therapy and between 5 and 17% in control conditions (see Table 5)
Increased session frequency	Higher frequency of sessions may be associated with better outcomes	Indirect evidence from meta-analyses[346]; more RCTs needed to confirm the findings
Progress feedback	Outcome instruments are administered regularly throughout therapy and monitored by the therapist	Meta-analyses show small, but significant effects[349]
Dissemination and simplification of therapies		
Task sharing	Tasks are delegated to non-specialist workers with no formal degree or training in mental health	Meta-analyses find positive effects in depression and anxiety[388,390]
Digital interventions in LMICs	Guided and unguided self-help interventions applied digitally, developed mostly for depression and anxiety	Meta-analyses show positive results in depression and anxiety[393]; no significant difference between guided and unguided interventions[62]
Single-session interventions	Structured programs that intentionally involve only one visit or encounter with a clinic, provider or program	Review of 16 meta-analyses found overall positive effects on anxiety and depression[394]

RCT – randomized controlled trial, FDA – US Food and Drug Administration, ADHD – attention-deficit/hyperactivity disorder, PTSD – post-traumatic stress disorder, MATCH – Modular Approach to Therapy for Children with Anxiety, Depression, or Conduct Problems, LMICs – low- and middle-income countries

psychological treatments for depression has shown that the number of sessions in individual therapy are not associated with the outcome[344,345]. This suggests that it may be possible to reduce the number of sessions without reducing the effectiveness of therapies. It has also been found that dropout rates are very high in psychotherapies, and that many patients who start therapy often do not receive more than one session[394-396]. This is in stark contrast with the design of most therapies, which typically include 6 to 60 sessions[344,345].

Single-session interventions can be defined as "structured programs that intentionally involve only one visit or encounter with a clinic, provider, or program"[394,397]. Other names that have been used include "one-session treatment"[398], "ultra brief intervention"[399], and "one-at-a-time therapy"[400]. Research on these interventions is not new, going back to the 1980s[398,401]. However, since the need for scaling up interventions has been emphasized in recent years[383,384], research on single-session interventions has increased considerably.

A recent umbrella review covered 24 systematic reviews of single-session interventions[394], including 16 meta-analyses encompassing 322 RCTs (40,629 participants). Most included meta-analyses reported positive outcomes for anxiety (significant effects in 8 of 9 meta-analyses), depression (5 of 6), substance use (8 of 10) and externalizing problems in children (2 of 2). Outcomes were less certain in eating problems (one meta-analysis with positive effects and one without) and suicidal behavior (one meta-analysis with positive outcomes in adults, but not in youth). Four meta-analyses included trials directly comparing single-session with multi-session interventions, with two indicating no significant differences[402,403], one better outcomes for single-session interventions[404], and one better outcomes for multi-session interventions[405]. A second-order meta-analysis of the trials from 12 meta-analyses resulted in a pooled effect of SMD=0.25 in favor of single-session interventions[394].

Overall, it seems that single-session interventions can have positive effects on mental health problems. Because they are much more scalable than longer interventions, their potential is considerable. However, not all research on these interventions is positive. An earlier meta-analysis of single-session debriefing after psychological traumas (not included in the above-mentioned umbrella review) did not find that these interventions were effective in this population[406]. This suggests that single-session interventions have the potential to be effective, but research on the type of interventions, the population and the setting is needed, before dissemination can be considered.

CONCLUSIONS

We reviewed the current state of innovations that may improve outcomes and uptake of psychotherapies for mental disorders (see Table 6 for a summary). We categorized the innovations into the domains of the digital field, stratification and personalization, new and improved therapies, and the dissemination and simplification of treatments. We also touched upon methodological innovations, such as new methods to personalize therapies, and new trial designs that can improve or speed up clinically relevant outcome research.

We recently developed a simple method to assess the strength of innovations in the treatment of depressive disorders, based on the total number of treatments needed to achieve a response in 100% of patients[407]. This method indicates that none of the current innovations is likely to serve as a "silver bullet" that will dramatically improve outcomes. Although obtained for depression, similar results can be expected for other mental disorders. Rather than expecting a paradigm-shifting breakthrough, we should therefore focus on innovating the practice of psychotherapies incrementally, through various small-scale improvements. This path is more laborious, and it may often yield solutions that remain imperfect, context-dependent, or elusive. Yet, this approach aligns with modern theories of how science progresses in medicine and beyond [408-411], and it has the potential to meaningfully enhance outcomes in the future.

In this paper, we have specifically focused on innovations that have the potential to improve outcomes and uptake of psychotherapies for mental disorders. There are many other innovations in relevant areas that we did not focus on, such as for example the rapidly developing field of digital phenotyping[412], and alternative systems for diagnosing mental disorders[413].

We did not conduct pre-planned, systematic searches for each of the innovations, because that was not feasible, considering the number of innovations and the width of such searches. This means that we may have missed relevant studies that support some innovations. We also had no way of systematically identifying the innovations, so we relied on our knowledge and reading of the literature. Because of the large number of studies that we included in this paper, it was also not possible to assess the quality and risk of bias in the included trials and meta-analyses.

We can conclude that there are currently many innovations in the field of psychotherapies in different stages of development and with varying levels of empirical support. None of these innovations will be a silver bullet that dramatically improves the outcomes and uptake of treatments, and only the joint implementation of several of them may produce tangible improvements.

REFERENCES

1. World Health Organization. World mental health report: transforming mental health for all. Geneva: World Health Organization, 2022.
2. Cuijpers P, Quero S, Noma H et al. Psychotherapies for depression: a network meta-analysis covering efficacy, acceptability and long-term outcomes of all main treatment types. World Psychiatry 2021;20:283-93.
3. Furukawa TA, Shinohara K, Sahker E et al. Initial treatment choices to achieve sustained response in major depression: a systematic review and network meta-analysis. World Psychiatry 2021;20:387-96.
4. Papola D, Ostuzzi G, Tedeschi F et al. Comparative efficacy and acceptability of psychotherapies for panic disorder with or without agoraphobia: systematic review and network meta-analysis of randomised controlled trials. Br J Psychiatry 2022;221:507-19.
5. Papola D, Ostuzzi G, Tedeschi F et al. CBT treatment delivery formats for panic disorder: a systematic review and network meta-analysis of randomized controlled trials. Psychol Med 2023;53:614-24.
6. de Ponti N, Matbouriahi M, Cuijpers P et al. The efficacy of psychotherapy for social anxiety disorder, a systematic review and meta-analysis. J Anxiety Disord 2024;104:102881.
7. Van Dis EA, Van Veen SC, Hagenaars MA et al. Long-term outcomes of cognitive behavioral therapy for anxiety-related disorders: a systematic review and meta-analysis. JAMA Psychiatry 2020;77:265-73.
8. Pompoli A, Furukawa TA, Imai H et al. Psychological therapies for panic disorder with or without agoraphobia in adults: a network meta-analysis. Cochrane Database Syst Rev 2016;4:CD011004.
9. Mavranezouli I, Megnin-Viggars O, Daly C et al. Psychological treatments for post-traumatic stress disorder in adults: a network meta-analysis. Psychol Med 2020;50:542-55.
10. Hoppen TH, Jehn M, Holling H et al. The efficacy and acceptability of psychological interventions for adult PTSD: a network and pairwise meta-analysis of randomized controlled trials. J Consult Clin Psychol 2023;91:445-61.
11. Reid JE, Laws KR, Drummond L et al. Cognitive behavioural therapy with exposure and response prevention in the treatment of obsessive-compulsive disorder: a systematic review and meta-analysis of randomised controlled trials. Compr Psychiatry 2021;106:152223.
12. Wang Y, Amarnath A, Miguel C et al. The effectiveness of unguided self-help psychological interventions for obsessive-compulsive disorder: a meta-analysis of randomized controlled trials. Compr Psychiatry 2024;130:152453.
13. Furukawa Y, Sakata M, Yamamoto R et al. Components and delivery formats of cognitive behavioral therapy for chronic insomnia in adults: a systematic review and component network meta-analysis. JAMA Psychiatry 2024;81:357-65.
14. Setkowski K, Palantza C, van Ballegooijen W et al. Which psychotherapy is most effective and acceptable in the treatment of adults with a (sub)clinical borderline personality disorder? A systematic review and network meta-analysis. Psychol Med 2023;53:3261-80.
15. Cristea IA, Gentili C, Cotet CD et al. Efficacy of psychotherapy for borderline personality disorder: a systematic review and meta-analysis. JAMA Psychiatry 2017;74:319-28.
16. McGlanaghy E, Turner D, Davis GA et al. A network meta-analysis of psychological interventions for schizophrenia and psychosis: impact on symptoms. Schizophr Res 2021;228:447-59.
17. Miklowitz DJ, Efthimiou O, Furukawa TA et al. Adjunctive psychotherapy for bipolar disorder: a systematic review and component network meta-analysis. JAMA Psychiatry 2021;78:141-50.
18. Chiang KJ, Tsai JC, Liu D et al. Efficacy of cognitive-behavioral therapy in patients with bipolar disorder: a meta-analysis of randomized controlled trials. PLoS One 2017;12:e0176849.
19. Leichsenring F, Steinert C, Rabung S et al. The efficacy of psychotherapies and pharmacotherapies for mental disorders in adults: an umbrella review and meta-analytic evaluation of recent meta-analyses. World Psychiatry 2022; 21:133-45.
20. Andrews G, Issakidis C, Sanderson K et al. Utilising survey data to inform public policy: comparison of the cost-effectiveness of treatment of ten mental disorders. Br J Psychiatry 2004;184:526-33.
21. Cuijpers P, Miguel C, Ciharova M et al. Absolute and relative outcomes of psychotherapies for eight mental disorders: a systematic review and meta-analysis. World Psychiatry 2024;23:267-75.
22. Prochaska JO, Norcross JC, Saul SF. Generating psychotherapy breakthroughs: transtheoretical strategies from population health psychology. Am Psychol 2020;75:996-1010.
23. Cuijpers P. How to improve outcomes of psychological treatment of depression: lessons from 'next-level' meta-analytic research. Am Psychol 2024;79: 1407-17.
24. Chisholm D, Sweeny K, Sheehan P et al. Scaling-up treatment of depression and anxiety: a global return on investment analysis. Lancet Psychiatry 2016; 3:415-24.
25. Evans-Lacko S, Aguilar-Gaxiola S, Al-Hamzawi A et al. Socio-economic variations in the mental health treatment gap for people with anxiety, mood, and substance use disorders: results from the WHO World Mental Health (WMH) surveys. Psychol Med 2018;48:1560-71.
26. Thornicroft G, Chatterji S, Evans-Lacko S et al. Undertreatment of people with major depressive disorder in 21 countries. Br J Psychiatry 2017;210:119-24.
27. Merikangas KR, He JP, Burstein M et al. Lifetime prevalence of mental disorders in US adolescents: results from the National Comorbidity Survey Replication - Adolescent Supplement (NCS-A). J Am Acad Child Adolesc Psychiatry 2010;49:980-9.
28. Rickwood DJ, Mazzer KR, Telford NR. Social influences on seeking help from mental health services, in-person and online, during adolescence and young adulthood. BMC Psychiatry 2015;15:1-9.
29. Suresh K, Bhui K. Ethnic minority patients' access to mental health services. Psychiatry 2006;5:413-6.

30. Morichi V, Dell'Aquila G, Trotta F et al. Diagnosing and treating depression in older and oldest old. Curr Pharm Des 2015;21:1690-8.
31. Rathod S, Pinninti N, Irfan M et al. Mental health service provision in low- and middle-income countries. Health Serv Insights 2017;10:1178632917694350.
32. Damiano RJ Jr. What is innovation? Innovations 2011;6:65.
33. Consoli D, Mina A, Nelson RR et al (eds). Medical innovation. Science, technology and practice. London: Routledge, 2016.
34. Campbell LF, Norcross JC, Vasquez MJ et al. Recognition of psychotherapy effectiveness: the APA resolution. Psychotherapy 2013;50:98-101.
35. Carlbring P, Ekselius L, Andersson G. Treatment of panic disorder via the Internet: a randomized trial of CBT vs. applied relaxation. J Behav Ther Exp Psychiatry 2003;34:129-40.
36. Christensen H, Griffiths KM, Jorm AF. Delivering interventions for depression by using the internet: randomised controlled trial. BMJ 2004;328:265.
37. Andersson G, Bergström J, Holländare F et al. Internet-based self-help for depression: randomised controlled trial. Br J Psychiatry 2005;187:456-61.
38. Marks IM, Kenwright M, McDonough M et al. Saving clinicians' time by delegating routine aspects of therapy to a computer: a randomized controlled trial in phobia/panic disorder. Psychol Med 2004;34:9-17.
39. Mars RW. A meta-analysis of bibliotherapy studies. Am J Community Psychol 1995;23:843-70.
40. Cotler SB. Sex differences and generalization of anxiety reduction with automated desensitization and minimal therapist interaction. Behav Res Ther 1970;8:273-85.
41. Donner L, Guerney BG Jr. Automated group desensitization for test anxiety. Behav Res Ther 1969;7:1-13.
42. Miller WR. Behavioral treatment of problem drinkers: a comparative outcome study of three controlled drinking therapies. J Consult Clin Psychol 1978;46:74-86.
43. Scogin F, Hamblin D, Beutler L. Bibliotherapy for depressed older adults: a self-help alternative. Gerontologist 1987;27:383-7.
44. Brown RA, Lewinsohn PM. A psychoeducational approach to the treatment of depression: comparison of group, individual, and minimal contact procedures. J Consult Clin Psychol 1984;52:774-83.
45. Cuijpers P, Schuurmans J. Self-help interventions for anxiety disorders: an overview. Curr Psychiatry Rep 2007;9:284-90.
46. Zhang M, Fan C, Ma L et al. Assessing the effectiveness of internet-based interventions for mental health outcomes: an umbrella review. Gen Psychiatry 2024;37:e101355.
47. Plessen CY, Panagiotopoulou OM, Karyotaki E et al. Digital mental health interventions for the treatment of depression: a multiverse meta-analysis. J Affect Disord 2025;369:1031-44.
48. Pauley D, Cuijpers P, Papola D et al. Two decades of digital interventions for anxiety disorders: a systematic review and meta-analysis of treatment effectiveness. Psychol Med 2023;53:567-79.
49. Steubl L, Sachser C, Baumeister H et al. Mechanisms of change in Internet- and mobile-based interventions for PTSD: a systematic review and meta-analysis. Eur J Psychotraumatol 2021;12:1879551.
50. Torok M, Han J, Baker S et al. Suicide prevention using self-guided digital interventions: a systematic review and meta-analysis of randomised controlled trials. Lancet Digit Health 2020;2:e25-36.
51. Gregory VL Jr, Wilkerson DA, Wolfe-Taylor SN et al. Digital cognitive-behavioral therapy for substance use: systematic review and meta-analysis of randomized controlled trials. Am J Drug Alcohol Abuse 2024;50:771-85.
52. Sagoe D, Griffiths MD, Erevik EK et al. Internet-based treatment of gambling problems: a systematic review and meta-analysis of randomized controlled trials. J Behav Addict 2021;10:546-65.
53. Lindsay JAB, McGowan NM, Henning T et al. Digital interventions for symptoms of borderline personality disorder: systematic review and meta-analysis. J Med Internet Res 2024;26:e54941.
54. Etzelmueller A, Vis C, Karyotaki E et al. Effects of Internet-based cognitive behavioral therapy in routine care for adults in treatment for depression and anxiety: systematic review and meta-analysis. J Med Internet Res 2020;22:e18100.
55. Hedman-Lagerlöf E, Carlbring P, Svärdman F et al. Therapist-supported Internet-based cognitive behaviour therapy yields similar effects as face-to-face therapy for psychiatric and somatic disorders: an updated systematic review and meta-analysis. World Psychiatry 2023;22:305-14.
56. Carlbring P, Andersson G, Cuijpers P et al. Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: an updated systematic review and meta-analysis. Cogn Behav Ther 2018;47:1-18.
57. Cuijpers P, Noma H, Karyotaki E et al. Effectiveness and acceptability of cognitive behavior therapy delivery formats in adults with depression: a network meta-analysis. JAMA Psychiatry 2019;76:700-7.
58. Cuijpers P, Harrer M, Miguel C et al. Delivery formats of cognitive behavior therapy in adults with eating disorders: a network meta-analysis. Cogn Behav Ther 2025; doi: 10.1080/16506073.2025.2495950.
59. Wang Y, Miguel C, Ciharova M et al. Effectiveness and acceptability of cognitive-behavior therapy delivery formats for obsessive-compulsive disorder – A network meta-analysis. Br J Psychiatry 2025; doi: 10.1192/bjp.2024.197.
60. Karyotaki E, Efthimiou O, Miguel C et al. Internet-based cognitive behavioral therapy for depression; an individual patient data network meta-analysis. JAMA Psychiatry 2021;78:361-71.
61. Furukawa TA, Suganuma A, Ostinelli EG et al. Dismantling, optimising, and personalising internet cognitive behavioural therapy for depression: a systematic review and component network meta-analysis using individual participant data. Lancet Psychiatry 2021;8:500-11.
62. Karyotaki E, Miguel C, Panagiotopoulou OM et al. Digital interventions for common mental disorders in low- and middle-income countries: a systematic review and meta-analysis. Glob Ment Health 2023;10:e68.
63. Zainal NH, Soh CP, Van Doren N et al. Do the effects of internet-delivered cognitive-behavioral therapy (i-CBT) last after a year and beyond? A meta-analysis of 154 randomized controlled trials (RCTs). Clin Psychol Rev 2024;114:102518.
64. Tong L, Panagiotopoulou OM, Cuijpers P et al. The effectiveness of self-guided interventions in adults with depressive symptoms: a systematic review and meta-analysis. EBioMedicine 2024;105:105208.
65. Clark DM. Realizing the mass public benefit of evidence-based psychological therapies: the IAPT program. Annu Rev Clin Psychol 2018;14:159-83.
66. Johansson R, Ekbladh S, Hebert A et al. Psychodynamic guided self-help for adult depression through the internet: a randomised controlled trial. PLoS One 2012;7:e38021.
67. Andersson G, Paxling B, Roch-Norlund P et al. Internet-based psychodynamic versus cognitive behavioral guided self-help for generalized anxiety disorder: a randomized controlled trial. Psychother Psychosom 2012;81:344-55.
68. Käll A, Bäck M, Fahlroth O et al. Internet-based therapist-supported interpersonal psychotherapy for depression: a randomized controlled trial. J Affect Disord 2025;369:188-94.
69. Dagöö J, Asplund RP, Bsenko HA et al. Cognitive behavior therapy versus interpersonal psychotherapy for social anxiety disorder delivered via smartphone and computer: a randomized controlled trial. J Anxiety Disord 2014;28:410-7.
70. Donker T, Bennett K, Bennett A et al. Internet-delivered interpersonal psychotherapy versus internet-delivered cognitive behavioral therapy for adults with depressive symptoms: randomized controlled noninferiority trial. J Med Internet Res 2013;15:e82.
71. Furukawa TA, Tajika A, Toyomoto R et al. Cognitive behavioral therapy skills via a smartphone app for subthreshold depression among adults in the community: the RESiLIENT randomized controlled trial. Nat Med 2025;31:1830-9.
72. Linardon J, Torous J, Firth J et al. Current evidence for the efficacy of mental health smartphone apps for symptoms of depression and anxiety. A meta-analysis of 176 randomized controlled trials. World Psychiatry 2024;23:139-49.
73. Fürstenau D, Gersch M, Schreiter S. Digital therapeutics (DTx). Bus Inf Syst Eng 2023;65:349-60.
74. Insel TR. Digital phenotyping: technology for a new science of behavior. JAMA 2017;318:1215-6.
75. Choi A, Ooi A, Lottridge D. Digital phenotyping for stress, anxiety, and mild depression: systematic literature review. JMIR Mhealth Uhealth 2024;12:e40689.
76. Terhorst Y, Knauer J, Philippi P et al. The relation between passively collected GPS mobility metrics and depressive symptoms: systematic review and meta-analysis. J Med Internet Res 2024;26:e51875.
77. Stinson L, Liu Y, Dallery J. Ecological momentary assessment: a systematic review of validity research. Perspect Behav Sci 2022;45:469-93.
78. Balaskas A, Schueller SM, Cox AL et al. Ecological momentary interventions for mental health: a scoping review. PLoS One 2021;16:e0248152.
79. Heron KE, Smyth JM. Ecological momentary interventions: incorporating mobile technology into psychosocial and health behaviour treatments. Br J Health Psychol 2010;15:1-39.
80. Shiffman S, Stone AA, Hufford MR. Ecological momentary assessment. Annu Rev Clin Psychol 2008;4:1-32.
81. Nahum-Shani I, Smith SN, Spring BJ et al. Just-in-time adaptive interventions (JITAIs) in mobile health: key components and design principles for ongoing health behavior support. Ann Behav Med 2018;52:446-62.
82. Torous J, Larsen ME, Depp C et al. Smartphones, sensors, and machine learning to advance real-time prediction and interventions for suicide prevention: a review of current progress and next steps. Curr Psychiatry Rep 2018;20:51.
83. Coppersmith DD, Dempsey W, Kleiman EM et al. Just-in-time adaptive interventions for suicide prevention: promise, challenges, and future directions.

Psychiatry 2022;85:317-33.

84. Jiménez-Muñoz L, Peñuelas-Calvo I, Díaz-Oliván I et al. Suicide prevention in your pocket: a systematic review of ecological momentary interventions for the management of suicidal thoughts and behaviors. Harv Rev Psychiatry 2022;30:85-99.
85. Kaya R, Kaplan V, Solmaz F et al. Just-in-time adaptive interventions for depression. Psikiyatride Guncel Yaklasimlar 2024;16:585-94.
86. Perski O, Hébert ET, Naughton F et al. Technology-mediated just-in-time adaptive interventions (JITAIs) to reduce harmful substance use: a systematic review. Addiction 2022;117:1220-41.
87. Wang L, Miller LC. Just-in-the-moment adaptive interventions (JITAI): a meta-analytical review. Health Commun 2020;35:1531-44.
88. Dewhirst A, Laugharne R, Shankar R. Therapeutic use of serious games in mental health: scoping review. BJPsych Open 2022;8:e37.
89. Kato PM. Video games in health care: closing the gap. Rev Gen Psychol 2010;14:113-21.
90. Adams SA. Use of 'serious health games' in health care: a review. Stud Health Technol Inform 2010;157:160-6.
91. Landers RN, Auer EM, Collmus AB et al. Gamification science, its history and future: definitions and a research agenda. Simul Gaming 2018;49:315-37.
92. Cheng C, Ebrahimi OV. A meta-analytic review of gamified interventions in mental health enhancement. Comput Human Behav 2023;141:107621.
93. Abd-Alrazaq A, Al-Jafar E, Alajlani M et al. The effectiveness of serious games for alleviating depression: systematic review and meta-analysis. JMIR Serious Games 2022;10:e32331.
94. Abd-Alrazaq A, Alajlani M, Alhuwail D et al. The effectiveness of serious games in alleviating anxiety: systematic review and meta-analysis. JMIR Serious Games 2022;10:e29137.
95. Kim Y, Hong S, Choi M. Effects of serious games on depression in older adults: systematic review and meta-analysis of randomized controlled trials. J Med Internet Res 2022;24:e37753.
96. Freeman D, Reeve S, Robinson A et al. Virtual reality in the assessment, understanding, and treatment of mental health disorders. Psychol Med 2017;47:2393-400.
97. Mühlberger A, Herrmann MJ, Wiedemann GC et al. Repeated exposure of flight phobics to flights in virtual reality. Behav Res Ther 2001;39:1033-50.
98. Rothbaum BO, Hodges LF, Kooper R et al. Effectiveness of computer-generated (virtual reality) graded exposure in the treatment of acrophobia. Am J Psychiatry 1995;152:626-8.
99. Emmelkamp PM, Meyerbröker K. Virtual reality therapy in mental health. Annu Rev Clin Psychol 2021;17:495-519.
100. Kothgassner OD, Goreis A, Kafka JX et al. Virtual reality exposure therapy for posttraumatic stress disorder (PTSD): a meta-analysis. Eur J Psychotraumatol 2019;10:1654782.
101. Heo S, Park JH. Effects of virtual reality-based graded exposure therapy on PTSD symptoms: a systematic review and meta-analysis. Int J Environ Res Public Health 2022;19:15911.
102. Zeka F, Clemmensen L, Valmaggia L et al. The effectiveness of immersive virtual reality-based treatment for mental disorders: a systematic review with meta-analysis. Acta Psychiatr Scand 2025;151:210-30.
103. Fodor LA, Coteț CD, Cuijpers P et al. The effectiveness of virtual reality based interventions for symptoms of anxiety and depression: a meta-analysis. Sci Rep 2018;8:10323.
104. Donker T, Cornelisz I, Van Klaveren C et al. Effectiveness of self-guided app-based virtual reality cognitive behavior therapy for acrophobia: a randomized clinical trial. JAMA Psychiatry 2019;76:682-90.
105. van Gelderen MJ, Nijdam MJ, Haagen JFG et al. Interactive motion-assisted exposure therapy for veterans with treatment-resistant posttraumatic stress disorder: a randomized controlled trial. Psychother Psychosom 2020;89:215-27.
106. Tang KS, Cheng DL, Mi E et al. Augmented reality in medical education: a systematic review. Can Med Educ J 2019;11:e81-96.
107. Bakır ÇN, Abbas SO, Sever E et al. Use of augmented reality in mental health-related conditions: a systematic review. Digit Health 2023;9:20552076231203649.
108. Grimaldos J, Fernández-Buendía S, Bretón-López J et al. Augmented reality exposure treatments in anxiety and related disorders: a systematic review. Internet Interv 2025;39:100812.
109. Brezing CA, Brixner DI. The rise of prescription digital therapeutics in behavioral health. Adv Ther 2022;39:5301-6.
110. Phan P, Mitragotri S, Zhao Z. Digital therapeutics in the clinic. Bioeng Transl Med 2023;8:e10536.
111. Goeldner M, Gehder S. Digital health applications (DiGAs) on a fast track: insights from a data-driven analysis of prescribable digital therapeutics in Germany from 2020 to mid-2024. J Med Internet Res 2024;26:e59013.
112. Wang C, Lee C, Shin H. Digital therapeutics from bench to bedside. NPJ Digit Med 2023;6:38.
113. Torous J, Linardon J, Goldberg SB et al. The evolving field of digital mental health: current evidence and implementation issues for smartphone apps, generative artificial intelligence, and virtual reality. World Psychiatry 2025;24:156-74.
114. Nunes-Zlotkowski KF, Shepherd HL, Beatty L et al. Blended psychological therapy for the treatment of psychological disorders in adult patients: systematic review and meta-analysis. Interact J Med Res 2024;13:e49660.
115. Cross SP, Karin E, Staples LG et al. Factors associated with treatment uptake, completion, and subsequent symptom improvement in a national digital mental health service. Internet Interv 2022;27:100506.
116. Fleming T, Bavin L, Lucassen M et al. Beyond the trial: systematic review of real-world uptake and engagement with digital self-help interventions for depression, low mood, or anxiety. J Med Internet Res 2018;20:e199.
117. Wallin EE, Mattsson S, Olsson EM. The preference for internet-based psychological interventions by individuals without past or current use of mental health treatment delivered online: a survey study with mixed-methods analysis. JMIR Ment Health 2016;3:e25.
118. Davies F, Shepherd HL, Beatty L et al. Implementing web-based therapy in routine mental health care: systematic review of health professionals' perspectives. J Med Internet Res 2020;22:e17362.
119. Aali G, Kariotis T, Shokraneh F. Avatar therapy for people with schizophrenia or related disorders. Cochrane Database Syst Rev 2020;5:CD011898.
120. Clarke S, Hanna D, Mulholland C et al. A systematic review and meta-analysis of digital health technologies effects on psychotic symptoms in adults with psychosis. Psychosis 2019;11:362-73.
121. Craig TK, Rus-Calafell M, Ward T et al. AVATAR therapy for auditory verbal hallucinations in people with psychosis: a single-blind, randomised controlled trial. Lancet Psychiatry 2018;5:31-40.
122. Garety PA, Edwards CJ, Jafari H et al. Digital AVATAR therapy for distressing voices in psychosis: the phase 2/3 AVATAR2 trial. Nat Med 2024;30:3658-68.
123. Hua J, Siddals S, Ma Z et al. Charting the evolution of artificial intelligence mental health chatbots from rule-based systems to large language models: a systematic review. World Psychiatry 2025;24:383-94.
124. Guo Z, Lai A, Thygesen JH et al. Large language models for mental health applications: systematic review. JMIR Ment Health 2024;11:e57400.
125. Chung NC, Dyer G, Brocki L. Challenges of large language models for mental health counseling. arXiv 2023;2311.13857.
126. Vaidyam AN, Wisniewski H, Halamka JD et al. Chatbots and conversational agents in mental health: a review of the psychiatric landscape. Can J Psychiatry 2019;64:456-64.
127. Li H, Zhang R, Lee YC et al. Systematic review and meta-analysis of AI-based conversational agents for promoting mental health and well-being. NPJ Digit Med 2023;6:236.
128. Nicol G, Wang R, Graham S et al. Chatbot-delivered cognitive behavioral therapy in adolescents with depression and anxiety during the COVID-19 pandemic: feasibility and acceptability study. JMIR Form Res 2022;6:e40242.
129. Paul GL. Strategy of outcome research in psychotherapy. J Consult Psychol 1967;31:109-18.
130. Simon GE, Perlis RH. Personalized medicine for depression: can we match patients with treatments? Am J Psychiatry 2010;167:1445-55.
131. Topol EJ, Lauer MS. The rudimentary phase of personalised medicine: coronary risk scores. Lancet 2003;362:1776-7.
132. Hamburg MA, Collins FS. The path to personalized medicine. N Engl J Med 2010;363:301-4.
133. Fried EI. Moving forward: how depression heterogeneity hinders progress in treatment and research. Expert Rev Neurother 2017;17:423-5.
134. Baumeister H, Gordon P. Meta-review of depressive subtyping models. J Affect Disord 2012;139:126-40.
135. Pjrek E, Friedrich ME, Cambioli L et al. The efficacy of light therapy in the treatment of seasonal affective disorder: a meta-analysis of randomized controlled trials. Psychother Psychosom 2020;89:17-24.
136. Maj M, Stein DJ, Parker G et al. The clinical characterization of the adult patient with depression aimed at personalization of management. World Psychiatry 2020;19:269-93.
137. Boschloo L, Bekhuis E, Borsboom D et al. The symptom-specific efficacy of cognitive behavioral therapy versus antidepressant medication in the treatment of depression: results from an individual patient data meta-analysis. World Psychiatry 2019;18:183-91.
138. Brown WA. Treatment response in melancholia. Acta Psychiatric Scand 2007;115:125-9.

139. Cuijpers P, Weitz E, Lamers F et al. Melancholic and atypical depression as predictor and moderator of outcome in cognitive behavior therapy and pharmacotherapy for adult depression. Depress Anxiety 2016;34:246-56.
140. Driessen E, Cuijpers P, Hollon SD et al. Does pretreatment severity moderate the efficacy of psychological treatment of adult outpatient depression? A meta-analysis. J Consult Clin Psychol 2010;78:668-80.
141. Weitz ES, Hollon SD, Twisk J et al. Baseline depression severity as moderator of depression outcomes between cognitive behavioral therapy vs pharmacotherapy: an individual patient data meta-analysis. JAMA Psychiatry 2015;72:1102-9.
142. Cuijpers P, Reynolds CF, Donker T et al. Personalized treatment of adult depression: medication, psychotherapy or both? A systematic review. Depress Anxiety 2012;29:855-64.
143. Kessler RC, van Loo HM, Wardenaar KJ et al. Using patient self-reports to study heterogeneity of treatment effects in major depressive disorder. Epidemiol Psychiatr Sci 2017;26:22-36.
144. Carter JD, Luty SE, McKenzie JM et al. Patient predictors of response to cognitive behaviour therapy and interpersonal psychotherapy in a randomised clinical trial for depression. J Affect Disord 2011;128:252-61.
145. Joyce PR, McKenzie JM, Carter JD et al. Temperament, character and personality disorders as predictors of response to interpersonal psychotherapy and cognitive-behavioural therapy for depression. Br J Psychiatry 2007;190:503-8.
146. Barber JP, Muenz LR. The role of avoidance and obsessiveness in matching patients to cognitive and interpersonal psychotherapy: empirical findings from the Treatment for Depression Collaborative Research Program. J Consult Clin Psychol 1996;64:951-8.
147. Dimidjian S, Dobson KS, Kohlenberg RJ et al. Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the acute treatment of adults with major depression. J Consult Clin Psychol 2006;74:658-70.
148. McBride C, Atkinson L, Quilty LC et al. Attachment as moderator of treatment outcome in major depression: a randomized control trial of interpersonal psychotherapy versus cognitive behavior therapy. J Consult Clin Psychol 2006;74:1041.
149. Elkin I, Shea MT, Watkins JT et al. National Institute of Mental Health Treatment of Depression Collaborative Research Program: general effectiveness of treatments. Arch Gen Psychiatry 1989;46:971-82.
150. Luty SE, Carter JD, McKenzie JM et al. Randomised controlled trial of interpersonal psychotherapy and cognitive-behavioural therapy for depression. Br J Psychiatry 2007;190:496-502.
151. Fournier JC, DeRubeis RJ, Shelton RC et al. Prediction of response to medication and cognitive therapy in the treatment of moderate to severe depression. J Consult Clin Psychol 2009;77:775-87.
152. Nemeroff CB, Heim CM, Thase ME et al. Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma. Proc Natl Acad Sci USA 2003;100:14293-6.
153. Fournier JC, DeRubeis RJ, Shelton RC et al. Antidepressant medications v. cognitive therapy in people with depression with or without personality disorder. Br J Psychiatry 2008;192:124-9.
154. Bagby RM, Quilty LC, Segal ZV et al. Personality and differential treatment response in major depression: a randomized controlled trial comparing cognitive-behavioural therapy and pharmacotherapy. Can J Psychiatry 2008;53:361-70.
155. Frank E, Cassano GB, Rucci P et al. Predictors and moderators of time to remission of major depression with interpersonal psychotherapy and SSRI pharmacotherapy. Psychol Med 2011;41:151-62.
156. Cuijpers P, Ciharova M, Quero S et al. The contribution of "individual participant data" meta-analyses of psychotherapies for depression to the development of personalized treatments: a systematic review. J Pers Med 2022;12:93.
157. Brookes ST, Whitely E, Egger M et al. Subgroup analyses in randomized trials: risks of subgroup-specific analyses; power and sample size for the interaction test. J Clin Epidemiol 2004;57:229-36.
158. Cuijpers P, Harrer M, Miguel C et al. Five decades of research on psychological treatments of depression: a historical and meta-analytic overview. Am Psychol 2025;80:297-310.
159. Rahman A, Malik A, Sikander S et al. Cognitive behaviour therapy-based intervention by community health workers for mothers with depression and their infants in rural Pakistan: a cluster-randomised controlled trial. Lancet 2008;372:902-9.
160. Patel V, Weiss HA, Chowdhary N et al. Effectiveness of an intervention led by lay health counsellors for depressive and anxiety disorders in primary care in Goa, India (MANAS): a cluster randomised controlled trial. Lancet 2010;376:2086-95.
161. Benjet C, Albor Y, Alvis-Barranco L et al. Internet-delivered cognitive behavior therapy versus treatment as usual for anxiety and depression among Latin American university students: a randomized clinical trial. J Consult Clin Psychol 2023;91:694-707.
162. Benjet C, Zainal NH, Albor Y et al. A precision treatment model for internet-delivered cognitive behavioral therapy for anxiety and depression among university students: a secondary analysis of a randomized clinical trial. JAMA Psychiatry 2023;80:768-77.
163. Toyomoto R, Sakata M, Yoshida K et al. Prognostic factors and effect modifiers for personalisation of internet-based cognitive behavioural therapy among university students with subthreshold depression: a secondary analysis of a factorial trial. J Affect Disord 2023;322:156-62.
164. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. BMJ 2010;340:c221.
165. Bower P, Kontopantelis E, Sutton A et al. Who should get low-intensity treatments for depression? An individual patient data meta-analysis. BMJ 2013;346:f540.
166. Furukawa TA, Weitz ES, Tanaka S et al. Initial severity of depression and efficacy of cognitive-behavioural therapy: individual-participant data meta-analysis of pill-placebo-controlled trials. Br J Psychiatry 2017;210:190-6.
167. Karyotaki E, Ebert DD, Donkin L et al. Do guided internet-based interventions result in clinically relevant changes for patients with depression? An individual participant data meta-analysis. Clin Psychol Rev 2018;63:80-92.
168. Karyotaki E, Riper H, Twisk J et al. Efficacy of self-guided internet-based cognitive behavioral therapy (iCBT) in treatment of depressive symptoms: an individual participant data meta-analysis. JAMA Psychiatry 2017;74:351-9.
169. Kuyken W, Warren FC, Taylor RS et al. Efficacy of mindfulness-based cognitive therapy in prevention of depressive relapse: an individual patient data meta-analysis from randomized trials. JAMA Psychiatry 2016;73:565-74.
170. Reins JA, Buntrock C, Zimmermann J et al. Efficacy and moderators of internet-based interventions in adults with subthreshold depression: an individual participant data meta-analysis of randomized controlled trials. Psychother Psychosom 2021;90:94-106.
171. Wienicke FJ, Beutel ME, Zwerenz R et al. Efficacy and moderators of short-term psychodynamic psychotherapy for depression: a systematic review and meta-analysis of individual participant data. Clin Psychol Rev 2023;101:102269.
172. Driessen E, Fokkema M, Dekker JJ et al. Which patients benefit from adding short-term psychodynamic psychotherapy to antidepressants in the treatment of depression? A systematic review and meta-analysis of individual participant data. Psychol Med 2023;53:6090-101.
173. Karyotaki E, Araya R, Kessler RC et al. Association of task-shared psychological interventions with depression outcomes in low- and middle-income countries: a systematic review and individual patient data meta-analysis. JAMA Psychiatry 2022;79:430-43.
174. Buntrock C, Harrer M, Sprenger AA et al. Psychological interventions to prevent the onset of major depression in adults: a systematic review and individual participant data meta-analysis. Lancet Psychiatry 2024;11:990-1001.
175. Wright SL, Karyotaki E, Cuijpers P et al. EMDR v. other psychological therapies for PTSD: a systematic review and individual participant data meta-analysis. Psychol Med 2024;54:1580-8.
176. de Haan A, Meiser-Stedman R, Landolt MA et al. Efficacy and moderators of efficacy of cognitive behavioural therapies with a trauma focus in children and adolescents: an individual participant data meta-analysis of randomised trials. Lancet Child Adolesc Health 2024;8:28-39.
177. Hien DA, Morgan-López AA, Saavedra LM et al. Project Harmony: a meta-analysis with individual patient data on behavioral and pharmacologic trials for comorbid posttraumatic stress and alcohol or other drug use disorders. Am J Psychiatry 2023;180:155-66.
178. Riper H, Hoogendoorn A, Cuijpers P et al. Effectiveness and treatment moderators of internet interventions for adult problem drinking: an individual patient data meta-analysis of 19 randomised controlled trials. PLoS Med 2018;15:e10027.
179. Sander LB, Beisemann M, Doebler P et al. The effects of internet-based cognitive behavioral therapy for suicidal ideation or behaviors on depression, anxiety, and hopelessness in individuals with suicidal ideation: systematic review and meta-analysis of individual participant data. J Med Internet Res 2023;25:e46771.
180. Fernández-Álvarez J, Rozental A, Carlbring P et al. Deterioration rates in virtual reality therapy: an individual patient data level meta-analysis. J Anxiety Disord 2019;61:3-17.
181. Furukawa TA, Efthimiou O, Weitz ES et al. Cognitive-behavioral analysis system of psychotherapy (CBASP), drug, or their combination for persistent depressive disorder: personalizing the treatment choice using individual partici-

pant data network meta-regression. Psychother Psychosom 2018;87:140-53.

182. Williamson PR, Altman DG, Blazeby JM et al. Developing core outcome sets for clinical trials: issues to consider. Trials 2012;13:1-8.
183. Shatte ABR, Hutchinson DM, Teague SJ. Machine learning in mental health: a scoping review of methods and applications. Psychol Med 2019;49:1426-48.
184. Jordan MI, Mitchell TM. Machine learning: trends, perspectives, and prospects. Science 2015;349:255-60.
185. Chekroud AM, Bondar J, Delgadillo J et al. The promise of machine learning in predicting treatment outcomes in psychiatry. World Psychiatry 2021;20:154-70.
186. Iniesta R, Stahl D, McGuffin P. Machine learning, statistical learning and the future of biological research in psychiatry. Psychol Med 2016;46:2455-65.
187. Iyortsuun NK, Kim SH, Jhon M et al. A review of machine learning and deep learning approaches on mental health diagnosis. Healthcare 2023;11:285.
188. Harrer M, Baumeister H, Cuijpers P et al. Predicting effects of a digital stress intervention for patients with depressive symptoms: development and validation of meta-analytic prognostic models using individual participant data. J Consult Clin Psychol 2024;92:226-35.
189. DeRubeis RJ, Cohen ZD, Forand NR et al. The Personalized Advantage Index: translating research on prediction into individualized treatment recommendations. A demonstration. PLoS One 2014;9:1-8.
190. Cohen ZD, DeRubeis RJ. Treatment selection in depression. Annu Rev Clin Psychol 2018;14:209-36.
191. DeRubeis RJ, Hollon SD, Amsterdam JD et al. Cognitive therapy vs medications in the treatment of moderate to severe depression. Arch Gen Psychiatry 2005;62:409-16.
192. Meinke C, Hornstein S, Schmidt J et al. Advancing the personalized advantage index (PAI): a systematic review and application in two large multi-site samples in anxiety disorders. Psychol Med 2024;54:4843-55.
193. Kessler RC, Luedtke A. Pragmatic precision psychiatry – a new direction for optimizing treatment selection. JAMA Psychiatry 2021;78:1384-90.
194. Kessler RC, Bossarte RM, Luedtke A et al. Machine learning methods for developing precision treatment rules with observational data. Behav Res Ther 2019;120:103412.
195. Zainal NH, Bossarte RM, Gildea SM et al. Developing an individualized treatment rule for Veterans with major depressive disorder using electronic health records. Mol Psychiatry 2024;29:2335-45.
196. Lorenzo-Luaces L, DeRubeis RJ, van Straten A et al. A prognostic index (PI) as a moderator of outcomes in the treatment of depression: a proof of concept combining multiple variables to inform risk-stratified stepped care models. J Affect Disord 2017;213:78-85.
197. Delgadillo J, Huey D, Bennett H et al. Case complexity as a guide for psychological treatment selection. J Consult Clin Psychol 2017;85:835-53.
198. Delgadillo J, Rubel J, Barkham M. Towards personalized allocation of patients to therapists. J Consult Clin Psychol 2020;88:799-808.
199. Fisher AJ, Bosley HG, Fernandez KC et al. Open trial of a personalized modular treatment for mood and anxiety. Behav Res Ther 2019;116:69-79.
200. Lutz W, Rubel JA, Schwartz B et al. Towards integrating personalized feedback research into clinical practice: development of the Trier Treatment Navigator (TTN). Behav Res Ther 2019;120:103438.
201. Ewbank MP, Cummins R, Tablan V et al. Quantifying the association between psychotherapy content and clinical outcomes using deep learning. JAMA Psychiatry 2020;77:35-43.
202. Ewbank MP, Cummins R, Tablan V et al. Understanding the relationship between patient language and outcomes in internet-enabled cognitive behavioural therapy: a deep learning approach to automatic coding of session transcripts. Psychother Res 2020;31:326-38.
203. Aafjes-van Doorn K, Kamsteeg C, Bate J et al. A scoping review of machine learning in psychotherapy research. Psychother Res 2021;31:92-116.
204. Riley RD, Pate A, Dhiman P et al. Clinical prediction models and the multiverse of madness. BMC Med 2023;21:502.
205. Steyerberg EW. Clinical prediction models: a practical approach to development, validation, and updating. New York: Springer, 2019.
206. Meehan AJ, Lewis SJ, Fazel S et al. Clinical prediction models in psychiatry: a systematic review of two decades of progress and challenges. Mol Psychiatry 2022;27:2700-8.
207. Riley RD, Snell KI, Ensor J et al. Minimum sample size for developing a multivariable prediction model: Part I – Continuous outcomes. Stat Med 2019;38:1262-75.
208. Christodoulou E, Ma J, Collins GS et al. A systematic review shows no performance benefit of machine learning over logistic regression for clinical prediction models. J Clin Epidemiol 2019;110:12-22.
209. Schwartz B, Giesemann J, Delgadillo J et al. Comparing three neural networks to predict depression treatment outcomes in psychological therapies. Behav Res Ther 2025;190:104752.
210. Chekroud AM, Hawrilenko M, Loho H et al. Illusory generalizability of clinical prediction models. Science 2024;383:164-7.
211. Wampold BE, Imel ZE. The great psychotherapy debate: the evidence for what makes psychotherapy work, 2nd ed. New York: Routledge, 2015.
212. Johns RG, Barkham M, Kellett S et al. A systematic review of therapist effects: a critical narrative update and refinement to review. Clin Psychol Rev 2019;67:78-93.
213. Kraus DR, Bentley JH, Alexander PC et al. Predicting therapist effectiveness from their own practice-based evidence. J Consult Clin Psychol 2016;84:473-83.
214. Constantino MJ, Boswell JF, Coyne AE et al. Effect of matching therapists to patients vs assignment as usual on adult psychotherapy outcomes: a randomized clinical trial. JAMA Psychiatry 2021;78:960-9.
215. Constantino MJ. Measurement-based matching of patients to psychotherapists' strengths. J Consult Clin Psychol 2024;92:327-9.
216. Delgadillo J, Ali S, Fleck K et al. Stratified care vs stepped care for depression: a cluster randomized clinical trial. JAMA Psychiatry 2022;79:101-8.
217. Lutz W, Deisenhofer AK, Rubel J et al. Prospective evaluation of a clinical decision support system in psychological therapy. J Consult Clin Psychol 2022;90:90-106.
218. Nye A, Delgadillo J, Barkham M. Efficacy of personalized psychological interventions: a systematic review and meta-analysis. J Consult Clin Psychol 2023;91:389-97.
219. Chorpita BF, Daleiden EL, Weisz JR. Modularity in the design and application of therapeutic interventions. Appl Prev Psychol 2005;11:141-56.
220. Schramm E, Elsaesser M, Jenkner C et al. Algorithm-based modular psychotherapy vs. cognitive-behavioral therapy for patients with depression, psychiatric comorbidities and early trauma: a proof-of-concept randomized controlled trial. World Psychiatry 2024;23:257-66.
221. Weisz JR, Chorpita BF, Palinkas LA et al. Testing standard and modular designs for psychotherapy treating depression, anxiety, and conduct problems in youth. Arch Gen Psychiatry 2012;69:274-82.
222. Chorpita BF, Weisz JR, Daleiden EL et al. Long-term outcomes for the Child STEPs randomized effectiveness trial: a comparison of modular and standard treatment designs with usual care. J Consult Clin Psychol 2013;81:999-1009.
223. Chorpita BF, Daleiden EL, Park AL et al. Child STEPs in California: a cluster randomized effectiveness trial comparing modular treatment with community implemented treatment for youth with anxiety, depression, conduct problems, or traumatic stress. J Consult Clin Psychol 2017;85:13-25.
224. Weisz JR, Bearman SK, Ugueto AM et al. Testing robustness of child STEPs effects with children and adolescents: a randomized controlled effectiveness trial. J Clin Child Adolesc Psychol 2020;49:883-96.
225. Merry SN, Hopkins S, Lucassen MF et al. Effect of clinician training in the modular approach to therapy for children vs usual care on clinical outcomes and use of empirically supported treatments: a randomized clinical trial. JAMA Netw Open 2020;3:e2011799.
226. Hukkelberg SS, Torsheim T, Nordahl KB et al. The modular approach to therapy for youths with anxiety, depression, trauma, and conduct problems (MATCH): results from the Norwegian randomized-controlled trial. BMC Psychol 2024;12:569.
227. Wood JJ, Sze Wood K, Chuen Cho A et al. Modular cognitive behavioral therapy for autism-related symptoms in children: a randomized controlled trial. J Consult Clin Psychol 2021;89:110-25.
228. Ginsburg GS, Becker KD, Drazdowski TK et al. Treating anxiety disorders in inner city schools: results from a pilot randomized controlled trial comparing CBT and usual care. Child Youth Care Forum 2012;41:1-19.
229. Chiu AW, Langer DA, McLeod BD et al. Effectiveness of modular CBT for child anxiety in elementary schools. Sch Psychol Q 2013;28:141-53.
230. Coates JM, Gullo MJ, Feeney GFX et al. A randomized trial of personalized cognitive-behavior therapy for alcohol use disorder in a public health clinic. Front Psychiatry 2018;9:297.
231. Berger T, Boettcher J, Caspar F. Internet-based guided self-help for several anxiety disorders: a randomized controlled trial comparing a tailored with a standardized disorder-specific approach. Psychotherapy 2014;51:207-19.
232. Wetherell JL, Ayers CR, Sorrell JT et al. Modular psychotherapy for anxiety in older primary care patients. Am J Geriatr Psychiatry 2009;17:483-92.
233. Wikipedia. List of psychotherapies. https://en.wikipedia.org/wiki/List_of_psychotherapies.
234. Omylinska-Thurston J, Karkou V, Parsons A et al. Arts for the blues: the development of a new evidence-based creative group psychotherapy for depression. Couns Psychother Res 2021;21:597-607.

235. Pearce MJ, Koenig HG, Robins CJ et al. Religiously integrated cognitive behavioral therapy: a new method of treatment for major depression in patients with chronic medical illness. Psychotherapy 2015;52:56-66.
236. Riches S, Schrank B, Rashid T et al. WELLFOCUS PPT: modifying positive psychotherapy for psychosis. Psychotherapy 2016;53:68-77.
237. Carey TA, Mansell W, Tai S. Principles-based counselling and psychotherapy: a method of levels approach. London: Routledge, 2015.
238. Hofmann SG, Hayes SC. Process-based therapy as a novel treatment approach and framework for classifying psychopathology. Clin Psychol Eur 2024; 6:e13727.
239. Cuijpers P, Miguel C, Ciharova M et al. Non-directive supportive therapy for depression: a meta-analytic review. J Affect Disord 2024;349:452-61.
240. Papola D, Miguel C, Mazzaglia M et al. Psychotherapies for generalized anxiety disorder in adults: a systematic review and network meta-analysis of randomized clinical trials. JAMA Psychiatry 2024;81:250-9.
241. Gerger H, Munder T, Gemperli A et al. Integrating fragmented evidence by network meta-analysis: relative effectiveness of psychological interventions for adults with post-traumatic stress disorder. Psychol Med 2014;44:3151-64.
242. Mayo-Wilson E, Dias S, Mavranezouli I et al. Psychological and pharmacological interventions for social anxiety disorder in adults: a systematic review and network meta-analysis. Lancet Psychiatry 2014;1:368-76.
243. Cuijpers P, Reijnders M, Huibers MJ. The role of common factors in psychotherapy outcomes. Annu Rev Clin Psychol 2019;15:207-31.
244. Cristea IA, Vecchi T, Cuijpers P. Top-down and bottom-up pathways to developing psychological interventions. JAMA Psychiatry 2021;78:593-4.
245. Wolpe J. Psychotherapy by reciprocal inhibition. Stanford: Stanford University Press, 1958.
246. Astill Wright L, Horstmann L, Holmes EA et al. Consolidation/reconsolidation therapies for the prevention and treatment of PTSD and re-experiencing: a systematic review and meta-analysis. Transl Psychiatry 2021;11:453.
247. Barry TJ, Sze WY, Raes F. A meta-analysis and systematic review of memory specificity training (MeST) in the treatment of emotional disorders. Behav Res Ther 2019;116:36-51.
248. Bryant RA, Dawson KS, Yadav S et al. Augmenting trauma-focused cognitive behavior therapy for post-traumatic stress disorder with memory specificity training: a randomized controlled trial. World Psychiatry 2025;24:113-9.
249. Platt B, Waters AM, Schulte-Koerne G et al. A review of cognitive biases in youth depression: attention, interpretation and memory. Cogn Emot 2017;31: 462-83.
250. LeMoult J, Gotlib IH. Depression: a cognitive perspective. Clin Psychol Rev 2019;69:51-66.
251. Mineka S, Sutton SK. Cognitive biases and the emotional disorders. Psychol Sci 1992;3:65-9.
252. Mathews A, Mackintosh B, Fulcher EP. Cognitive biases in anxiety and attention to threat. Trends Cogn Sci 1997;1:340-5.
253. Aspen V, Darcy AM, Lock J. A review of attention biases in women with eating disorders. Cogn Emot 2013;27:820-38.
254. Schmidt UH, Claudino A, Fernández-Aranda F et al. The current clinical approach to feeding and eating disorders aimed to increase personalization of management. World Psychiatry 2025;24:4-31.
255. Ramey T, Regier PS. Cognitive impairment in substance use disorders. CNS Spectr 2019;24:102-13.
256. Zhang MW, Ying J, Wing T et al. Cognitive biases in cannabis, opioid, and stimulant disorders: a systematic review. Front Psychiatry 2018;9:376.
257. Livet A, Navarri X, Potvin S et al. Cognitive biases in individuals with psychotic-like experiences: a systematic review and a meta-analysis. Schizophr Res 2020; 222:10-22.
258. MacLeod C, Mathews A. Cognitive bias modification approaches to anxiety. Annu Rev Clin Psychol 2012;8:189-217.
259. Martinelli A, Grüll J, Baum C. Attention and interpretation cognitive bias change: a systematic review and meta-analysis of bias modification paradigms. Behav Res Ther 2022;157:104180.
260. Fodor LA, Georgescu R, Cuijpers P et al. Efficacy of cognitive bias modification interventions in anxiety and depressive disorders: a systematic review and network meta-analysis. Lancet Psychiatry 2020;7:506-14.
261. Boffo M, Zerhouni O, Gronau QF et al. Cognitive bias modification for behavior change in alcohol and smoking addiction: Bayesian meta-analysis of individual participant data. Neuropsychol Rev 2019;29:52-78.
262. Cristea IA, Mogoase C, David D et al. Practitioner review: Cognitive bias modification for mental health problems in children and adolescents: a meta-analysis. J Child Psychol Psychiatry 2015;56:723-34.
263. Ciesinski NK, Himelein-Wachowiak M, Krick LC et al. A systematic review with meta-analysis of cognitive bias modification interventions for anger and aggression. Behav Res Ther 2023;167:104344.
264. Hang Y, Xu L, Wang C et al. Can attention bias modification augment the effect of CBT for anxiety disorders? A systematic review and meta-analysis. Psychiatry Res 2021;299:113892.
265. Kim EJ, Bahk YC, Oh H et al. Current status of cognitive remediation for psychiatric disorders: a review. Front Psychiatry 2018;9:461.
266. Millan MJ, Agid Y, Brüne M et al. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. Nat Rev Drug Discov 2012;11:141-68.
267. Bowie CR, Bell MD, Fiszdon JM et al. Cognitive remediation for schizophrenia: an expert working group white paper on core techniques. Schizophr Res 2020;215:49-53.
268. Green MF. Cognitive remediation in schizophrenia: is it time yet? Am J Psychiatry 1993;150:178-87.
269. Meichenbaum D, Cameron R. Training schizophrenics to talk to themselves: a means of developing attentional controls. Behav Ther 1973;4:515-34.
270. Motter JN, Pimontel MA, Rindskopf D et al. Computerized cognitive training and functional recovery in major depressive disorder: a meta-analysis. J Affect Disord 2016;189:184-91.
271. Grynszpan O, Perbal S, Pelissolo A et al. Efficacy and specificity of computer-assisted cognitive remediation in schizophrenia: a meta-analytical study. Psychol Med 2011;41:163-73.
272. Vita A, Barlati S, Ceraso A et al. Durability of effects of cognitive remediation on cognition and psychosocial functioning in schizophrenia: a systematic review and meta-analysis of randomized clinical trials. Am J Psychiatry 2024;181:520-31.
273. Cabreira V, Wilkinson T, Frostholm L et al. Systematic review and meta-analysis of standalone digital interventions for cognitive symptoms in people without dementia. NPJ Digit Med 2024;7:278.
274. Kambeitz-Ilankovic L, Betz LT, Dominke C et al. Multi-outcome meta-analysis (MOMA) of cognitive remediation in schizophrenia: revisiting the relevance of human coaching and elucidating interplay between multiple outcomes. Neurosci Biobehav Rev 2019;107:828-45.
275. Lejeune JA, Northrop A, Kurtz MM. A meta-analysis of cognitive remediation for schizophrenia: efficacy and the role of participant and treatment factors. Schizophr Bull 2021;47:997-1006.
276. Legemaat AM, Semkovska M, Brouwer M et al. Effectiveness of cognitive remediation in depression: a meta-analysis. Psychol Med 2021;52:1-16.
277. Goldberg Z, Kuslak B, Kurtz MM. A meta-analytic investigation of cognitive remediation for mood disorders: efficacy and the role of study quality, sample and treatment factors. J Affect Disord 2023;330:74-82.
278. Therond A, Pezzoli P, Abbas M et al. The efficacy of cognitive remediation in depression: a systematic literature review and meta-analysis. J Affect Disord 2021;284:238-46.
279. Samamé C, Durante P, Cattaneo B et al. Efficacy of cognitive remediation in bipolar disorder: systematic review and meta-analysis of randomized controlled trials. Psychol Med 2023;53:5361-73.
280. East-Richard C, Cayouette A, Allott K et al. Cognitive remediation for adolescents with mental health disorders: a systematic review and meta-analysis. Early Interv Psychiatry 2025;19:e70016.
281. Hagan KE, Christensen KA, Forbush KT. A preliminary systematic review and meta-analysis of randomized-controlled trials of cognitive remediation therapy for anorexia nervosa. Eat Behav 2020;37:101391.
282. Yao Y, Guo D, Lu TS et al. Efficacy and safety of psychedelics for the treatment of mental disorders: a systematic review and meta-analysis. Psychiatry Res 2024;335:115886.
283. Mithoefer MC, Grob CS, Brewerton TD. Novel psychopharmacological therapies for psychiatric disorders: psilocybin and MDMA. Lancet Psychiatry 2016;3:481-8.
284. Nichols DE. Psychedelics. Pharmacol Rev 2016;68:264-355.
285. Shahrour G, Sohail K, Elrais S et al. MDMA-assisted psychotherapy for the treatment of PTSD: a systematic review and meta-analysis of randomized controlled trials (RCTs). Neuropsychopharmacol Rep 2024;44:672-81.
286. Yang J, Wang N, Luo W et al. The efficacy and safety of MDMA-assisted psychotherapy for treatment of posttraumatic stress disorder: a systematic review and meta-analysis from randomized controlled trials. Psychiatry Res 2024;339:116043.
287. Dominguez-Clave E, Soler J, Pascual JC et al. Ayahuasca improves emotion dysregulation in a community sample and in individuals with borderline-like traits. Psychopharmacology 2019;236:573-80.
288. Schneier FR, Feusner J, Wheaton MG et al. Pilot study of single-dose psilocybin for serotonin reuptake inhibitor-resistant body dysmorphic disorder. J Psychiatr Res 2023;161:364-70.

289. Moreno FA, Wiegand CB, Taitano EK et al. Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. J Clin Psychiatry 2006;67:1735-40.
290. Sessa B, Higbed L, O'Brien S et al. First study of safety and tolerability of 3,4-methylenedioxymethamphetamine-assisted psychotherapy in patients with alcohol use disorder. J Psychopharmacol 2021;35:375-83.
291. Haikazian S, Chen-Li DC, Johnson DE et al. Psilocybin-assisted therapy for depression: a systematic review and meta-analysis. Psychiatry Res 2023;329: 115531.
292. Yehuda R, Lehrner A. Psychedelic therapy – a new paradigm of care for mental health. JAMA 2023;330:813-4.
293. van Elk M, Fried EI. History repeating: guidelines to address common problems in psychedelic science. Ther Adv Psychopharmacol 2023;13: 20451253231198466.
294. Muthukumaraswamy SD, Forsyth A, Lumley T. Blinding and expectancy confounds in psychedelic randomized controlled trials. Expert Rev Clin Pharmacol 2021;14:1133-52.
295. Seybert C, Schimmers N, Silva L et al. Quality of reporting on psychological interventions in psychedelic treatments: a systematic review. Lancet Psychiatry 2025;12:54-66.
296. Cristea IA, Cuijpers P, Halvorsen JO. The psychotherapy in MDMA-assisted psychotherapy. JAMA Psychiatry 2024;81:1053-4.
297. Cuijpers P, Harrer M, Miguel C et al. Cognitive behavior therapy for mental disorders in adults: a unified series of meta-analyses. JAMA Psychiatry 2025;82: 563-71.
298. Harrer M, Miguel C, van Ballegooijen W et al. Effectiveness of psychotherapy: synthesis of a "meta-analytic research domain" across world regions and twelve mental health problems. Psychol Bull 2025;151:600-67.
299. Kessler RC, Sampson NA, Berglund P et al. Anxious and non-anxious major depressive disorder in the World Health Organization World Mental Health Surveys. Epidemiol Psychiatr Sci 2015;24:210-26.
300. Cuijpers P, Miguel C, Ciharova M et al. Transdiagnostic treatment of depression and anxiety: a meta-analysis. Psychol Med 2023;53:6535-46.
301. Watson D, Levin-Aspenson HF, Waszczuk MA et al. Validity and utility of Hierarchical Taxonomy of Psychopathology (HiTOP): III. Emotional dysfunction superspectrum. World Psychiatry 2022;21:26-54.
302. Fairburn CG, Cooper Z, Shafran R. Cognitive behavior therapy for eating disorders: a "transdiagnostic" theory and treatment. Behav Res Ther 2003;41:509-28.
303. McEvoy PM, Nathan P, Norton PJ. Efficacy of transdiagnostic treatments: a review of published outcome studies and future research directions. J Cogn Psychother 2009;23:20-33.
304. Pearl SB, Norton PJ. Transdiagnostic versus diagnosis specific cognitive behavioural therapies for anxiety: a meta-analysis. J Anxiety Disord 2017;46:11-24.
305. Schaeuffele C, Schulz A, Knaevelsrud C et al. CBT at the crossroads: the rise of transdiagnostic treatments. Int J Cogn Ther 2021;14:86-113.
306. Liu J, Li C, Qiu Y et al. Efficacy of internet-delivered universal and tailored transdiagnostic interventions for anxiety and depression: a systematic review and meta-analysis of randomized controlled trials. Psychiatry Res 2025;344:116324.
307. Kolaas K, Berman AH, Hedman-Lagerlöf E et al. Internet-delivered transdiagnostic psychological treatments for individuals with depression, anxiety or both: a systematic review with meta-analysis of randomised controlled trials. BMJ Open 2024;14:e075796.
308. Vogel M, Ebert C, Gensichen J et al. A systematic review and meta-analysis of transdiagnostic interventions for common mental disorders in primary care. Gen Hosp Psychiatry 2024;91:167-79.
309. Schaeuffele C, Meine LE, Schulz A et al. A systematic review and meta-analysis of transdiagnostic cognitive behavioural therapies for emotional disorders. Nat Hum Behav 2024;8:493-509.
310. Newby JM, McKinnon A, Kuyken W et al. Systematic review and meta-analysis of transdiagnostic psychological treatments for anxiety and depressive disorders in adulthood. Clin Psychol Rev 2015;40:91-110.
311. Cuijpers P, Harrer M, Miguel C et al. Absolute and relative outcomes of cognitive behavior therapy for eating disorders in adults: a meta-analysis. Eat Disord 2024;8:1-22.
312. Barlow DH, Allen LB, Choate ML. Toward a unified treatment for emotional disorders. Behav Ther 2004;35:205-30.
313. Carlucci L, Saggino A, Balsamo M. On the efficacy of the unified protocol for transdiagnostic treatment of emotional disorders: a systematic review and meta-analysis. Clin Psychol Rev 2021;87:101999.
314. Watkins ER, Newbold A. Factorial designs help to understand how psychological therapy works. Front Psychiatry 2020;11:429.
315. Collins LM. Optimization of behavioral, biobehavioral, and biomedical interventions: the Multiphase Optimization Strategy (MOST). New York: Springer, 2018.
316. Cuijpers P, Cristea IA, Karyotaki E et al. Component studies of psychological treatments of adult depression: a systematic review and meta-analysis. Psychother Res 2017;29:15-29.
317. Bell EC, Marcus DK, Goodlad JK. Are the parts as good as the whole? A meta-analysis of component treatment studies. J Consult Clin Psychol 2013;81:722-36.
318. Wampold BE, Mondin GW, Moody M et al. A meta-analysis of outcome studies comparing bona fide psychotherapies: empirically, 'all must have prizes.' Psychol Bull 1997;122:203-15.
319. Lubsen J, Pocock SJ. Factorial trials in cardiology: pros and cons. Eur Heart J 1994;15:585-8.
320. McAlister FA, Straus SE, Sackett DL et al. Analysis and reporting of factorial trials: a systematic review. JAMA 2003;289:2545-53.
321. Montgomery AA, Peters TJ, Little P. Design, analysis and presentation of factorial randomized controlled trials. BMC Med Res Methodol 2003;3:26.
322. Sakata M, Toyomoto R, Yoshida K et al. Components of smartphone cognitive-behavioural therapy for subthreshold depression among 1093 university students: a factorial trial. Evid Based Ment Health 2022;25:e18-25.
323. Andersson G, Käll A, Juhlin S et al. Free choice of treatment content, support on demand and supervision in internet-delivered CBT for adults with depression: a randomized factorial design trial. Behav Res Ther 2023;162:104265.
324. Bur OT, Krieger T, Moritz S et al. Optimizing the context of support of web-based self-help in individuals with mild to moderate depressive symptoms: a randomized full factorial trial. Behav Res Ther 2022;152:104070.
325. Kelders SM, Bohlmeijer ET, Pots WT et al. Comparing human and automated support for depression: fractional factorial randomized controlled trial. Behav Res Ther 2015;72:72-80.
326. Šipka D, Lopes R, Krieger T et al. Active components in internet-based cognitive-behavioral therapy for social anxiety disorder: a randomized full factorial trial. Psychother Psychosom 2025;94:40-59.
327. Watkins E, Newbold A, Tester-Jones M et al. Investigation of active ingredients within internet-delivered cognitive behavioral therapy for depression: a randomized optimization trial. JAMA Psychiatry 2023;80:942-51.
328. Welton NJ, Caldwell DM, Adamopoulos E et al. Mixed treatment comparison meta-analysis of complex interventions: psychological interventions in coronary heart disease. Am J Epidemiol 2009;169:1158-65.
329. Petropoulou M, Efthimiou O, Rücker G et al. A review of methods for addressing components of interventions in meta-analysis. PLoS One 2021;16: e0246631.
330. Coventry PA, Meader N, Melton H et al. Psychological and pharmacological interventions for posttraumatic stress disorder and comorbid mental health problems following complex traumatic events: systematic review and component network meta-analysis. PLoS Med 2020;17:e1003262.
331. Pompoli A, Furukawa TA, Efthimiou O et al. Dismantling cognitive-behaviour therapy for panic disorder: a systematic review and component network meta-analysis. Psychol Med 2018;48:1945-53.
332. Williams R, Ostinelli EG, Agorinya J et al. Comparing interventions for early psychosis: a systematic review and component network meta-analysis. EClinicalMedicine 2024;70:102537.
333. Kazdin AE. Mediators and mechanisms of change in psychotherapy research. Annu Rev Clin Psychol 2007;3:1-27.
334. Hernán MA, Robins JM. Causal inference: what if. Boca Raton: Chapman & Hall/CRC, 2020.
335. Narita ZC, Miyashita M, Furukawa TA et al. Key considerations in mediation analysis for psychiatric research. JAMA Psychiatry 2025;82:634-6.
336. VanderWeele TJ. Mediation analysis: a practitioner's guide. Annu Rev Public Health 2016;37:17-32.
337. Wampold BE. How important are the common factors in psychotherapy? An update. World Psychiatry 2015;14:270-7.
338. Flückiger C, Del Re AC, Wampold BE et al. The alliance in adult psychotherapy: a meta-analytic synthesis. Psychotherapy 2018;55:316-40.
339. Zilcha-Mano S. Is the alliance really therapeutic? Revisiting this question in light of recent methodological advances. Am Psychol 2017;72:311-25.
340. Fonagy P, Luyten P. Fidelity vs. flexibility in the implementation of psychotherapies: time to move on. World Psychiatry 2019;18:270-1.
341. Kendall PC, Frank HE. Implementing evidence-based treatment protocols: flexibility within fidelity. Clin Psychol Sci Pract 2018;25:e12271.
342. Power N, Noble LA, Simmonds-Buckley M et al. Associations between treatment adherence-competence-integrity (ACI) and adult psychotherapy outcomes: a systematic review and meta-analysis. J Consult Clin Psychol 2022;90: 427-45.

343. Webb CA, DeRubeis RJ, Barber JP. Therapist adherence/competence and treatment outcome: a meta-analytic review. J Consult Clin Psychol 2010;78:200-11.
344. Cuijpers P, Huibers M, Ebert DD et al. How much psychotherapy is needed to treat depression? A metaregression analysis. J Affect Disord 2013;149:1-13.
345. Ciharova M, Karyotaki E, Miguel C et al. Amount and frequency of psychotherapy as predictors of treatment outcome for adult depression: a meta-regression analysis. J Affect Disord 2024;359:92-9.
346. Bruijniks SJ, Lemmens LH, Hollon SD et al. The effects of once- versus twice-weekly sessions on psychotherapy outcomes in depressed patients. Br J Psychiatry 2020;216:222-30.
347. Lambert MJ, Whipple JL, Hawkins EJ et al. Is it time for clinicians to routinely track patient outcome? A meta-analysis. Clin Psychol Sci Pract 2003;10:288-301.
348. Kazdin AE, Blase SL. Rebooting psychotherapy research and practice to reduce the burden of mental illness. Perspect Psychol Sci 2011;6:21-37.
349. de Jong K, Conijn JM, Gallagher RAV et al. Using progress feedback to improve outcomes and reduce drop-out, treatment duration, and deterioration: a multilevel meta-analysis. Clin Psychol Rev 2021;85:102002.
350. Hannan C, Lambert MJ, Harmon C et al. A lab test and algorithms for identifying clients at risk for treatment failure. J Clin Psychol 2005;61:155-63.
351. Lambert MJ, Whipple JL, Kleinstauber M. Collecting and delivering progress feedback: a meta-analysis of routine outcome monitoring. Psychotherapy 2018; 55:520-37.
352. Østergård OK, Randa H, Hougaard E. The effect of using the Partners for Change Outcome Management System as feedback tool in psychotherapy – a systematic review and meta-analysis. Psychother Res 2018;30:195-212.
353. Tam HE, Ronan K. The application of a feedback-informed approach in psychological service with youth: systematic review and meta-analysis. Clin Psychol Rev 2017;55:41-55.
354. Kendrick T, El-Gohary M, Stuart B et al. Routine use of patient reported outcome measures (PROMs) for improving treatment of common mental health disorders in adults. Cochrane Database Syst Rev 2016;7:CD011119.
355. Bergman H, Kornør H, Nikolakopoulou A et al. Client feedback in psychological therapy for children and adolescents with mental health problems. Cochrane Database Syst Rev 2018;8:CD011729.
356. O'Neil A, Rossell SL, Berk M. Understanding side effects of psychotherapies: implications for clinical practice and research trials. World Psychiatry 2025; 24:194-5.
357. Linden M, Schermuly-Haupt ML. Definition, assessment and rate of psychotherapy side effects. World Psychiatry 2014;13:306-9.
358. Cuijpers P. Research on negative effects of psychotherapies: the next steps. Clin Psychol Sci Pract 2021;28:142-4.
359. Cuijpers P, Reijnders M, Karyotaki E et al. Negative effects of psychotherapies for adult depression: a meta-analysis of deterioration rates. J Affect Disord 2018;239:138-45.
360. Rozental A, Andersson G, Boettcher J et al. Consensus statement on defining and measuring negative effects of Internet interventions. Internet Interv 2014;1:12-9.
361. Mohr DC. Negative outcome in psychotherapy: a critical review. Clin Psychol Sci Pract 1995;2:1-27.
362. Herzog P, Lauff S, Rief W et al. Assessing the unwanted: a systematic review of instruments used to assess negative effects of psychotherapy. Brain Behav 2019;9:e01447.
363. Cuijpers P, Karyotaki E, Ciharova M et al. The effects of psychotherapies for depression on response, remission, reliable change, and deterioration: a meta-analysis. Acta Psychiatr Scand 2021;144:288-99.
364. Cuijpers P, Karyotaki E, Ciharova M et al. The effects of psychological treatments of depression in children and adolescents on response, reliable change, and deterioration: a systematic review and meta-analysis. Eur Child Adolesc Psychiatry 2023;32:177-92.
365. Hoppen TH, Lindemann AS, Morina N. Safety of psychological interventions for adult post-traumatic stress disorder: meta-analysis on the incidence and relative risk of deterioration, adverse events and serious adverse events. Br J Psychiatry 2022;221:658-67.
366. Karyotaki E, Kemmeren L, Riper H et al. Is self-guided internet-based cognitive behavioural therapy (iCBT) harmful? An individual participant data meta-analysis. Psychol Med 2018;48:2456-66.
367. Lofthouse K, Davies A, Hodgekins J et al. Systematic review and meta-analysis: imputing response rates for first-line psychological treatments for posttraumatic stress disorder in youth. J Am Acad Child Adolesc Psychiatry 2025; doi: 10.1016/j.jaac.2024.12.014.
368. Mather S, Fisher P, Nevitt S et al. The limited efficacy of psychological interventions for depression in people with Type 1 or Type 2 diabetes: an individual participant data meta-analysis (IPD-MA). J Affect Disord 2022;310:25-31.
369. Rozental A, Magnusson K, Boettcher J et al. For better or worse: an individual patient data meta-analysis of deterioration among participants receiving internet-based cognitive behavior therapy. J Consult Clin Psychol 2017;85:160-77.
370. Hemming K, Haines TP, Chilton PJ et al. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. BMJ 2015;350:h391.
371. López-del-Hoyo Y, Fernández-Martínez S, Perez-Aranda A et al. Effectiveness of a web-based self-guided intervention (MINDxYOU) for reducing stress and promoting mental health among health professionals: results from a stepped-wedge cluster randomized trial. J Med Internet Res 2025;27:e59653.
372. McBain RK, Mwale O, Mpinga K et al. Effectiveness, cost-effectiveness, and positive externalities of integrated chronic care for adults with major depressive disorder in Malawi (IC3D): a stepped-wedge, cluster-randomised, controlled trial. Lancet 2024;404:1823-34.
373. Angerhofer Richards J, Cruz M, Stewart C et al. Effectiveness of integrating suicide care in primary care: secondary analysis of a stepped-wedge, cluster randomized implementation trial. Ann Intern Med 2024;177:1471-81.
374. Vis C, Schuurmans J, Aouizerate B et al. Effectiveness of self-guided tailored implementation strategies in integrating and embedding internet-based cognitive behavioral therapy in routine mental health care: results of a multicenter stepped-wedge cluster randomized trial. J Med Internet Res 2023;25:e41532.
375. Zatzick D, Jurkovich G, Heagerty P et al. Stepped collaborative care targeting posttraumatic stress disorder symptoms and comorbidity for US trauma care systems: a randomized clinical trial. JAMA Surg 2021;156:430-42.
376. Gold SM, Mäntylä FL, Donoghue K et al. Transforming the evidence landscape in mental health with platform trials. Nat Ment Health 2025;3:276-85.
377. Griessbach A, Schönenberger CM, Heravi AT et al. Characteristics, progression, and output of randomized platform trials: a systematic review. JAMA Netw Open 2024;7:e243109.
378. Park JJ, Detry MA, Murthy S et al. How to use and interpret the results of a platform trial: users' guide to the medical literature. JAMA 2022;327:67-74.
379. Cuijpers P, Miguel C, Papola D et al. From living systematic reviews to meta-analytical research domains. Evid Based Mental Health 2022;25:145-7.
380. Cuijpers P, Miguel C, Harrer M et al. Psychological treatment of depression: a systematic overview of a 'Meta-Analytic Research Domain.' J Affect Disord 2023;335:141-51.
381. Weisz JR, Kuppens S, Ng MY et al. What five decades of research tells us about the effects of youth psychological therapy: a multilevel meta-analysis and implications for science and practice. Am Psychol 2017;72:79-117.
382. Hu MX, Palantza C, Setkowski K et al. Comprehensive database and individual patient data meta-analysis of randomised controlled trials on psychotherapies reducing suicidal thoughts and behaviour: study protocol. BMJ Open 2020;10:e037566.
383. Fairburn CG, Patel V. The global dissemination of psychological treatments: a road map for research and practice. Am J Psychiatry 2014;171:495-98.
384. Patel V, Saxena S, Lund C et al. The Lancet Commission on global mental health and sustainable development. Lancet 2018;392:1553-98.
385. Singla DR, Schleider JL, Patel V. Democratizing access to psychological therapies: innovations and the role of psychologists. J Consult Clin Psychol 2023;91: 623-5.
386. Raviola G, Naslund JA, Smith SL et al. Innovative models in mental health delivery systems: task sharing care with non-specialist providers to close the mental health treatment gap. Curr Psychiatry Rep 2019;21:44.
387. Singla DR, Silver RK, Vigod SN et al. Task-sharing and telemedicine delivery of psychotherapy to treat perinatal depression: a pragmatic, noninferiority randomized trial. Nat Med 2025;31:1214-24.
388. Singla DR, Lawson A, Kohrt BA et al. Implementation and effectiveness of nonspecialist-delivered interventions for perinatal mental health in high-income countries: a systematic review and meta-analysis. JAMA Psychiatry 2021;78:498-509.
389. Anvari MS, Hampton T, Tong MP et al. Behavioral activation disseminated by non-mental health professionals, paraprofessionals, and peers: a systematic review. Behav Ther 2023;54:524-38.
390. Ó hAnrachtaigh É, Brown G, Beck A et al. Transdiagnostic psychological interventions for symptoms of common mental disorders delivered by non-specialist providers in low-and middle-income countries: a systematic review and meta-analysis. Depress Anxiety 2024;2024:5037662.
391. Hassan AA, Ibrahim AM, Nadkarni A. A systematic review of task-sharing interventions for substance use and substance use disorder in low- and middle-income countries. Drug Alcohol Depend 2024;256:111093.
392. Chakrabarti S. Digital psychiatry in low-and-middle-income countries: new developments and the way forward. World J Psychiatry 2024;14:350-61.

393. Kim J, Aryee LM, Bang H et al. Effectiveness of digital mental health tools to reduce depressive and anxiety symptoms in low- and middle-income countries: systematic review and meta-analysis. JMIR Ment Health 2023;10:e43066.
394. Schleider JL, Zapata JP, Rapoport A et al. Single-session interventions for mental health problems and service engagement: umbrella review of systematic reviews and meta-analyses. Annu Rev Clin Psychol 2025;21:279-303.
395. Abel MR, Bianco A, Gilbert R et al. When is psychotherapy brief? Considering sociodemographic factors, problem complexity, and problem type in U.S. adolescents. J Clin Child Adolesc Psychol 2022;51:740-9.
396. Ono Y, Furukawa TA, Shimizu E et al. Current status of research on cognitive therapy/cognitive behavior therapy in Japan. Psychiatry Clin Neurosci 2011;65:121-9.
397. Schleider JL, Weisz JR. Little treatments, promising effects? Meta-analysis of single-session interventions for youth psychiatric problems. J Am Acad Child Adolesc Psychiatry 2017;56:107-15.
398. Ost LG. One-session treatment for specific phobias. Behav Res Ther 1989;27:1-7.
399. Chartier GB, Lam F, Bergmans Y et al. "Psychotherapy in the pressure cooker": a systematic review of single session psychosocial interventions in emergency departments for suicide-related thoughts or behaviors. J Psychiatr Pract 2023;29:291-307.
400. Dryden W. Single session one-at-a-time therapy: a personal approach. Aust N Z J Fam Ther 2020;41:283-301.
401. Talmon M. Single-session therapy: maximizing the effect of the first (and often only) therapeutic encounter. San Francisco: Jossey-Bass, 1990.
402. Stice E, Shaw H, Marti CN. A meta-analytic review of eating disorder prevention programs: encouraging findings. Annu Rev Clin Psychol 2007;3:207-31.
403. Wolitzky-Taylor KB, Horowitz JD, Powers MB et al. Psychological approaches in the treatment of specific phobias: a meta-analysis. Clin Psychol Rev 2008;28:1021-37.
404. Ghosh A, Singh P, Das N et al. Efficacy of brief intervention for harmful and hazardous alcohol use: a systematic review and meta-analysis of studies from low middle-income countries. Addiction 2022;117:545-58.
405. Riper H, van Straten A, Keuken M et al. Curbing problem drinking with personalized-feedback interventions: a meta-analysis. Am J Prev Med 2009;36:247-55.
406. van Emmerik AA, Kamphuis JH, Hulsbosch AM et al. Single session debriefing after psychological trauma: a meta-analysis. Lancet 2002;360:766-71.
407. Cuijpers P, Harrer M, Furukawa T. Assessing the strength of innovations in the treatment of depression. Br J Psychiatry 2025;227:1-4.
408. Cartwright N. Nature's capacities and their measurement. Oxford: Clarendon Press, 1989.
409. Cartwright N. The dappled world: a study of the boundaries of science. Cambridge: Cambridge University Press, 1999.
410. Hacking I. The social construction of what? Cambridge: Harvard University Press, 1999.
411. Stein DJ, Shoptaw SJ, Vigo DV et al. Psychiatric diagnosis and treatment in the 21st century: paradigm shifts versus incremental integration. World Psychiatry 2022;21:393-414.
412. Birk RH, Samuel G. Digital phenotyping for mental health: reviewing the challenges of using data to monitor and predict mental health problems. Curr Psychiatry Rep 2022;24:523-8.
413. Malott KM, Barraclough S, Yee T. Towards decolonizing diagnosis: a critical review and suggested alternatives. Int J Adv Couns 2023;45:1-17.

DOI:10.1002/wps.70002

The lived experience of persons who attempt suicide: a bottom-up review co-designed, co-produced and co-written by experts by experience and academics

Paolo Fusar-Poli[1-4], Cecilia Maria Esposito[5], Andres Estradé[2], Renè Rosfort[6], Milena Mancini[7], Matthew Jackman[8], Anto Sugianto[9-11], Elza Berk[12], Benny Prawira[13], Latifah N. Wangui[14], Arnold Agaba[15], Julieann Cullen[16], Rory R. O'Connor[17], Ian Marsh[18], Farshid Shamsaei[19], Ilaria Bonoldi[3], Alberto Stefana[20], Stefano Damiani[1], Ilaria Basadonne[1], Angad Singh[21], Silvia Fontana[1], Irene Curti[1], Laura Massari[1], Aurora Legittimo[1], Samuele Cortese[22-24], Dong Keon Yon[25], Jae Il Shin[26], Luis Madeira[27], Giovanni Stanghellini[28,29], Mario Rossi Monti[30], Matthew Ratcliffe[31], Maurizio Pompili[32], Mario Maj[33]

[1]Department of Brain and Behavioural Sciences, University of Pavia, Pavia, Italy; [2]Early Psychosis: Interventions and Clinical-detection (EPIC) Lab, Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; [3]OASIS Service, South London and Maudsley NHS Foundation Trust, London, UK; [4]National Institute for Health Research, Maudsley Biomedical Research Centre, South London and Maudsley, London, UK; [5]Department of Neurosciences and Mental Health, IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [6]S. Kierkegaard Research Centre, University of Copenhagen, Copenhagen, Denmark; [7]Department of Psychology, School of Medicine and Health Sciences, G. D'Annunzio University of Chieti and Pescara, Chieti, Italy; [8]Australian Centre for Lived Experience, Melbourne, Australia; [9]Global Mental Health Peer Network, Jakarta, Indonesia; [10]Indonesian Community Care for Schizophrenia, Jakarta, Indonesia; [11]University of Manchester, Manchester, UK; [12]Global Mental Health Peer Network, Cape Town, South Africa; [13]Into The Light Indonesia, Jakarta, Indonesia; [14]Global Mental Health Peer Network, Nairobi, Kenya; [15]Global Mental Health Peer Network, Kigali, Rwanda; [16]Global Mental Health Peer Network, Dublin, Ireland; [17]Centre for Applied Behavioural Sciences, Heriot-Watt University, Edinburgh, UK; [18]Canterbury Christ Church University, Canterbury, UK; [19]School of Nursing & Midwifery, Hamadan University of Medical Sciences, Hamadan, Iran; [20]Center for Behavioural Sciences and Mental Health, National Institute of Health, Rome, Italy; [21]Department of Psychiatry, University of Toronto, Toronto, ON, Canada; [22]Developmental EPI (Evidence synthesis, Prediction, Implementation) lab, Centre for Innovation in Mental Health, School of Psychology, Faculty of Environmental and Life Sciences, University of Southampton, Southampton, UK; [23]Solent NHS Trust, Southampton, UK; [24]Hassenfeld Children's Hospital at NYU Langone, New York University Child Study Center, New York, NY, USA; [25]Department of Pediatrics, Kyung Hee University College of Medicine, Yonsei University College of Medicine, Seoul, South Korea; [26]Severance Underwood Meta-Research Center, Institute of Convergence Science, Yonsei University, Seoul, South Korea; [27]Faculty of Medicine, University of Lisbon, Lisbon, Portugal; [28]Department of Health Sciences, University of Florence, Florence, Italy; [29]D. Portales University, Santiago, Chile; [30]Department of Humanistic Studies, University of Urbino, Urbino, Italy; [31]Department of Philosophy, University of York, York, UK; [32]Suicide Prevention Center, Department of Neurosciences, Mental Health and Sensory Organs, St. Andrea Hospital, Sapienza University of Rome, Rome, Italy; [33]Department of Psychiatry, University of Campania "L. Vanvitelli", Naples, Italy

This is the first bottom-up review of the lived experience of persons who attempt suicide. The study has been co-designed, co-conducted and co-written by experts by experience and academics, focusing on first-person narratives within and outside the medical field. The lived world of individuals who attempt suicide is characterized by experiences related to the attempt itself ("contemplating suicide as a deliberate death", "contemplating suicide as an escape route", "looking for online answers about suicide", "planning suicide", "finding rest between the suicidal decision and the final act", "changing one's mind during the suicide attempt", "acting on suicidal impulses"); experiences related to the self and time ("feeling unworthy", "feeling detached from oneself or the world and lacking a sense of agency", "splitting the self between the decision to live or die", "perceiving an abortive and doomed future"); and experience of emotions and the body ("feeling overwhelmed by hopelessness and despair", "feeling empty and drained of energy", "feeling alone"). The lived experience of individuals who attempt suicide is also described in terms of the social and cultural context, including the experience of others ("feeling that no one cares", "feeling like a burden to others", "facing others' difficulty in understanding"); cultural, gender and age differences ("experiencing geographical, cultural and religious taboos about suicide", "feeling inadequate in relation to gender stereotypes", "feeling abandoned in old age"); and the perception of stigma ("facing social stigma", "experiencing a stigmatized self", "silencing suicidal behaviors"). The lived experience of persons after an attempted suicide is characterized as a complex process of self-acceptance and rediscovery ("living with suicidal thoughts", "navigating the challenges of recovery", "gaining new perspectives during recovery", "restoring interpersonal relationships to recover"). Finally, the lived experience of individuals who attempt suicide is described with respect to their access to general health care ("seeking help before the suicide attempt", "feeling abandoned after a suicide attempt") and mental health care ("experiencing shame as a barrier to care", "fearing mental disorder label", "feeling accepted and listened to", "facing economic difficulties in accessing support", "coping with distress during hospitalization"). The experiences described in this paper hold educational and social value, informing medical and psychological practices and research, public health approaches, and promotion of social change. This research overcomes embarrassment, fear and stigma, and helps us to understand the fragile nature of our emotions and feelings, our immersion in the social world, and our sense of meaning in life.

Key words: Suicide, suicide attempts, lived experience, first-person accounts, stigma, mental health care, recovery, public health approaches

(World Psychiatry 2026;25:34–49)

Suicide, defined as "the act of deliberately killing oneself"[1], is a complex, multidimensional phenomenon that has been studied from philosophical, sociological and medical perspectives. Suicidal behavior can be conceptualized as a continuum ranging from suicidal ideation to suicide attempts and completed suicide. Attempted suicide is defined as a potentially self-injurious act with a non-fatal outcome in which there is evidence that the individual deliberately intended to kill him/herself[2]. Attempted and completed suicide are associated with a complex interplay of clinical, biological, psychological, social, spiritual and cultural factors[3,4], leading to distorted beliefs, painful emotions and unmet needs[5,6].

Suicide is a global public health issue, accounting for more than 700,000 deaths annually (about one every 40 seconds)[7]. It is the fourth leading cause of mortality among individuals aged 15-29 years[8]. Rates of completed suicide are not evenly distributed around the world, being higher in high-income countries than in low- and middle-income ones (although there are issues concerning the reliability of data from some countries)[7,9]. Rates of completed suicide also differ by gender, being three times higher in men than in women. On the other hand, suicide attempts are more common in women[10]. The number of suicide attempts is estimated to be 10-30 times higher than that of completed suicides[1].

From a historical perspective, suicide is a human behavior that has been interpreted primarily within moral, religious, legal and existential frameworks, while it has been considered in medical terms only from the 19th century[11,12]. Suicide itself is not coded as a formal diagnosis and is not regarded as a symptom[13]. Notably, although the majority (about 90%) of completed suicides are associated with a mental disorder[14-16], and mental disorders are associated with a 16-fold increase in the suicide risk[17], suicide does not equate to having a mental disorder. K. Jaspers first observed that suicide is not always associated with mental disorders[18], and there are instances of completed suicide resulting from personal or existential circumstances without pre-existing mental health difficulties[19].

Completed or attempted suicide poses numerous complex empirical challenges. For the general population, it often emerges as a silent tragedy. For the media, it is either a treacherous taboo or a sensationalized event[20]. For mental health professionals, it is a deeply disturbing occupational hazard and the most common psychiatric emergency[21]. Any attempt to interpret, explain, predict, and ultimately prevent suicide requires a deep understanding of what suicidal thoughts and feelings mean to those who live them, essentially asking the phenomenological question: "What is this kind of experience like?"[2].

In addressing this question, academics have typically proposed top-down (i.e., from theory to lived experience) accounts, driven by the historical context of psychiatry[22-24]. However, this approach encounters the limitations of a theoretical interpretative framework and of a technical language that may obscure the whole subjective nature of the lived experience. On the other hand, first-person experiences are described in contributions from almost every time and place in the world[25-30]. However, these take several different forms, reflect a variety of contexts, and are challenging to integrate into a broader understanding of suicidality.

In the present study, experts with lived experience and academics collaborated to create a shared narrative. To our knowledge, this is the first study to address the lived experience of those who attempt suicide by adopting a collaborative, bottom-up approach based on co-design, co-production, co-writing and eventually co-authorship[31]. The methodological process expanded upon earlier studies conducted by our group to explore the lived experience of psychosis, depression, mental disorders in adolescents, and postpartum depression and psychosis[31-34], and is briefly detailed below.

In the first step, we established a collaborative core writing team of experts with lived, learned or laboured experience (patients, families and caregivers) and academics (psychiatrists, psychologists, philosophers and social researchers). Notably, several experts by experience were academics themselves (or international activists). This team conducted a search of Web of Science, PubMed and SciELO from inception until March 15, 2024, to identify an initial set of qualitative studies providing first-person accounts published in English, Spanish or Italian. The search terms were: ("suicide attempt*" OR "suicidal*" OR "suicid*") AND (qualitative OR "focus group" OR "grounded theory" OR interviews OR "content analysis" OR etnograph* OR phenomenol* OR "in depth interview" OR hermeneut* OR autobiography OR biograph*) AND ("lived experience" OR "first person" OR first-person OR "user experience" OR "patient experience" OR meaning OR beliefs OR narrative OR self-narrative OR "illness experience"). Additional sources, such as autobiographical books written by individuals with lived experience, were included[35-43] (see Table 1).

We excluded the narratives of individuals with non-suicidal self-harm, given its distinct psychopathology and phenomenology[44]. We did not include psychological autopsies of individuals after completing suicide (as these typically do not reflect first-person accounts)[45]. We sought to capture the broader phenomenological characteristics of suicide attempts, not limiting ourselves to mental disorders[46]. We did not address suicide attempts in individuals with terminal illnesses or end-of-life conditions, where distinctive circumstances apply that are potentially associated with different forms of experience[47]. We did not focus on young individuals, as this was discussed in a previous publication[33].

In the second step, first-person narratives were extracted from included papers. A thematic synthesis of the selected reports was undertaken by three independent researchers, using line-by-line coding of the text[48,49]. This process produced a preliminary list of descriptive themes and sub-themes. The material was then shared with the core writing team and initially grouped into four overarching descriptive themes: "The lived world of individuals who attempt suicide", "The experience of individuals who attempt suicide in the social and cultural context", "The lived experience after an attempted suicide", and "The lived experience of accessing health care services in individuals who attempt suicide", each with several sub-themes.

In the third step, the preliminary themes and sub-themes were discussed in a collaborative workshop involving a wider global network of experts by experience across different age groups, genders, and ethnic and cultural backgrounds. Individuals were recruited from the Global Mental Health Peer Network (www.gmhpn.org), which includes people with lived experience from

Table 1 Selection of complementary sources considered for the review

Artaud A. *Van Gogh, the man suicided by society*[35]

Améry J. *On suicide: a discourse on voluntary death*[36]

Kane S. *4.48 Psychosis*[37]

Plath S. *The bell jar*[38]

Pavese C. *This business of living*[39]

Morselli G. *Dissipatio H.G.*[40]

Webb D. *Thinking about suicide: contemplating and comprehending the urge to die*[41]

Woolf W. "*Dearest, I feel certain I am going mad again*"*: the suicide note of Virginia Woolf*[42]

Linehan M. *Building a life worth living: a memoir*[43] over 40 countries, and the South London and Maudsley NHS Recovery College (www.slamrecoverycollege.co.uk), which includes experts by experience of recovering after a suicide attempt. Experts by experience were invited to share their lived experiences in their narrative style, without a prescribed framework[31-34,50,51].

In the fourth step, the final selection of themes and sub-themes was enriched using phenomenologically informed perspectives[52,53], as suggested by the broader group of experts by experience and academics, who collaborated in the drafting of the manuscript through a shared Google Drive platform. All experts by experience who actively participated in the manuscript were invited to become co-authors. They were offered reimbursement for their time in accordance with guidelines for participatory research[54].

In this paper, written or spoken quotes from experts by experience are reproduced verbatim in italics. We have followed clinical and ethical guidelines for writing about suicidality (e.g., www.samaritans.org). There is no expectation that the described experiences are exhaustive or applicable to all individuals.

THE LIVED WORLD OF INDIVIDUALS WHO ATTEMPT SUICIDE

In this section, we will describe the lived world of individuals who attempt suicide across the following domains: a) the experience of attempting suicide; b) the experience of the self, agency and time in individuals who attempt suicide; and c) the experience of emotions and the body in these individuals.

The experience of attempting suicide

Contemplating suicide as a deliberate death

Individuals who attempt suicide often describe an all-enveloping, primary intention for death, which distinguishes their experience from that of non-suicidal self-harm. A drive towards suicide may be reported: "*I felt the appetite for non-being*"[35]. Reference may be made to the futility of seeking a purpose in life ("*I wanted to die and end all these useless attempts to find purpose*", *personal communication*) or to the worthlessness of one's own life or human life in general ("*No one ever lacks a good reason to kill himself*"[39]). In some cases, suicidal intention is described as a destiny, as an inexorable call from which one cannot escape: "*Suicide, that's programmed in my brain*"[55]. However, in other cases, contemplating suicide is not described in terms of an intention to die, but as an automatic response to an altered world: "*It was like I was a robot and suicide was the automatic response*"[56].

Some individuals imagine their own death: "*I've gotten used to imagining my death: I visualize the final decision, the physical pain, the moment when you understand that it's over… sometimes it gives me relief, as I had really done it*" (*personal communication*). Others imagine the consequences of their suicide attempt, such as their own funeral, with great vividness: "*I could feel it, that cold, damp feeling and being in a coffin*"[57]. Self-imagining suicide attempt may be perceived as a way of creating a meaningful narrative: "*You're creating a narrative that's special and meaningful to you… And like making it… a spectacle and theatrical*"[58].

Contemplating suicide as an escape route

Individuals who attempt suicide may often experience their will to die as an escape route from the struggle of living: "*There was no other option even though I didn't even want to die, but the pain was just too overwhelming, and it seemed like the only way to escape*" (*personal communication*). Life is experienced as hard work and suffering ("*Every day costs me so much effort… why should I live? Why should I continue to suffer like this?*", *personal communication*), while they describe a comparative easiness in the state of being dead ("*My pain would go away because either I would be dead or I would be in so much physical pain that I didn't have to think about the emotional pain I was experiencing*"[59,60]).

Suicide is often contemplated in the context of hopelessness, despair and a sense of purposelessness: "*Why keep going on in life with all these thoughts*"[61]. Individuals want to escape from the insurmountable challenges that they face in life and the psychological pain they experience: "*It's not about succeeding to die. That's not the primary thing. That's to… somehow… get on… from what you can't get out of*"[57]; "*It's not so much you want to die. It's more that you want to get away from the pain that you're dealing with*"[62].

Death is seen as the only possible way to escape problems and personal suffering ("*I didn't want to feel that way anymore*"[62]), the only solution left when all the other sources of hope have been exhausted. An individual with a history of multiple suicide attempts said: "*When I feel I can't cope any more, then I have to take that way out*"[55]. Suicide may thus appear as the only solution within an inner dialogue in which the subject analyzes various options for escaping suffering: "*There was no other alternative except killing myself*"[63].

Suicide can be constructed as an escape route akin to drugs or alcohol, which are frequently used by individuals who attempted suicide: "*The feeling of wanting to escape my world was there all the time. I was escaping via substance abuse*"; "*In many ways, drugs or alcohol saved my life as I would lean into that to get away from the suicidal thoughts*" (*personal communications*).

Looking for online answers about suicide

Individuals who attempt suicide may search the Internet while contemplating the idea of ending their life. According to their accounts, the online digital world, which may include websites, mobile apps and social media, is ubiquitous and intricately interwoven with the lived experience of people contemplating suicide[64].

On one side, online resources can provide supportive advice to people who contemplate suicide. Support may include digital educational material that helps individuals to recognize that they are unwell and need help: "*You, people who read this post, you're my only confidants*"[64]. Online networks and social communities of other experts by experience may also help individuals to feel less alone and understand that other people share their feelings: "*Anyone else feels the same?*"[64]. Overall, these supportive experiences may help persons who are contemplating suicide to consider alternative solutions: "*I was very determined to leave asap and had absolutely no will of going forward… Finding this [digital] community, I believe, is the main reason I was able to stay this long*"[64].

On the other side, visiting online resources can be experienced as an addictive habit, which increases isolation within the family and social withdrawal, and reinforces feelings of loneliness, key triggers of depressive thoughts: "*It forms the habit of staying alone even when you have your whole family with you and not being able to talk to them*"[65]. Other individuals who contemplate suicide may describe that exaggerated images of happiness and success in social media foster social comparison, impair their self-confidence, and amplify suicidal tension: "*Someone may not be happy in real life but tries to show they are happy and rich in social media. These increase tension*"[65]. Online resources can also provide potentially harmful practical information about methods to commit suicide: "*I went on the internet and started to research suicide methods*"[58]. The Internet is one of the most frequently accessed sources of information that may lead to suicide attempts: "*I'm not sure I would have actually tried [suicide] if I hadn't found all that news about suicide online*" (*personal communication*).

Planning suicide

Most individuals who have attempted suicide describe a long history of living with thoughts of death, but then comes a time when they start feeling that they should act on them: "*I simply felt like it was time*"[66]. The planning of suicide is sometimes described as a manoeuvre to get closer to death ("*It became more and more intense… [Suicide] began to colour everything. It sort of was the background, or the wallpaper, to every situation I had in my mind at that time*"[56]), or as an attempt to test themselves to understand if they will be able to make the final gesture ("*The more I thought about suicide, the closer death seemed to me: like a welcoming embrace into which to throw me*", *personal communication*).

Many individuals describe their experience of attempting suicide as a well-planned and organized decision: "*People think that to kill yourself you have to be crazy, while I had the feeling that I had never been so lucid as in that moment*", *personal communication*). In these cases, the priority is not the urgency but the precision of the chosen method, time and place. The details of the suicide attempt are studied carefully, and individuals choose one that suits them best: "*A quick, violent death is quite attractive*"[58].

However, a degree of impulsivity is typical of many individuals who attempt suicide. J. Améry, an intellectual who wrote a monograph on suicide and died by suicide, described the moment when suicidal intention turns into suicidal behavior as "*the moment of jumping*"[36], similar to when leaning over the ledge turns into jumping into the void. The "moment of jumping" represents the final common pathway shared across multiple motives triggering suicide, establishing an "insane equality"[36] among many individuals who attempt suicide[13].

Finding rest between the suicidal decision and the final act

The decision to live or die is often experienced as a painful doubt that is difficult to live with: "*Doubt is exhausting, better to die*" (*personal communication*). Some individuals who eventually decide to attempt suicide describe a sense of rediscovered peace, compared to the period of agonizing doubt that they had previously experienced[60]: "*I was trying to figure out what was going on, couldn't sleep and I suddenly thought about suicide. And my mind calmed down*"[58]. The sense of calm that results from the decision to die can itself be strange and unsettling to the person: "*I was calm as I was sitting in this chair, calm, that was what scared me the most looking back at it, how calm I was*"[67].

These narratives suggest that, during the time between the decision and the suicide attempt, individuals often live in a "suicidal world" markedly different from the one that precedes the suicidal decision. They may experience a paradoxical rediscovery and enrichment of their existence: "*I dreamed of something magnificent: the war had broken out, I had to go to the front. I took leave of everyone in the joyful certainty that I would soon die*"[68].

The idea of being able to end one's suffering by taking one's own life may attenuate the manifestations of the suffering itself[69], and give a purpose to one's life, even if the purpose is just to end that life: "*I felt like at least there was an out, that instead of staying in the pain or situation or with myself there was at least movement into some sort of solution, and the solution became suicide*" (*personal communication*).

Some authors[70] have therefore suggested that the act of suicide may sometimes paradoxically represent an "optimistic" decision toward a solution (e.g., since there is no meaning in life, the only hope for meaning would have to be found in death), as opposed to an act of despair or resigned sadness. Calmness may, therefore, originate from a re-organization of one's purposes in the face of death, which re-establishes a foothold[71]: "*Death has become my only goal*" (*personal communication*).

Changing one's mind during the suicide attempt

Many individuals report the experience of changing their mind during the suicide attempt and retracting their initial decision[72]. Often, these people realize that they do not want to cause pain to family members or carers: "*I was doing fine till he said, 'You know how hard it is for a child to see his mother in hospital after she's just attempted suicide?' And my kids came to mind, and that was a bit of a struggle*"[73].

Concern about causing pain or harm to the loved ones is a critical driver in changing suicide plans: "*I didn't want to hurt my family… that's the only reason I can't bring myself to do it*" (*personal communication*). Individuals may be struck by the idea of what would happen to their loved ones after they are gone: "*I was thinking about my wife, my parents… if I go, who will take care of them? It was a mistake*"[74]. The thought of loved ones can provide strength to resist suicidal temptations and lead to a rediscovery of hope: "*I gave up trying to attempt suicide because, most of the time, I thought that life has many aspects to enjoy and continue, such as my children and my family*"[75]. These feelings are typically ambivalent and intensify the struggle: "*I know my family will suffer more than me… But I am not able to go on like this*"[74].

In other cases, the suicidal act may be interrupted by a sudden external event ("*I heard a baby screaming, that's what stopped me*")[58], or by the thought of causing suffering to those who may inadvertently witness the suicide attempt or unwillingly participate in it: "*I couldn't do that, because that's making somebody else complicit, so that's almost making them feel as if they'd killed me*"[58]. Other factors that may lead individuals to change their mind during the suicide attempt relate to the culture of reference, religion, and the social meaning attributed to suicide (see below).

Acting on suicidal impulses

Some degree of impulsiveness is almost always involved in triggering the movement from suicidal plans to action. Individuals who gradually develop a suicidal plan may eventually act on it following some degree of impulsiveness: "*I spend my entire life, or have spent my entire life, planning, and looking and… so you ask me a method, and I could probably tell you about it. But the actual impulse to do it… well… is it an impulse? Not quite sure what it is, but the compulsion to do so is uncontrollable*"[59]. In this context, some individuals describe the suicide attempt as the culmination of tension, in which they try to resist an impulse as long as possible and then the impulsiveness takes over: "*I wondered if I didn't just do it because I couldn't think about it anymore*" (*personal communication*).

Other individuals do not develop a suicidal plan, but describe an impulsive suicidal moment or urge as an overwhelming and irrepressible desire[41], an unexpected impulsive moment of loss of control, so strong and inescapable that it cannot be contained: "*I felt like I did not have any control*" (*personal communication*). Impulsivity can override the natural instinct to preserve one's own life and render an individual capable of self-harm. Some authors maintain that painful experiences throughout lifetime (e.g., trauma and abuse) can override the fear of pain and death associated with suicide and consolidate a "capability" for death[76].

The experience of the self, agency and time in individuals who attempt suicide

Feeling unworthy

Individuals who have attempted suicide often describe how this experience is usually accompanied by a range of negative feelings, both about the world around them and about themselves: "*The trouble was, I had been inadequate all along; I simply hadn't thought about it*"[38]. Feelings of unworthiness ("*It's as if my life isn't worth anything… I didn't feel I was worth anything*"[63]), poor self-esteem and failure ("*I felt like I am just a loser. I wasn't good enough*"'[77]; "*This is who I am, a bad person. It would be easier if I were not here*"[78]) are frequently reported.

Some individuals may describe experiences of feeling unworthy because they are unable to live up to others' expectations: "*Shame crept in that I couldn't do life as everyone else, that I was weak and pathetic and then would sit in the shame for a couple of weeks and then the pain would get too much and then the [suicidal] thoughts would start again*" (*personal communication*).

A failed suicide attempt can itself be described in terms of feelings of incompetence, ineffectiveness and unworthiness. After a suicide attempt, individuals frequently describe a feeling of shame and embarrassment, as if their failure had exacerbated their feelings of inadequacy: "*I was told to be grateful to be alive as if I had been naughty… This just contributed to feeling more ashamed and thinking of ways to do 'better' when I attempt again*" (*personal communication*). These individuals may mention that they are not only unable to live satisfactorily, but even unable to attempt suicide effectively: "*Embarrassment is common after a suicide attempt that was unsuccessful. Certainly, my experience*" (*personal communication*).

Feeling detached from oneself or the world and lacking a sense of agency

Suicidal experiences may be accompanied by a feeling of being detached from oneself ("*I cannot touch my essential self*"[37]) or one's body ("*I spent a large part of my life living in dissociation, feeling like I was floating outside of my body and actually being connected to myself was too painful*"; "*Being in my body was unbearable, then suicide would creep in*", *personal communications*).

This can be a stable feature, which accompanies the period of life in which suicidal ideation and planning occur. Alternatively, it can be an episodic feeling that turns on suddenly or in response to specific triggers and then goes off ("*I had these, like, moments… I don't know, it's just where I don't feel like I'm myself, like I'm looking over myself*"[60,79]). In some cases, it can be associated with a sense of impulsiveness and loss of control, as described above.

The individual may report "*feeling dissociated from oneself*" (*personal communication*) during the attempt itself, as if he/she wasn't the one doing it. When it is especially pronounced, this sense of detachment may lead to an inability to experience any emotions, including psychological distress: "*I just didn't feel anything anymore*" (*personal communication*). These feelings may involve a sense of lacking agency (i.e., self-authorship of one's own thoughts and actions): "*I did not feel connected to myself, as if I was an automaton, and suicide was the natural response*"[56].

The sense of detachment may also relate to the external world, which is experienced as inaccessible, hostile or manipulative, and the individual may feel disconnected from others: "*I am immune to any stimuli, be they people, colours, tastes… I am separate from everything and everyone, detached and unable to interact*"[56].

Splitting the self between the decision to live or die

The lack of self-agency is sometimes experienced as a disconnectedness between different parts of the self: "*When I am feeling well, I have no awareness of any division of my self into parts. I just operate as a normal, functioning being. However, if I am experiencing suicidal thoughts… I seem to feel the dislocation…: my normal 'self' is quite sure that suicide is not a solution but… another entity within me is emitting [suicidal] thoughts*"[56]; "*My mind wants to kill myself – but my body won't let me*"[56].

Individuals may experience a visceral sense of a battle being fought between distinct parts of the self, associated with a sense of despair and a fear of carrying out the act, of feeling pain, of regret: "*There were two parts in me… to die or not to die… it was unbearable to be so divided*" (*personal communication*). The perceived internal battle may also affect the body: "*I physically tremble as the battle takes place inside… I spend hours fighting with myself*"[56].

Some people may state that the suicidal act is directed towards a hated part of the self[21]: "*I just wanted to kill that part of me that I can't stop hating*"; "*I wanted to kill the part of myself that was wrapped up in shame, a huge part of myself that I hated*" (*personal communications*). Indeed, S. Freud[80] suggested that individuals who attempt suicide may split their selves in two: trying to kill one part (what they have become) to preserve what they were (what goodness they had). Along these lines, the philosopher S. Critchley argues that we cannot kill our self but only the hated part of our self[70].

However, in many cases, the split of the self is not so well demarcated[81], to the point that individuals may want to live and die at the same moment: "*Choosing to live or to die makes no difference at this point*" (*personal communication*). The case was reported of a man who attempted suicide by throwing himself off a bridge and, when discovered by a passing policeman, refused to hang on to the rope that the policeman had thrown him until he was threatened to be shot: he did not experience the will to live or to die, he experienced both[82].

Perceiving an abortive and doomed future

In people who attempt suicide, past experiences of joy and pain may seem distant as if they belonged to someone else: "*Was I really that person capable of controlling his life?*" (*personal communication*). The present self may appear as impoverished and object-like when compared to whom the person once was: "*A total horror at what your life has become and a despair at ever getting back your old self*"[56].

The future is often perceived as abortive, impossible to visualize[83], and doomed: "*Not finding a path in my life for the future*"[61]; "*Had no purposes in life and do not imagine myself having a future*"[61]; "*If you are going to live, you must have something to live for or at least something to look forward to, and that I have never had and will never get. So, I see no reason why I should stay here then*"[27].

In the time that elapses between the decision and the suicide attempt, there may be a paradoxical re-organization of planning, as if the thought of death was to reconstitute a movement beyond the painful stagnation of the individual's existence[68]. While the anguish of suicidal planning is described as a moment of suspension that makes death present and eliminates the possibilities of change, the actual choice to die lets time flow again[30]: "*Everything was stagnant, but when I decided to kill myself, it was as if everything happened faster*"; "*The moment I decided to die, time started to flow again*" (*personal communications*).

The experience of emotions and the body in individuals who attempt suicide

Feeling overwhelmed by hopelessness and despair

Individuals who have attempted suicide often describe the experience of being overwhelmed by strong negative emotions, leaving them exhausted: "*What has taken me to the attempt was the negative emotions*" (*personal communication*). This is linked to the experience of losing control over one's mental state and being unable to cope with the emotional burden: "*Somehow, I lost all ability to regulate not only my emotions but my behavior as well… It was an alarmingly rapid and complete descent into hell*"[43].

The emotions most frequently described by individuals who attempted suicide are anger, sadness and despair: "*I felt distressed, sick of it all*"[62]; "*I felt so sad and so angry at myself that I wished for death*" (*personal communication*). However, the most dramatic experiences include a profound sense of overwhelming despair (*"unbearable suffering and anguish"*[84]) and the lack of any hope[85]. S. Kierkegaard[86] delivered an insightful description of this desperate state of mind, and D. Webb provided a personal account of how, due to absence of purpose, positive change may appear impossible: "*For me, hopelessness arises from an absence of meaningfulness. If I feel that my life is entirely without any meaning and purpose, and no hope of it ever being otherwise, then suicide becomes a progressively more and more logical and attractive option*"[41]. In this context, suicide is characterized as an attempt to escape unbearable emotions ("psychache")[87,88] when the individual has no hope about the future, rather than a primary movement towards death[89].

Feeling empty and drained of energy

Individuals who have attempted suicide often describe a feeling of exhaustion, both physical and psychological, linked to the difficulty of continuing to live with so much suffering: "*My attempt had nothing to do with how 'good' or 'bad' my life is. It came from being tired. Tired of being me, tired of pretending, tired of being depressed. The emotional pain we feel becomes physical and it feels like there is no light at the end of our tunnel*"[64].

Fatigue is a factor that further reduces future prospects and life plans and narrows individuals' horizons: "'*I don't have the energy to live for the sake of others; I want to live the way I want to. And that is to not live at all*"[64]. In some cases, this lack of energy may be experienced as a foretaste of death, the feeling "*of being like a corpse among living people*"[68].

Feeling alone

Individuals who have attempted suicide often describe how feeling alone plays a central role in the onset and development of suicidal ideation: "*When I was alone, those were the times when my suicidal thoughts returned*" (*personal communication*). Feelings of loneliness can trigger thoughts of death: "*Because of my feelings of loneliness, I felt that life was just very difficult… and so I thought of various ways of committing suicide*"[90].

People who have attempted suicide may also report that they felt abandoned and rejected by others: "*You're trying to reach out, and everybody is just walking away*"[77]. They often state that the suicide attempt could have been prevented if a loved one had been close by: "*So in all three times it happened because some people in my life decided not to be there any more… so that's what led to the suicidal thing*"[91].

The expression "thwarted belongingness"[92,93] has been used to indicate a psychologically painful mental state that results when the fundamental need for connectedness is unmet. It describes a profound sense of loneliness and social disconnection and, according to some authors, it represents one of the three core components of suicidal behavior, along with "capability" for death (addressed above) and "perceived burdensomeness" (addressed below)[92].

THE EXPERIENCE OF INDIVIDUALS WHO ATTEMPT SUICIDE IN THE SOCIAL AND CULTURAL CONTEXT

In this section, we will describe how individuals who attempt suicide experience their social and cultural surroundings through the following overarching domains: a) the experience of others in individuals who attempt suicide; b) cultural, gender and age differences in the experience of individuals who attempt suicide; and c) experiences of stigma in these individuals.

The experience of others in individuals who attempt suicide

Feeling that no one cares

As noted above, individuals who attempt suicide often experience feelings of hopelessness and unworthiness. They may think that they are not worthy of care, and no one will care when they are dead: "*It was something that would linger in my mind, … like who's going to notice… what difference is it going to make?*"[78]. These thoughts can involve the partner, family, friends, school or work colleagues. For example, individuals who have attempted suicide may describe a sense that their loved ones did not care and had abandoned them: "*My family slowly abandoned me*"[63].

Young individuals may feel that friends are awkward around the topic of suicide and may find it difficult to talk about it without feeling rejected: "*The few friends I retained from then get nervous if I ever try and talk about it with them*"[94]. They may also feel that schoolmates strongly disapprove their experiences: "*At one point I would have people at school… telling me, you're disgusting. And if someone tells you something enough, you start to believe it*"[78].

Regarding work colleagues, individuals attempting suicide may feel cut off from everyone or may express the feeling of not being cared for in relation to issues of efficacy and performance: "*My boss only cared about the results I brought home, not how bad I was. If I died his only thought would be to replace me*" (*personal communication*).

Feeling like a burden to others

As noted above, individuals who contemplate suicide may feel themselves to be unworthy of any kind of appreciation for their efforts or regard themselves as a burden to others[95]: "*I know that I am spoiling your life, that without me you could work. And you will I know*"[42]. V. Woolf, who took her life, wrote to her husband: "*I can no longer continue ruining your life*"[42]. In these cases, individuals may feel that their family does, in fact, care but should not care because of their unworthiness: "*I am sure my husband will be relieved by my death*" (*personal communication*).

While attachment to family and friends represents a protective factor, the perception of being a burden to others can foster suicidal intentions: "*I believed my existence was doing more harm to those around me than good. I believed the pain of dealing with my death would be temporary, but if I stayed, I would cause more harm to those I loved*"[64]; "*My family would be better off without me since my influence on their lives was negative*"[64].

In this perspective, suicide can be seen by the suicidal person as an act of altruism. When contemplating suicide, these individuals may expect that the pain of their family members or friends will be soon replaced by a sense of peace and relief: "*I truly believed I was doing what was best for my family. When people say that suicide is selfish, it bothers me. I can honestly say I wasn't thinking at all about myself*"[64].

According to some authors, the perception of being a burden to others (also termed "perceived burdensomeness") represents one of the three core components of suicidal behavior, along with "capability" for death and thwarted belongingness (defined above)[96].

Facing others' difficulty in understanding

One of the most painful challenges experienced after a failed suicide attempt can be dealing with the reactions of others. Some individuals may feel misunderstood, faced with the tendency to belittle the suffering that led to the suicide attempt: "*When you suffer so much, it's so disheartening when people just say: 'Really, are you depressed? No, I don't think so'*"[97]; or even "*Others… par-*

ents, doctors, etc., find it very hard to understand"[61]. The feelings, thoughts and actions of individuals who attempted suicide may be labelled as a form of weakness, unworthy of further understanding: "*'Ahh', they say, 'what a weak thing she was, she couldn't cope with it, couldn't deal with it herself!'*"[98].

Patronizing attitudes may exacerbate a sense of shame, fear of judgement, and inability to communicate one's feelings: "*Do you understand how much it hurts to be criticized for having this in our past? Do you know how much it hurts to be called 'selfish', 'stupid' and 'crazy'? If you have never had suicidal ideation, please do not place judgement on those of us who have*"[2]. Individuals who attempted suicide describe a very different need: "*We deserve help, not hate*"[2].

Individuals who attempt suicide may experience others as incapable of understanding their hopelessness behind suicidal thoughts: "*They don't understand the fact that the will of suicide is more than just a simple desire. Even though you try not to think about it, even though you don't want to do it, there is this strong and hopeless feeling of just… doing it*"[64]. In some cases, people who attempted suicide feel that their behavior is perceived as a danger to others, worsening their feelings of shame and unworthiness: "*I wish others understood I am not a danger to them. After my attempt, my friends kept me at arm's length rather than drawing close to me because they were afraid I would hurt them too. It left me feeling more isolated and rejected than ever*"[64].

The experience of not feeling understood can be particularly distressing when it relates to family members. Sometimes adolescents who attempt suicide perceive their parents' concerns but find them unprepared to handle the situation: "*I know for my parents they didn't really understand what I was going through… They didn't see the signs leading up to the attempt*"[99]. Overall, these feelings may substantially corroborate and amplify the experience of perceived burdensomeness described above.

Cultural, gender and age differences in the experience of individuals who attempt suicide

Experiencing geographical, cultural and religious taboos about suicide

Many individuals who have attempted suicide feel that, even in today's world, it is difficult to talk about suicide, because "*Suicide is still a taboo in society*" and "*We won't reach the point that it's a topic that you can really talk about*"[98]. This attitude makes individuals with suicidal thoughts feel even more alone. They describe various reasons for this persistent taboo, including geographical, cultural and religious factors that affect the shared perspective on suicide[100].

In some cultural contexts, suicide is experienced as unacceptable and unjustifiable: "*People think suicide or suicide attempt is not acceptable. Therefore, it should not be disclosed*"[101]; "*In African tradition, there is no room for suicide*" (*personal communication*). The experience of being judged negatively for attempting suicide is also commonly reported across different religions: "*According to my religion, if you commit suicide, then you will go to hell*" (*personal communication*); "*Suicide is forbidden among our people. It is not acceptable in sharia that I killed myself*"[101]. Therefore, religion can be experienced both as a protective factor for not committing suicide and a contributing factor to shame and stigma for those who have attempted suicide and their families.

On the other hand, there are some cultures in which suicide is instead conceived of as a respectful and dignified solution to life problems[102,103]: "*I just want to add that cultural aspect is not only about living taboo and stigmatizing but also living some values that get normalized or maybe even glorified the suicide, to the extent that it has been seen as a response whenever you have problems. So, it's what you have in some Asian countries like Japan, China, India*" (*personal communication*). For example, in certain socially-normed situations (e.g., associated with *Seppuku*, the ancient Samurai ritual of suicide by self-stabbing)[104], suicide may be idealized as a redeeming and dignified solution behavior from shame and guilt[103,105].

Feeling inadequate in relation to gender stereotypes

Enculturated gender roles can also play an essential part in shaping experiences of failure, uselessness and worthlessness that trigger suicide attempts. For example, in cultures where work and duty are traditionally gendered prerogatives of men, they can experience worthlessness relating to working roles: "*I began thinking that nothing is going to work out for me. I am a useless, unemployed 24-year-old man*"[106]. Feeling useless is, in this case, an expression of oppressive stereotypical norms that the suffering individual has internalized, and that have thus become part of his identity.

In other family-centered societies, women's experience of attempting suicide may be shaped by overarching societal conventions and family traditions: "*Our culture is so family-oriented! You can't do anything else than say what the family thinks. Like a puppet. And that's why many girls don't know how to get out of their situation because then they would stand there all alone!*"[98]; "*How can you continue to live if you have the sole purpose of being a mother and you cannot?*" (*personal communication*). In some areas of rural China, women who have no recourse to social control mechanisms against their husbands or husbands' families may resort to suicide as the most effective means of being heard[107].

There are also cultures in which suicide itself might be considered acceptable for women, who are viewed as more fragile creatures, but not for men, who are expected to be strong and overcome even the most adverse conditions[108]: "*People were saying, 'Is it right to do such a thing?' Can a man do such things? They insulted me in many different ways, using demeaning language… I felt like a circus animal. Friends and family members used to visit me and passed many comments. They said as a man, I should not have done it. This is a cowardly act*"[108].

Feeling abandoned in old age

The experience of attempting suicide can also take on differing characteristics across the lifespan. Older individuals who attempt suicide may feel particularly isolated, abandoned or a burden on their families: "*My family has everything that's needed, but doesn't help me and doesn't even visit me; I have no one to share anything with, who am I going to talk to?*"[109]. This type of suffering is exacerbated in situations of practical or financial family problems and conflicts, where the greater frailty of the elderly may not be understood: "*Sometimes a person doesn't treat you well, doesn't have any more patience*"[109].

The loss of a beloved relative, especially a spouse, is often described as the starting point of an experience of hopelessness and impossibility of seeing any future, leading to the suicide attempt: "*It was just one thing piling up on another. First, I lost my husband, then there was the loss of a brother-in-law, and in one year, I lost my three sons. That disturbed me a lot. I feel that I don't like life; I feel that from now on, everything will go wrong, and the energy to keep living is running out*"[109].

As noted above, worries about being a burden on others (perceived burdensomeness) can lead older individuals, particularly in some cultures[110,111], to view death as a dignified solution: "*The truth is that there's a lot of depression amongst the elderly and also the value that is better to preserve your dignity than asking for help to others in your old life, and culture approves that*" (*personal communication*).

Facing stigma in individuals who attempt suicide

Facing social stigma

Stigma is often described as one of the core aspects of the interpersonal experience of those who have attempted suicide, stemming from social or cultural factors: "*I will never, never, forget the judgement in their eyes… It got inside me*" (*personal communication*). One individual who attempted suicide, and whose father died by suicide, reported: "*What was making me angry, frustrated and a bit ratty, was all of the social context – cultural beliefs, attitudes, stigma, etc. and untrained (as well as trained) people's views and expectations that I was genetically tainted/pre-determined to have a mental illness/underprivileged existence*"[112].

Institutional discrimination is also frequently experienced, and may amplify feelings of unworthiness and loneliness: "*School shaming for having suicidal ideation and wanting to have [me] expelled from the school as a danger to the children around and the school's reputation*" (*personal communication*).

High levels of social stigma are often perceived as a barrier to open communication: "*Most people don't talk [about suicide] because they don't want to be thought of as someone who is ungrateful*" (*personal communication*). Individuals feel that other people often consider suicide as a weakness, as madness, or as an immoral act: "*Society treats you as if you are ungrateful if you commit suicide*" (*personal communication*). Consequently, individuals who attempt suicide frequently report an experience of loneliness (as described above), where others are not available to listen to their reasons. Following a suicide attempt, one person reported: "*So, I was kind of labelled. Everybody treated me like I was some fragile victim that they couldn't trust to do anything because they didn't know when I was going to fall apart*"[113].

Experiencing a stigmatized self

The stigma is sometimes internalized, leading individuals to perceive themselves as less valuable because of their mental suffering[114], and to conceal their personal suffering[115]: "*It's that whole stigma thing, in part… you don't officially want the system thinking that you are damaged goods ever, right?*"[116].

Individuals often describe difficulties in accepting their own experience of attempting suicide, judging it as a weakness, and end up hiding it from others: "*I did not want them to know. It is not acceptable for them. I did not say about suicide to someone. It is a negative point of me. Nobody accepts suicide. Any reason I give, they will say you should not do it! It's not justifiable*"[101].

Silencing suicidal behaviors

The intricate relationships between social stigma and self-stigma are particularly pronounced in young individuals who are defining their self-image and are forced to conceal their thoughts under a mask of fake happiness in order not to raise any suspicion: "*I constantly had suicidal thoughts, yet people knew me as the smiling girl who was friends with everyone, always happy. No one knew of my suicidal thoughts as I told no one*"[117].

Many individuals who attempted suicide describe an insurmountable difficulty in talking about their experience, along with the unavailability of individuals to listen to it. Silence around suicide is subjectively experienced as a main driver of stigma, hindering the ability to access support: "*It's the silence around suicide I believe hurts people the most*"[112]. Individuals who attempt suicide feel that most people consider suicide a subject that is best left untouched (e.g., because they may be afraid to make the individual more suicidal), with the result of making them even more alone and misunderstood: "*[It is difficult] talking about my problems and getting close to people*"[61].

THE LIVED EXPERIENCE AFTER AN ATTEMPTED SUICIDE

Living with suicidal thoughts

Individuals who have attempted suicide may realize that they were making a mistake and stop thinking about suicide, but, for others, suicidal thoughts remain for a prolonged and indefinite period. The thought of suicide in some cases may remain "*an option I am always thinking about*"[61], the possibility of a comforting escape route. In Binswanger's account of E. West, death and suicide are described as constant thoughts in the patient's life since childhood, associated with several attempts[68]. In some cases, the thought of suicide remains a latent threat, a temptation to resist, ready to emerge in moments of weakness: "*Yeah, it never really goes away. You'll have days where, yeah, it's better, but it's still there. Any one little setback, any one little thing can trigger it off into a spiral*"[62].

The persistence of suicidal thoughts is rarely described as a condition to which one becomes accustomed, but often as evidence of an irrevocable fate hanging over the person: "*Nothing I can do, it will happen in the future*"[118]. Experiencing suicidal thoughts can cause such suffering that it encourages the intention that the person is trying to resist: "*The suicidal thoughts are horrible. They eat me up inside. When I made the attempt... I just wanted to get away from my own suicidal thoughts*"[119]. Many individuals may find themselves "*stuck in a vicious circle and the only way out is to ask for help*" (*personal communication*) to cope with ongoing suicidal thoughts.

Navigating the challenges of recovery

The journey of recovery from an attempted suicide is "*not an easy one; it [is] physically painful and emotionally draining*"[94], a perilous pathway during which the individual restores a desire to live[26]. For a long part of this journey, the "*[suicidal] feeling never goes away; it is there at the back of my head all the time*"[120] and is amplified by loneliness: "*When I was alone, those were the times when my thoughts returned*" (*personal communication*).

The recovery process may be complex and lead individuals to confront their own limits and difficulties. During recovery, there may be moments when these individuals feel like giving up: "*Sometimes I feel lost, trapped... but now I know there is a way out and it does not involve leaving, it involves staying. Staying through the pain, the silence, and the darkness. No one said life would be easy, but it is worth it*"[94]. The dawning supporting thought is "*I want to get on my feet again, and I want to go forward*"[121].

Gaining new perspectives during recovery

Recovering from an attempted suicide is often enriched by gaining a deeper understanding of the helplessness and fear experienced and by a greater ability to "*recognize the need for help and reach out for it*"[117]. At the same time, a meaningful experience is that of adopting "*a different perspective, seeing things in a different, more positive way*"[122], stopping "*blaming everyone in my life for making me feel miserable*"[94], "*reprocessing all the horror that I went through, and some of the problems I even go through now, instead of playing the old tapes*"[123].

Individuals also begin to understand that they are responsible for how their life will be, and nobody can take that away from them[40]. Spirituality can also help in changing perspective, in learning to "*stop, sit, listen – to me and others – and be just now*"[123]: "*I am finding that the strength in that strongly disables the idea of any suicidal ideations*"[123].

Restoring interpersonal relationships to recover

Individuals who have attempted suicide may feel that interpersonal relationships and peer support are particularly supportive in the phases following the failed attempt. Interpersonal relationships encompass both professional and personal connections. Professionals, for example, "*gave [me] options*"[117] and "*help [me] think differently about myself and my circumstances*"[120]. Relationships with other individuals who attempted suicide also provide support, as it is comforting to know that "*there are other people like me*"[120] and that "*others have been through the same stuff that I went through but dealt with it better, had different ways of coping... it's made me realize that life is more precious really*"[90].

Relationships with friends and relatives are a crucial motivational driver: "*I've been thinking and... I have little kids who need me, and I can't waste my time thinking about stupid things like that*"[124]. Some individuals contemplating suicide may experience spiritual and existential crises that are not well captured by the mainstream medical approach. For these individuals, peer-led movements can be experienced as particularly valuable because they create spaces where people can openly explore their existential struggles without fear of judgement or coercion[125].

THE LIVED EXPERIENCE OF ACCESSING HEALTH CARE SERVICES IN INDIVIDUALS WHO ATTEMPT SUICIDE

In this section, we describe the experience of accessing general health care and mental health care services in individuals who attempt suicide.

The lived experience of accessing general health care

Seeking help before the suicide attempt

Individuals contemplating suicide can face significant difficulties in accessing general health care before the attempt. Some of them may feel emotionally dismissed by health care professionals when seeking help: "*I've gone to the doctor multiple times saying I'm suicidal and depressed, and they tried to put me on pills. And they didn't do anything for me, so I stopped taking them and then a few years later just tried to kill myself*"[62]. In some cases, they feel that health providers could have better understood their feelings and thus prevented their suicide attempt: "*If someone had taken the time to sit down with me and say, did you notice this, this and this?... They might have understood a bit better and been more acting about it*"[99].

Receiving poor care that is focused only on medical issues may elicit feelings of being "*ignored and overlooked*"[27], or not being considered as a human being ("*I often feel treated more like a patient than like a person*", *personal communication*), which often lead to a sense of resignation amplifying loneliness: "*At first I tried to communicate, tried to share my problems, but I noticed that nobody actually cared, nobody listened, nobody tried to get a deeper understanding. So I simply gave up; I stopped doing it*"[126].

The difficulty in accessing care and the feeling of not being listened to may discourage individuals from seeking help, triggering suicidal ideation: "*I sought professional help myself – but that was only very recently. I wish there had been some sort of counselling or service that offered me assistance... But it was not easy to access*"[2].

Feeling abandoned after a suicide attempt

When accessing and receiving general health care after suicidal crises, individuals often find themselves grappling with the stark reality of not getting the psychological help they need. Their experiences amplify the sense of self-degradation and disillusionment about the future: "*When you are down, it doesn't take much to get you further down; I never felt so degraded before*"[97].

A sentiment of mistrust and inadequacy towards health care professionals' understanding of mental health may prevail, especially when the clinician's and the patient's culture mismatch. For example, a clinician with a different cultural background may be perceived as uncaring: "*He didn't understand me... He can't put himself into my position, or he can't understand my culture!*"[99].

More generally, some individuals seeking help after suicidal crises feel that general health care professionals "*don't... know enough about the psyche*"[97]. Moreover, these individuals often experience professionals as having patronizing attitudes, a situation that may exacerbate feelings of frustration and disempowerment: "*I felt that they pampered me, talked to me like I was a child, and... a little sort of, 'poor little you'. That... attitude, annoyed me*"[97].

The lived experience of accessing mental health care

Experiencing shame as a barrier to care

Individuals who attempted suicide often describe stigma and fear of being labelled as weak or ungrateful as core barriers to access mental health care[125]: "*When you have suicidal thoughts, you think if you tell someone you're weak*"[61]. They are particularly concerned about societal labelling: "*Society treats you as if you are ungrateful if you commit suicide*" (*personal communication*). A participant from the military observed: "*If I would have known that this whole situation would have happened, there's no way I would have gone to mental health and there's no way I would have recommended it to anybody else either*"[113].

The feeling of shame which is described can be so pervasive as to prevent individuals from seeking mental health treatment: "*I am embarrassed to be here [in the hospital]. I didn't want anyone to know it. I didn't want to seek treatment. It's like a weakness*"[127]. In some cases, this can be so extreme that the individual may feel unworthy of receiving care and support: "*Feeling others deserved my place in hospital*" (*personal communication*).

Fearing mental disorder label

Sometimes, individuals who attempted suicide experience fear of mental health labelling ("*You are 100% labelled and referred to as high risk for suicide by professionals... when you have any medical history taken, it is highlighted that you tried to commit suicide and you are automatically flagged*", *personal communication*), and a lack of support from mental health care professionals ("*You almost feel like you are contagious and they [doctors and nurses] are more worried about it not happening on their watch so you get passed from person to person and medication to medication*", *personal communication*).

This experience is again modulated by cultural differences and prejudices, which influence how phenomena are narrated and evaluated: "*Turks, especially women, don't come to psychiatric services. Because I went to see a psychiatrist, now I'm labelled, I'll be considered a crazy person!*"[98]. An Iranian woman stated: "*I did not allow someone to know [my suicide attempt]. If someone knows what happened, he not only doesn't help me but also destroys my dignity. I do not want them to assume that I'm not normal, mad, or crazy*"[101]. Sometimes, the fear of being labelled as mentally unwell can even involve the family of the person who attempted suicide: "*God knows what people say about my family and me*"[101].

Feeling accepted and listened to

However, many individuals who access mental health care after a suicide attempt feel welcomed and emotionally understood by professionals[97,128]: "*Connection, being heard and having a positive human rapport with a health care professional changed my life. Having one person that hears the deepest darkest hole you are in, sits there with you, accepts it without trying to leave you feeling judged*" (*personal communication*).

These experiences mainly relate to surviving the suicidal attempt ("*When I was admitted to hospital after taking an overdose of medication, I woke up feeling relieved I was alive and also hopeful that now the pain would stop*", *personal communication*), receiving follow-up care ("*I know mostly what I have to do and hopefully it helps. Follow-up care is an important thing. [Otherwise] you could end up being readmitted, or you could end up in a box*"[117]), and getting support to reduce the risk of relapse ("*It's something that I need to prevent me from being suicidal*"[117]).

This positive emotional response often stems from perceiving providers as attentive listeners who are "*much more curious about me, not just rubber-stamping me and signing me off*"[118]. For these individuals, "*It is very important to feel that someone understands what I am feeling*"[120]. What truly seems to make a difference is encountering a genuinely interested mental health professional[122,124], "*someone [who] cared whether I lived or not*"[118], who engages deeply in conversation[95]. Experiencing this kind of therapeutic relationship allows these individuals to "*talk to someone freely and openly and just get it all out and be able to have someone tell you that you know it's OK, it's OK for you to feel like that*"[129].

Facing economic difficulties in accessing support

Several individuals who attempt suicide face significant economic barriers in accessing mental health care, particularly in low- or middle-income countries: "*Psychologists cost a lot of money and a lot of people cannot afford it*"[77]. Such financial strains may be compounded by isolation, marginalization and systemic inequalities, preventing individuals from receiving essential psychological support, and leaving them vulnerable to further mental health crises. Economic stability can intertwine with a sense of hope: "*If I have a stable ground to stand on [economically] and I can get more help, or help in a different way, at the same time as I motivate myself to work harder with my situation, there is a possibility that things might get better*"[64].

Beyond economic difficulties, there can be broader structural determinants impeding access to mental health care: "*Economic and political determinants, e.g., capitalism in high-income contexts and reducing welfare state resulting in more unequal societies*" (*personal communication*). As a consequence, both the public and private mental health sectors can be perceived as presenting barriers to access and ongoing complex and inefficient pathways to care: "*In my experience, they are not fit for purpose, in terms of mental health… in the public system they can't wait to get rid of you, and in the private sector they can't wait to hospitalize you, because of how expensive it is*" (*personal communication*).

Coping with distress during hospitalization

For some individuals who attempted suicide, the experience of being hospitalized in a psychiatric ward is traumatic and exacerbates their mental distress. Some of these individuals do not want to go to a "crazy hospital"; they fear what might happen, such as receiving coercive medication[97]. Common feelings include isolation and a lack of connection with ward staff: "*I felt that I couldn't get close to him [the therapist], or he couldn't get close to me, I suppose*"[97].

This lack of rapport often leads to a sense of hopelessness and disengagement from the therapeutic process: "*I had no strength, and it was like I had lost so much energy, my ray of hope, and belief in the system*"[97]. Furthermore, it may fuel a feeling of having no autonomy or control over their treatment and being "*locked in, you don't decide by yourself whether you go out, and you don't decide by yourself whether to be discharged, and they can define what they want within a frame where it is not visible to many others*"[122]. These negative hospitalization experiences may actually deter some individuals from future suicide attempts: "*I wouldn't try to do that again because being in here is nothing good. Being in here is like if you will be in prison*"[130].

DISCUSSION

The principal aim of this paper was to give voice to individuals who have faced the experience of attempting suicide. We have followed and transcribed these individuals' lived, learned and laboured experiences of exhaustion, suffering, and their desperate attempts to be heard and to seek help. This paper, as our previous ones published in this journal, ultimately belongs to all individuals who directly or indirectly contributed to it, to their families and carers.

Through this lived experience series, our objective is to bring out and consolidate a co-design, co-production and co-writing approach, which integrates the perspectives of experts by experience and academics in order to get a better understanding of human behavior. Psychiatry cannot ignore the unfolding lived experiences of the individuals assessed and treated[18]. Instead, it should allow personal insights to emerge, minimizing the exclusion and misrepresentation of individuals' subjective perspectives[60,131].

Unfortunately, the trend in recent decades has been for the phenomenology of suicidality to almost disappear from the research agenda of the discipline[64]. In this context, it is essential to clarify that this paper does not aim to test researchers' hypotheses or present exhaustive lists of lived experiences. On the contrary, the paper shows that there is no such thing as a universal and unequivocal experience of attempting suicide[56]. Experiences of being suicidal are complicated and interrelated and cannot be understood from only one perspective, whether this is the dominant narrative or not. We are required to remain open-minded about the different ways by which individuals might view and express their unique experiences of attempting suicide[36].

As the experiences of attempting suicide are very different from one to another, it is very difficult to find common elements across them. The uniqueness of suicide corresponds to events, stories and meanings that are so heterogeneous in time and space that one doubts the possibility of placing all these phenomena in the same container[13]. Suicide remains a behavior, and, as such, a complex and multi-determined event: an identical behavior may constitute the point of arrival of very different paths[13]. We have thus allowed the emergence of different perspectives, favoring a person-centered approach over a disorder-centered one[132] and qualitatively analyzed the testimonies of individuals who attempted suicide in a transdiagnostic (i.e., across multiple mental disorders) and transversal (i.e., outside psychiatry, including accounts of philosophers) way. In this context, the importance of talking about suicide remains firm over time, as the philosopher A. Camus wrote: "There is but one truly serious philosophical problem and that is suicide"[133].

This approach allowed us to observe that, despite the underlying heterogeneity, many experiences of attempting suicide share core themes, which together comprise a radical change in the lived world. The experience of attempting suicide is often characterized by different phases, starting from contemplating suicide as a deliberate death or as an escape route, during which individuals may search responses in the online digital world, followed by a phase of suicide planning. Individuals who attempt suicide frequently describe finding rest between the suicidal decision and the final act, with ongoing experiences. There are also experiences of changing one's mind during the suicide attempt. Some degree of impulsiveness is almost always involved in triggering the movement from suicidal plans to action. In some cases, the planning phases may be entirely replaced by impulsive behaviors, and the final act is carried out via a rash decision, with little consideration of the severe negative consequences.

Individuals also report an altered experience of self and time, which is characterized by feeling unworthy and detached from oneself and/or the world, together with a lack of agency and a split of the self between the decision to live or die, and a perception of an abortive and doomed future. Finally, changes in the experience of emotions and the body include feeling overwhelmed by hopelessness and despair, feeling empty and drained of energy, and feeling alone.

As noted above, these lived experiences should not be interpreted as separate phenomenological components but as inextricable aspects of a unitary experience of an altered suicidal world, which emerges as an existential change and impacts the sense of the self and the surrounding environment[134,135]. Ultimately, these experiences alter the vital feeling of being immersed in the lived world[135] and integrate self, body, time, emotions and values[136].

The feeling of being suicidal is, therefore, what M. Ratcliffe[137] calls an "existential feeling", a way of finding oneself in the world that provides a variable but always present structure to the experiences of self and world. In this sense, Benson and colleagues suggest that individuals often do not choose or want to attempt suicide, in any familiar sense of "intention", "choice" or "desire"[56]. Instead, the whole experience of being an agent and acting within a world is radically altered in a way that involves changes in one's experience of the entire world[30]. One of the characteristic changes is a loss of the capacity for hope, an existential re-orientation that eradicates the very basic possibility of hoping for anything (i.e., the "ground of hope"[138]).

We also found that the existential shift experienced by many individuals who attempt suicide can be described not only in terms of the lived world, body and experience of time, but also of interpersonal experiences[135,139]. Interpersonal experiences among those who attempt suicide include feeling that no one cares, feeling like a burden to others, and facing others' difficulties in understanding. Interpersonal relationships are often reported as a source of frustration and misunderstanding related to feelings of being abandoned and criticized.

We also found a high variability of lived experiences across cultural and religious contexts, genders and ages. Different cultures at different moments in history have constructed suicide differently to a point where it is not so clear that there is one thing that can be called suicide[140]. Our study of lived experiences confirms that suicide is a socially and culturally embedded, temporally extended process involving suicidal ideations, communication of such intents, suicide attempts, and implicit and explicit negotiations with others about their meanings[141].

Our first-person accounts also indicate that social responses to suicidal experiences and behaviors take shape within a repertoire of local beliefs and practices[142]. For example, while suicide has been regarded as an act of honour throughout Japanese history, it has been mostly considered a sin and a crime, being completely rejected from a moral point of view, in Western history up until the Enlightenment[105,143,144]. An experience reported by many individuals who have attempted suicide is pervasive cultural and social discrimination, including negative attitudes that silence suicidal behaviors. These findings suggest that some "cultural humility" is always necessary when speaking about suicide – an ongoing process of self-reflection and exploration in which we examine our own beliefs and cultural identities and learn about those of others.

Finally, we described how some individuals who attempt suicide experience general and mental health care. Suicide often involves the intervention not only of mental health specialists but also of general practitioners and emergency room doctors. The experience of accessing general health care is characterized by difficulties in seeking help before a suicide attempt and frequent feelings of not receiving help after a suicide attempt. The experience of accessing mental health care may include negative aspects (such as experiencing shame as a barrier to care, fearing the label "mental disorder", coping with distress during hospitalization, and facing economic difficulties accessing support) as well as positive facets, such as feeling accepted and listened to. These mixed feelings modulate the lived experience after an attempt. Recovery itself is generally reported as a challenging process of self-acceptance and empowerment, in which individuals become able to live with suicidal thoughts, gaining new perspectives upon their suffering and life purposes, and restoring interpersonal relationships.

This study has some limitations. First, we did not aim to systematically address causes, risks and models of suicide, historical developments, or relevant philosophical or ethical frameworks, given that these dimensions of suicide are already investigated by empirical suicidology studies. Second, the study did not rely on a systematic review of all possible experiences presented by individuals who have attempted suicide. Third, any qualitative meta-synthesis not based on quantitative data allows for and demands some degree of co-interpretation by the writing team. First-person accounts themselves are not just bare, context-free reports of experience, but presuppose and draw upon concepts, narratives and practices into which individuals are enculturated. Our study is attentive to the existence of such differences, seeks to identify at least some of them, and provides a methodological and conceptual foundation from which to pursue more detailed and wide-ranging studies of cross-cultural and other differences.

This study has some direct practical implications. Understanding the lived experiences of those affected by suicidality has the potential to inform the innovation of clinical practice and public health and promote meaningful social change[145].

In clinical practice, our first-person perspective and phenomenological approach can be of help in the clinical relationship to clarify several complex emotional states underlying the experience of attempting suicide[28]. When faced with a person who is contemplating suicide, good care and phenomenologically informed practices should be first and foremost based on understanding what is like to have that experience and how meeting supportive professionals can make a difference. Improving the understanding of the lived world of individuals who attempt suicide, this study is proposed as a powerful educational tool to train health care professionals.

The lived narratives reviewed here also provide invaluable information that can help develop public health policies targeting the general population. For example, this paper can facilitate a non-judgemental comprehension of survivor experiences and assist policy makers and educators in providing effective psychoeducation and informed support. Similarly, family members can use the findings of this study to better understand and support their suicide survivors.

At a societal level, a wide dissemination of our study, mediated by experts by experience and family organizations, has the potential to reduce stigma and facilitate the communication and acceptance of these hard-to-communicate experiences, reducing cultural and social discrimination and loneliness in many fragile individuals[146,147].

We believe that understanding the lived experience of individuals who attempt suicide is an indispensable prerequisite not only for good clinical practice, but also for good and fairer societies. Hence, this paper has sought to move away from the academic complexities of traditional phenomenological and philosophical studies and to be accessible to many people.

This journey in the lived experience of individuals attempting suicide overcomes embarrassment, fear and stigma, helping to understand the fragile nature of our own emotions and feelings, our immersion in the social world and our sense of meaning in life.

ACKNOWLEDGEMENT

P. Fusar-Poli and C.M. Esposito contributed equally to this work.

REFERENCES

1. World Health Organization. Suicide. https://www.who.int/news-room/fact-sheets/detail/suicide.
2. Shamsaei F, Yaghmaei S, Haghighi M. Exploring the lived experiences of the suicide attempt survivors: a phenomenological approach. Int J Qual Stud Health Well-being 2020;15:1745478.
3. Pompili M. Phenomenology of suicide. Unlocking the suicidal mind. New York: Springer, 2018.
4. Turecki G, Brent DA, Gunnell D et al. Suicide and suicide risk. Nat Rev Dis Primers 2019;5:74.
5. Pompili M. Evidence-based practice in suicidology. Florence: Hogrefe, 2010.
6. Hawton K, Lascelles K, Pitman A et al. Assessment of suicide risk in mental health practice: shifting from prediction to therapeutic assessment, formulation, and risk management. Lancet Psychiatry 2022;9:922-8.
7. World Health Organization. Suicide data. https://www.who.int/teams/mental-health-and-substance-use/data-research/suicide-data.
8. International Association for Suicide Prevention. Global suicide statistics. https://www.iasp.info/wspd.
9. Lovero KL, Dos Santos PF, Come AX et al. Suicide in global mental health. Curr Psychiatry Rep 2023;25:255-62.
10. Freeman A, Mergl R, Kohls E et al. A cross-national study on gender differences in suicide intent. BMC Psychiatry 2017;17:234.
11. Berrios GE, Mohanna M. Durkheim and French psychiatric views of suicide during the 19th century: a conceptual history. Br J Psychiatry 1990;156:1-9.
12. Ronald M. Comprehensive textbook of suicidology. New York: Guilford, 2000.
13. Rossi Monti M, D'Agostino A. Il suicidio. Rome: Carocci, 2012.
14. Bachmann S. Epidemiology of suicide and the psychiatric perspective. Int J Environ Res Public Health 2018;15:1425.
15. Knipe D, Padmanathan P, Newton-Howes G et al. Suicide and self-harm. Lancet 2022;399:1903-16.
16. Bertolote JM, Fleischmann A. Suicide and psychiatric diagnosis: a worldwide perspective. World Psychiatry 2002;1:181-5.
17. Sutar R, Kumar A, Yadav V. Suicide and prevalence of mental disorders: a systematic review and meta-analysis of world data on case-control psychological autopsy studies. Psychiatry Res 2023;329:115492.
18. Jaspers K. Der philosophische Glaube. Zürich: Artemis, 1948.
19. Cavanagh JT, Carson AJ, Sharpe M et al. Psychological autopsy studies of suicide: a systematic review. Psychol Med 2003;33:395-405.
20. Prawira B. Preventing copycat suicide. Inside Indonesia, July 24, 2020.
21. French M. Death awaits me: an existential phenomenology of suicide. Eidos J Philos Cult 2020;4:70-89.
22. Jacobson C, Batejan K, Kleinman M et al. Reasons for attempting suicide among a community sample of adolescents. Suicide Life Threat Behav 2013;43:646-62.
23. Abbas MJ, Mohanna MA, Diab TA et al. Why suicide? The analysis of motives for self-harm. Behav Cogn Psychother 2018;46:209-25.
24. May AM, Pachkowski MC, Klonsky ED. Motivations for suicide: converging evidence from clinical and community samples. J Psychiatr Res 2020;123:171-7.
25. Orbach I. Taking an inside view: stories of pain. In: Michel K, Jobes DA (eds). Building a therapeutic alliance with the suicidal patient. Washington: American Psychological Association, 2011:111-28.
26. Lakeman R, FitzGerald M. How people live with or get over being suicidal: a review of qualitative studies. J Adv Nurs 2008;64:114-26.
27. Knizek BL, Hjelmeland H. To die or not to die: a qualitative study of men's suicidality in Norway. BMC Psychiatry 2018;18:263.
28. Madeira L, Miranda AT. A narrative review of suicide: aiming at a more encompassing understanding. Philosophies 2021;6:74.
29. Mrozynski H, Kuhn E. Reasoning for autonomous suicide? A qualitative approach to pre-suicidal decision-making. Soc Sci Med 2022;296:114764.
30. Ballerini AC. Psicopatologia e suicidio. In: Ballerini A, Callieri B (eds). Breviario di psicopatologia. La dimensione umana nella sofferenza mentale. Milan: Feltrinelli, 1996:13-22.
31. Fusar-Poli P, Estradé A, Stanghellini G et al. The lived experience of psychosis: a bottom-up review co-written by experts by experience and academics. World Psychiatry 2022;21:168-88.
32. Fusar-Poli P, Estradé A, Stanghellini G et al. The lived experience of depression: a bottom-up review co-written by experts by experience and academics. World Psychiatry 2023;22:352-65.
33. Fusar-Poli P, Estradé A, Esposito CM et al. The lived experience of mental disorders in adolescents: a bottom-up review co-designed, co-conducted and co-written by experts by experience and academics. World Psychiatry 2024;23:191-208.
34. Fusar-Poli P, Estradé A, Mathi K et al. The lived experience of postpartum depression and psychosis in women: a bottom-up review co-written by experts by experience and academics. World Psychiatry 2025;24:32-45.
35. Artaud A. Van Gogh, the man suicided by society. London: Vauxhall, 2019.
36. Améry J. On suicide: a discourse on voluntary death. Bloomington: Indiana University Press, 1999.
37. Kane S. 4.48 Psychosis. Bloomsbury: Bloomsbury Methuen Drama, 2000.
38. Plath S. The bell jar. New York: Harper, 2006.
39. Pavese C. This business of living. London: Routledge, 2009.
40. Morselli G. Dissipatio H.G. Milan: Adelphi, 2012.
41. Webb D. Thinking about suicide: contemplating and comprehending the urge to die. Monmouth: PCCS Books, 2013.
42. Woolf V. 'Dearest, I feel certain I am going mad again': the suicide note of Virginia Woolf. Cambridge: Cambridge University Press, 2018.
43. Linehan M. Building a life worth living: a memoir. New York: Random House, 2020.
44. Hamza CA, Stewart SL, Willoughby T. Examining the link between nonsuicidal self-injury and suicidal behavior: a review of the literature and an integrated model. Clin Psychol Rev 2012;32:482-95.
45. Favril L, Yu R, Uyar A et al. Risk factors for suicide in adults: systematic review and meta-analysis of psychological autopsy studies. Evid Based Ment Health 2022;25:148-55.

46. Marsh I. Suicide: Foucault, history and truth. Cambridge: Cambridge University Press, 2010.
47. Fässberg MM, Cheung G, Canetto SS et al. A systematic review of physical illness, functional disability, and suicidal behaviour among older adults. Aging Ment Health 2016;20:166-94.
48. Braum V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006;3:77-101.
49. Smith JA, Flowers P, Larkin M. Interpretative phenomenological analysis: theory, method and research. London: Sage, 2021.
50. de Serpa OD Jr, Leal EM, Muñoz NM. The centrality of narratives in the mental health clinic, care and research. Philos Psychiatry Psychol 2019;26:155-64.
51. Estradé A, Onwumere J, Venables J et al. The lived experiences of family members and carers of people with psychosis: a bottom-up review co-written by experts by experience and academics. Psychopathology 2023;56:371-82.
52. Broome MR. The Maudsley reader in phenomenological psychiatry. Cambridge: Cambridge University Press, 2012.
53. Stanghellini G, Broome M, Raballo A et al (eds). The Oxford handbook of phenomenological psychopathology. Oxford: Oxford University Press, 2019.
54. National Institute for Health and Care Excellence. Payments guidance for researchers and professionals. London: National Institute for Health and Care Excellence, 2022.
55. Wolk-Wasserman D. Suicidal communication of persons attempting suicide and responses of significant others. Acta Psychiatr Scand 1986;73:481-99.
56. Benson O, Gibson S, Brand SL. The experience of agency in feeling of being suicidal. J Conscious Stud 2013;20:56-79.
57. Holmes EA, Crane C, Fennell MJ et al. Imagery about suicide in depression – "flash-forwards"? J Behav Ther Exp Psychiatry 2007;38:423-34.
58. Marsh I, Marzano L, Mosse D et al. First-person accounts of the processes and planning involved in a suicide attempt on the railway. BJPsych Open 2021;7:e39.
59. Norman H, Marzano L, Winter R et al. Factors prompting and deterring suicides on the roads. BJPsych Open 2023;9:e81.
60. Pompili M. On mental pain and suicide risk in modern psychiatry. Ann Gen Psychiatry 2024;23:6.
61. Conner KR, Kearns JC, Denneson LM. Qualitative analysis of hospital patient narratives of warning signs on the day of their suicide attempt. Gen Hosp Psychiatry 2022;79:146-51.
62. Holliday C, Vandermause R. Teen experiences following a suicide attempt. Arch Psychiatr Nurs 2015;29:168-73.
63. Ribeiro DB, Terra MG, Soccol KL et al. Reasons for attempting suicide among men who use alcohol and other drugs. Rev Gaucha Enferm 2016;37:e54896.
64. SanctionedSuicide. Forums. https://sanctioned-suicide.net/threads.
65. Wahid SS, Ottman K, Bohara J et al. Adolescent perspectives on depression as a disease of loneliness: a qualitative study with youth and other stakeholders in urban Nepal. Child Adolesc Psychiatry Ment Health 2022;16:51.
66. Pavulans KS, Bolmsjö I, Edberg AK et al. Being in want of control: experiences of being on the road to, and making, a suicide attempt. Int J Qual Stud Health Well-being 2012;7.
67. Ridge D, Smith H, Fixsen A et al. How men step back – and recover – from suicide attempts: a relational and gendered account. Sociol Health Illn 2021; 43:238-52.
68. Binswanger L. The case of Ellen West: an anthropological-clinical study. In: May R, Angel E, Ellenberger HF (eds). Existence. New York: Basic Books, 1958: 237-364.
69. Heisman M. Mitchell Heisman suicide note. https://archive.org/details/Mitchell-HeismanSuicideNote/page/n7/mode/2up
70. Chritchley S. Notes on suicide. London: Fitzcarraldo, 2015.
71. Jaspers K. Allgemeine Psychopathologie. Berlin: Springer, 1913.
72. Barber ME, Marzuk PM, Leon AC et al. Aborted suicide attempts: a new classification of suicidal behavior. Am J Psychiatry 1998;155:385-9.
73. Wayland S, McKay K, Maple M. How is participating in suicide prevention activities experienced by those with lived and living experiences of suicide in Australia? A qualitative study. Int J Environ Res Public Health 2020;17:4635.
74. Aggarwal S, Patton G, Bahl D et al. Explanatory style in youth self-harm: an Indian qualitative study to inform intervention design. Evid Based Ment Health 2020;23:100-6.
75. Ariapooran S, Khezeli M, Janjani P et al. Protective factors against suicide attempt in Iranian Kurdish women: a qualitative content analysis. BMC Psychiatry 2023;23:58.
76. Chu C, Buchman-Schmitt JM, Stanley IH et al. The interpersonal theory of suicide: a systematic review and meta-analysis of a decade of cross-national research. Psychol Bull 2017;143:1313-45.
77. Ferlatte O, Oliffe JL, Salway T et al. Using photovoice to understand suicidality among gay, bisexual, and two-spirit men. Arch Sex Behav 2019;48:1529-41.
78. Marzetti H, McDaid L, O'Connor R. "Am I really alive?": understanding the role of homophobia, biphobia and transphobia in young LGBT+ people's suicidal distress. Soc Sci Med 2022;298:114860.
79. Marzetti H, McDaid L, O'Connor R. A qualitative study of young people's lived experiences of suicide and self-harm: intentionality, rationality and authenticity. Child Adolesc Ment Health 2023;28:504-11.
80. Freud S. Contributions to a discussion on suicide. In: Strachey J (ed). The standard edition of the complete psychological works of Sigmund Freud. New York: Vintage Editions, 1999;11:231-2.
81. Stengel E. Suicide and attempted suicide. London: Penguin Books, 1964.
82. Weiss JMA. Il paziente suicida. In: Arieti S (ed). Manuale di psichiatria. Turin: Boringhieri, 1980:480-95.
83. Szuła A, Moskalewicz M, Stanghellini G. Transdiagnostic Assessment of Temporal Experience (TATE) in mental disorders – empirical validation and adaptation of a structured phenomenological interview. J Clin Med 2024;13:4325.
84. Sousa AR, Machuca-Contreras FA, Morais AVC et al. Biographical ruptures by the COVID-19 pandemic on adolescent and young trans men and transmasculine people: demands for nursing. Rev Lat Am Enfermagem 2022;30(spe): e3753.
85. Pompili M. The increase of suicide rates: the need for a paradigm shift. Lancet 2018;392:474-5.
86. Kierkegaard S. Sygdommen til Døden. Kjøbenhavn: Reitzel, 1849.
87. Schneidman E. Suicide as psychache: a clinical approach to self-destructive behavior. J Nerv Ment Dis 1993;181:145-7.
88. Schneidman E. The psychological pain assessment scale. Suicide Life-Threat Behav 1999;29:287-94.
89. Pompili M, Innamorati M, Erbuto D et al. High depression symptomatology and mental pain characterize suicidal psychiatric patients. Eur Psychiatry 2022;65:e54.
90. Gajwani R, Larkin M, Jackson C. "What is the point of life?": an interpretative phenomenological analysis of suicide in young men with first-episode psychosis. Early Interv Psychiatry 2018;12:1120-7.
91. Littlewood DL, Gooding P, Kyle SD et al. Understanding the role of sleep in suicide risk: qualitative interview study. BMJ Open 2016;6:e012113.
92. Joiner T. Why people die by suicide. Boston: Harvard University Press, 2005.
93. Silva C, Ribeiro JD, Joiner TE. Mental disorders and thwarted belongingness, perceived burdensomeness, and acquired capability for suicide. Psychiatry Res 2015;226:316-27.
94. Keefner T, Minton M, Antonen K. Embracing emotional pain: a case study of adolescent suicidality and spirituality. J Am Psychiatr Nurses Assoc 2024; 30:397-408.
95. Van Orden KA, Witte TK, Cukrowicz KC et al. The interpersonal theory of suicide. Psychol Rev 2010;117:575-600.
96. Lieberman A, Gai AR, Rogers ML et al. Targeting perceived burdensomeness to reduce suicide risk. Behav Ther 2023;54:696-707.
97. Vatne M, Nåden D. Patients' experiences in the aftermath of suicidal crises. Nurs Ethics 2014;21:163-75.
98. Heredia Montesinos A, Aichberger MC, Temur-Erman S et al. Explanatory models of suicidality among women of Turkish descent in Germany: a focus group study. Transcult Psychiatry 2019;56:48-75.
99. Watling DP, Preece MHW, Hawgood J et al. Developing a post-discharge suicide prevention intervention for children and young people: a qualitative study of integrating the lived-experience of young people, their carers, and mental health clinicians. Child Adolesc Psychiatry Ment Health 2022;16:24.
100. Reyes-Foster B. The devil made her do it: understanding suicide, demonic discourse, and the social construction of "health" in Yucatan, Mexico. J Relig Violence 2013;1:363-81.
101. Azizpour M, Taghizadeh Z, Mohammadi N et al. Being at the center of attention: Iranian women's experience after suicide attempts. Perspect Psychiatr Care 2019;55:445-52.
102. Creese H. Ultimate loyalties. The self-immolation of women in Java and Bali. Journal of the Humanities and Social Sciences 2001;157:131-66.
103. Kitanaka J. Diagnosing suicides of resolve: psychiatric practice in contemporary Japan. Cult Med Psychiatry 2008;32:152-76.
104. Pierre JM. Culturally sanctioned suicide: euthanasia, seppuku, and terrorist martyrdom. World J Psychiatry 2015;5:4-14.
105. Russell R, Metraux D, Tohen M. Cultural influences on suicide in Japan. Psychiatry Clin Neurosci 2017;71:2-5.
106. Parkar SR, Dawani V, Weiss MG. Gender, suicide, and the sociocultural context of deliberate self-harm in an urban general hospital in Mumbai, India. Cult Med Psychiatry 2008;32:492-515.
107. Manning J. Suicide: the social causes of self-destruction. Charlottesville: Uni-

versity of Virginia Press, 2020.
108. Khan AR, Ratele K, Arendse N. Men's reflections on postsuicide attempt episode in Bangladesh. Omega 2021;84:582-95.
109. da Silva RM, Mangas RM, Figueiredo AE et al. The influence of family problems and conflicts on suicidal ideation and suicide attempts in elderly people. Cien Saude Colet 2015;20:1703-10.
110. Nurdiyanto FA, Jaroah S. The characteristics of suicide in Gunungkidul Indonesia. Disease Prevention and Public Health Journal 2020;14:69.
111. Andari S. Fenomena Bunuh Diri di Kabupaten Gunung Kidul. Sosio Konsepsia 2017;7:92-108.
112. Sanford RL, Frey LM, Thind N et al. Unpacking the meaning of closeness, reconsidering the concept of impact in suicide exposure, and expanding beyond bereavement: "Just, I hope you don't forget about us". Omega 2023; doi: 10.1177/00302228231196616.
113. LeFeber TP, Solorzano B. Putting suicide policy through the wringer: perspectives of military members who attempted to kill themselves. Int J Environ Res Public Health 2019;16:4274.
114. Boyd JE, Adler EP, Otilingam PG et al. Internalized Stigma of Mental Illness (ISMI) scale: a multinational review. Compr Psychiatry 2014;55:221-31.
115. Pompili M, Mancinelli I, Tatarelli R. Stigma as a cause of suicide. Br J Psychiatry 2003;183:173-4.
116. Denneson LM, Teo AR, Ganzini L et al. Military veterans' experiences with suicidal ideation: implications for intervention and prevention. Suicide Life Threat Behav 2015;45:399-414.
117. Maple M, McKay K, Sanford R. The attempt was my own! Suicide attempt survivors respond to an Australian community-based suicide exposure survey. Int J Environ Res Public Health 2019;16:4549.
118. Espeland K, Loa Knizek B, Hjelmeland H. Lifesaving turning points: first-person accounts of recovery after suicide attempt(s). Death Stud 2023;47:550-8.
119. Clark KA, Salway T, McConocha EM et al. How do sexual and gender minority people acquire the capability for suicide? Voices from survivors of near-fatal suicide attempts. SSM Qual Res Health 2022;2:100044.
120. Cutcliffe JR, Stevenson C, Jackson S et al. A modified grounded theory study of how psychiatric nurses work with suicidal people. Int J Nurs Stud 2006;43:791-802.
121. Herrestad H, Biong S. Relational hopes: a study of the lived experience of hope in some patients hospitalized for intentional self-harm. Int J Qual Stud Health Well-being 2010;5:10.3402/qhw.v5i1.4651.
122. Hagen J, Loa Knizek B, Hjelmeland H. " … I felt completely stranded": liminality and recognition of personhood in the experiences of suicidal women admitted to psychiatric hospital. Int J Qual Stud Health Well-being 2020;15:1731995.
123. Lusk J, Dobscha SK, Kopacz M et al. Spirituality, religion, and suicidality among veterans: a qualitative study. Arch Suicide Res 2018;22:311-26.
124. Michaud L, Dorogi Y, Gilbert S et al. Patient perspectives on an intervention after suicide attempt: the need for patient centred and individualized care. PLoS One 2021;16:e0247393.
125. Inner Compass Initiative. Alternatives to suicide (Alt2Su). www.theinnercompass.org.
126. Dadašev S, Skruibis P, Gailienė D et al. Too strong? Barriers from getting support before a suicide attempt in Lithuania. Death Stud 2016;40:507-12.
127. Riblet N, Shiner B, Scott R et al. Exploring psychiatric inpatients' beliefs about the role of post-discharge follow-up care in suicide prevention. Mil Med 2019; 184:e91-100.
128. Berg SH, Rørtveit K, Walby FA et al. Shared understanding of resilient practices in the context of inpatient suicide prevention: a narrative synthesis. BMC Health Serv Res 2022;22:967.
129. McGill K, Hackney S, Skehan J. Information needs of people after a suicide attempt: a thematic analysis. Patient Educ Couns 2019;102:1119-24.
130. Hausmann-Stabile C, Gulbas L, Zayas LH. Treatment narratives of suicidal Latina teens. Arch Suicide Res 2018;22:165-72.
131. Kidd IJ, Medina J, Pohlhaus G. The Routledge handbook of epistemic injustice. London: Routledge, 2017.
132. Fulford KWM, Handa A. New resources for understanding patients' values in the context of shared clinical decision-making. World Psychiatry 2021;20:446-7.
133. Camus A. The myth of Sisyphus. Paris: Gallimard, 1942.
134. Stanghellini G, Mancini M. The therapeutic interview in mental health. a values-based and person-centered approach. Cambridge: Cambridge University Press, 2017.
135. Schutz A, Luckman T. The structures of the life-world. Evanston: Northwestern University Press, 1989.
136. Fulford KW. The value of evidence and evidence of values: bringing together values-based and evidence-based practice in policy and service development in mental health. J Eval Clin Pract 2011;17:976-87.
137. Ratcliffe M. The feeling of being. J Conscious Stud 2005;12:43-60.
138. Steinbock A. The phenomenology of despair. Int J Philos Studies 2007;15:435-51.
139. Fuchs T. The phenomenology of affectivity. In: Fulford KWM, Davies M, Gipps RGT (eds). The Oxford handbook of philosophy and psychiatry. Oxford: Oxford University Press, 2013:612-31.
140. Marsh I. Historical phenomenology: understanding experiences of suicide and suicidality across time. In: Pompili M (ed). Phenomenology of suicide: unlocking the suicidal mind. Cham: Springer, 2017:1-12.
141. Wilkins J. Suicidal behavior. Am Sociol Rev 1967;32:286-98.
142. Coimbra BM, Hoeboer CM, Yik J et al. Meta-analysis of the effect of racial discrimination on suicidality. SSM Popul Health 2022;20:101283.
143. Hect JM. Stay: a history of suicide and the philosophies against it. New Haven: Yale University Press, 2013.
144. Tondo L. Brief history of suicide in Western cultures. In: Koslow SH, Ruiz P, Nemeroff CB (eds). A concise guide to understanding suicide. Cambridge: Cambridge University Press, 2014:3-11.
145. Pompili M, Belvederi Murri M, Patti S et al. The communication of suicidal intentions: a meta-analysis. Psychol Med 2016;46:2239-53.
146. Riblet NBV, Shiner B, Young-Xu Y et al. Strategies to prevent death by suicide: meta-analysis of randomised controlled trials. Br J Psychiatry 2017;210:396-402.
147. Nuij C, van Ballegooijen W, de Beurs D et al. Safety planning-type interventions for suicide prevention: meta-analysis. Br J Psychiatry 2021;219:419-26.

DOI:10.1002/wps.70003

Treatment resistance in first-episode psychosis

Psychosis usually emerges in early adulthood, a period in which a life's trajectory is being set. The impact of events at this juncture can be disproportionately large, altering interpersonal relationships, education, employment, and physical health. As a result, this is a time when providing the most effective treatment possible is particularly important.

The pharmacological treatment of first-episode psychosis usually begins with the prescription of a dopamine D2 receptor antagonist, and in most people this leads to clinically meaningful reduction in the presenting positive symptoms. However, the observed clinical response to antipsychotic treatment is variable, and reflects more than just differences in the direct effects of the drug[1]. The evolution of symptoms is also influenced by a host of broader interacting biological, psychological and social factors. A substantial minority of patients do not experience sufficient symptomatic relief. In some, this may reflect inadequate treatment adherence. However, in a proportion of patients, symptoms persist despite good adherence to therapeutic doses of at least two different antipsychotic medications, a phenomenon known as treatment resistance.

For the majority of individuals who develop treatment-resistant schizophrenia, this resistance is evident from the onset of psychosis[2]. Understanding what underlies treatment resistance remains a central question in psychosis research. Psychiatric symptoms can be conceptualized as emergent properties of a dynamic network comprising neurobiological vulnerability, life experiences, cognitive schemas, and social context. Within this framework, treatment resistance could represent a system that is stuck in a maladaptive attractor state. The longer an individual remains with symptoms, the more self-reinforced these may become. Offering effective treatment as early as possible maximizes the chance of shifting a dysfunctional system into a more adaptive state while patterns are still malleable.

Early intervention (EI) services were first developed around 30 years ago to provide clinical care at this stage of both vulnerability and opportunity. The rationale was that delivering optimal treatment early would reduce the likelihood of the chronicity and self-reinforcing functional decline that often accompany psychotic disorders. Although this logic applies equally to the recognition and management of treatment resistance, the original EI model places relatively little emphasis on how to help the substantial minority of individuals who do not benefit from standard treatment. As a result, many EI teams may lack the capacity to identify or manage people with treatment resistance and may not see this as part of their clinical remit.

Clozapine is the only licensed medication for treatment-resistant schizophrenia. Its use in treatment resistance is supported by both clinical trials and a host of real-world evidence showing benefits in terms of suicidality, substance use, and cost-effectiveness[3]. There do remain, however, some doubts as to whether clozapine is clearly superior to its closer pharmacological relatives, such as olanzapine, with a recent individual participant data meta-analysis not finding evidence of clozapine's superiority[4]. It should also be recognized that while "treatment resistance" refers to refractory positive symptoms, many individuals may have a relative resolution of positive symptoms, yet still be affected by cognitive and negative symptoms that severely impair functioning, and there is no evidence that clozapine is better than standard treatment for these domains.

Nevertheless, switching to clozapine in people with first-episode psychosis appears to have a greater benefit than switching to a different standard antipsychotic, and the earlier clozapine is started the better the outcome[5]. When clozapine is initiated earlier, there may be potential to engender symptomatic improvement through interruption of pathological symptomatic feedback loops. This improvement in core psychopathology may, in turn, facilitate engagement in psychosocial interventions, improve functioning, and restore a sense of agency – a virtuous cycle that promotes further improvement and catalyzes broader recovery. In addition to pharmacological optimization, addressing modifiable psychosocial contributors such as unhelpful family dynamics, housing insecurity, and substance use is critical to supporting recovery.

At present, clozapine is rarely used in EI services[6]. Indeed, the time to clozapine initiation is still over five years in many services[7]. In theory, the gold standard definition of treatment resistance – a lack of response to two antipsychotic trials of adequate dose and duration – can be determined within 2-3 months. However, in real-world practice, it can be difficult to precisely and promptly assess the response to treatment and the level of adherence. Moreover, once treatment resistance has been recognized, EI clinicians may be deterred from prescribing clozapine, and patients may be unwilling to accept it, because of the logistical burdens of initiation and monitoring, concerns about side effects, and a perception that being treated with clozapine is a marker of severe and enduring illness.

A further complexity is that, after their first experience of illness, young people are understandably hoping for recovery without a need for long-term mental health care, an ambition central to the traditional ethos of EI services. Treatment with clozapine, and indeed the stigma attached to the labels of "schizophrenia" and "treatment resistance", may seem incompatible with this goal. Communicating the rationale for early clozapine use in a way that aligns with a young person's hopes – emphasizing function, quality of life, and personal goals – is, therefore, critical.

Improving the care of individuals with treatment resistance in early psychosis requires change at multiple levels. Recent research has focused on predicting treatment resistance using clinical, cognitive or biological markers. While predictive tools might allow us to avoid the need for lengthy evaluations of treatment response, they cannot address the fact that, even when resistance has been recognized, clozapine is often not used. As such, changes should be designed to lead to better treatment implementation as well as earlier detection of resistance.

Reducing barriers to clozapine use is essential. Targeted community-based services can markedly increase clozapine initiation rates[8]. Point-of-care testing technologies that make blood monitoring more convenient and less invasive are now widely available. There is increasing evidence that the current stringency of longer-term blood monitoring is overzealous, and regulatory bodies in some countries are beginning to reconsider the frequency of blood tests and the absolute neutrophil count thresholds required for continuation[3,9]. The risk of weight gain, a major reason for discontinuation among young people, can be reduced through structured physical activity programmes, lifestyle counselling, and adjunctive treatments such as metformin. Updating the EI model, such that the detection and management of treatment resistance are included as a core part of the clinical offer, would ensure that patients who do not benefit from standard care have access to the right treatment at the right time.

While clozapine remains central to the management of treatment resistance, the advent of novel medications with non-dopaminergic mechanisms of action, such as xanomeline-trospium, evenamide and cannabidiol, offers hope for expanding the range of options available for those not responding to treatment in the first episode. While their precise role in the treatment pathway is not yet established, these compounds may eventually offer effective alternatives or adjuncts to clozapine, with potentially more tolerable side effect profiles.

In the long term, a more nuanced and flexible model of treatment resistance may be needed – one that recognizes the heterogeneity of underlying mechanisms and the need for personalized intervention strategies. In the short term, however, the goal should be to detect treatment resistance early and remove the systemic barriers that delay access to effective management. This means better education for clinicians, better communication with patients, and better clinical systems that enable rather than obstruct treatment. Treatment resistance in the first episode of psychosis is not rare; it is a predictable clinical reality for around 25% of patients[2]. Clinical pathways should be designed to not only identify it early, but also manage it with clarity, compassion, and evidence-based care. By doing so, we can prevent the entrenchment of disability and offer individuals the best possible chance of recovery when everything is still to play for.

Robert A. McCutcheon[1-3], **Philip McGuire**[1,2,4], **Rachel Upthegrove**[1,4-6], **Toby Pillinger**[3,7]

[1]Department of Psychiatry, University of Oxford, Oxford, UK; [2]Oxford Health NHS Foundation Trust, Oxford, UK; [3]Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; [4]Oxford Health Biomedical Research Centre, Oxford, UK; [5]Institute for Mental Health, University of Birmingham, Birmingham, UK; [6]Birmingham Early Intervention Service, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK; [7]South London and Maudsley NHS Foundation Trust, London, UK

R.A. McCutcheon's work is funded by a Wellcome Trust Clinical Research Career Development Fellowship (224625/Z/21/Z). R. Upthegrove, R.A. McCutcheon and P. McGuire are supported by the UK National Institute for Health and Care Research (NIHR) Oxford Health Biomedical Research Centre. The views expressed here are those of the authors and not necessarily those of the NIHR or the UK Department of Health and Social Care.

1. McCutcheon RA, Pillinger T, Efthimiou O et al. World Psychiatry 2022;21:287-94.
2. Siskind D, Orr S, Sinha S et al. Br J Psychiatry 2022;220:115-20.
3. Correll CU. World Psychiatry 2025;24:153-4.
4. Schneider-Thoma J, Hamza T, Chalkou K et al. Lancet Psychiatry 2025;12:254-65.
5. Yoshimura B, Yada Y, So R et al. Psychiatry Res 2017;250:65-70.
6. Stokes I, Griffiths SL, Jones R et al. BJPsych Open 2020;6:e107.
7. Thien K, O'Donoghue B. Early Interv Psychiatry 2019;13:18-23.
8. Khan ZA, Varvari I, Mancini V et al. medRxiv 2025;2025.04.04.25325236.
9. Fernandez-Egea E, Mc Cutcheon RA. Br J Psychiatry 2025;226:1-3.

DOI:10.1002/wps.70026

Cognitive consequences of COVID-19 infection: current evidence and future directions

It was evident early in the COVID-19 pandemic that some people experienced persistent symptoms beyond acute infection. Cognitive difficulties (including brain fog and memory complaints) were commonly reported features of what came to be termed Long COVID. Cohort studies soon supported these reports, showing elevated rates of persistent cognitive symptoms, even among those with mild or moderate illness[1].

Objective assessment of cognitive performance was enabled at scale by advances in online testing platforms. An early example was a citizen science study that assessed 81,337 UK participants during the first national lockdown[2]. Though not originally intended for this purpose, the scale and timing of the study enabled analysis of cognitive performance in relation to COVID-19 features. Small statistically significant cognitive deficits were observed in the group who reported having recovered from COVID-19 infection, after adjustment for demographic and clinical covariates.

These deficits correlated weakly with self-reported fatigue, anxiety or depression, indicating that they were unlikely to be due to affective disturbance. They were most pronounced in people who had been hospitalized, particularly those who had received respiratory support. However, small but measurable deficits were also evident in the non-hospitalized group who had recovered from biologically confirmed SARS-CoV-2 infection with milder acute symptoms. Across domains, the profile included attention, memory and executive deficits. While limited by their incidental nature, these results accorded with patient-reported symptoms, providing converging evidence that COVID-19 infection might have a persistent multi-domain impact on cognitive performance.

This hypothesis was subsequently tested in studies with rigorous designs, including the Long COVID extension of the Realtime Assessment of Community Transmission programme[3]. This programme had utilized random population sampling with biological test confirmation to monitor infection rates in England. Among 276,840 participants who responded to a follow-up survey (REACT-LC) in 2022-2023, 141,583 undertook an assessment on the same online platform (Cognitron) as the prior citizen science research.

Compared to a group without known infection, those who had recovered from SARS-CoV-2 showed a small average deficit in cognitive performance. More pronounced deficits were evident in those with ongoing symptoms persisting >12 weeks, consistent with Long COVID. The pattern across domains was again most pronounced for memory and executive tasks, with immediate memory deficits pointing to a role of attention. Deficits were greatest and spanned additional cognitive domains in those who had been hospitalized. Importantly, deficits were more prominent in individuals infected during early relative to late pandemic waves. This, viewed positively, indicated a mitigation of cognitive risk over time, likely through vaccination and viral evolution.

Lower-than-expected cognitive performance (at least –1 standard deviation, SD) was observed in 22.5% of individuals with ongoing persistent symptoms, 18.9% of those with resolved persistent symptoms, and 15.7% of the asymptomatic group, with rates of moderate impairment (at least –2 SD) being 5.2%, 3.5% and 2.2%, respectively. Conversely, superior performance (at least +1 SD) was seen in 11.8%, 13.5% and 16.0%, respectively. This cross-sectional pattern indicated that cognitive performance might improve when Long COVID symptoms eventually resolve, although longitudinal confirmation of recovery is pending.

REACT-LC was a large-scale study which employed rigorous epidemiological and statistical methods. However, absence of pre-infection cognitive data limited inference about cognitive change. A study from Norway of 111,992 participants with confirmed infection status partially addressed this limitation[4]. Participant-reported memory function, assessed using the Everyday Memory Questionnaire, was worse up to 36 months after a positive vs. a negative SARS-CoV-2 test, while being essentially the same for these groups before the test.

Experimental confirmation of longitudinal change in cognitive function was provided by a UK-based human challenge study[5]. Using the same Cognitron assessment platform as REACT-LC, healthy young adults were longitudinally monitored from pre- to 1-year post-inoculation with wild-type SARS-CoV-2. Relative to participants for whom the inoculation did not lead to infection, those who developed sustained viral load showed small persistent baseline-corrected cognitive deficits spanning from acute illness until the one-year study endpoint. Performance differences were again most pronounced in immediate memory and executive function. Intriguingly, participants only developed mild illness and did not report persistent cognitive symptoms when debriefed.

Further insight into long-term cognitive trajectories came from the PHOSP-COVID cohort[6]. In follow-up assessments 2-3 years post-hospitalization, patients continued to show objective cognitive impairments. In this more severe group, cognitive deficits occurred alongside psychiatric symptoms, including fatigue and depression. Notably, the scale of cognitive deficit was better predicted by symptom burden at six months than by acute illness severity, highlighting the importance of the early post-acute phase.

The biological underpinnings of post-COVID cognitive deficits remain less clear. In a UK-based neuroimaging study of previously hospitalized individuals[7], persistent cognitive impairment one year post-infection was associated with elevated serum markers of neuronal injury – neurofilament light chain and glial fibrillary acidic protein (GFAP) – and reduced anterior cingulate cortex volume. Tentative evidence of GFAP elevation was also reported in the wild-type SARS-CoV-2 human challenge study, where illness was mild[5]. These findings indicate a likely role for immune-mediated neuronal damage across varying severities of acute illness.

A recent transdiagnostic review characterized brain fog as a multifaceted symptom cluster involving cognitive, affective and fatigue-related elements, with heterogeneous neural correlates and weak associations with objective task performance[8]. It highlighted evidence of elevated blood-brain barrier permeability and pro-inflammatory cytokine profiles in individuals reporting brain fog, supporting a neurobiological basis for cognitive symptoms.

In addition to large-scale cohorts, frequent monitoring designs have potential for studying the mechanisms that underlie cognitive problems after COVID-19 infection[9]. They have shown that cognitive symptoms in Long COVID fluctuate and may be exacerbated by mental exertion and fatigue. Such designs could be extended to study whether objectively measured cognitive deficits also fluctuate, and how fluctuations covary with biological and psychological factors within-subject, mapping differences in potential causal mechanisms and informing the search for targeted interventions.

In summary, evidence from observational, experimental and mechanistic studies converge to support the hypothesis that COVID-19 infection can have a persistent impact on cognition and brain function. Despite considerable heterogeneity, a characteristic cognitive profile has emerged, with objectively measurable deficits in memory, executive function and attention. The scale of these deficits is greater in those with ongoing persistent symptoms, but may attenuate when their symptoms finally resolve. Objective deficits are weakly correlated with subjective symptoms in Long COVID, but appear more strongly related amongst hospitalized patients. Subjective cognitive symptoms fluctuate in Long COVID, but it remains unclear whether cognitive performance deficits also fluctuate.

More research is required to develop an integrative model linking heterogeneity in cognitive symptoms and deficits to underlying psychological and biological mechanisms. Large-scale longitudinal studies and detailed individual monitoring designs can offer tractable approaches for addressing this challenge.

Adam Hampshire
Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

1. Davis HE, Assaf GS, McCorkell L et al. EClinicalMedicine 2021;38:101019.
2. Hampshire A, Trender W, Chamberlain SR et al. EClinicalMedicine 2021;39:101044.
3. Hampshire A, Azor A, Atchison C et al. N Engl J Med 2024;390:806-18.
4. Ellingjord-Dale M, Brunvoll SH, Søraas A. N Engl J Med 2024;390:863-5.
5. Trender W, Hellyer PJ, Killingley B et al. EClinicalMedicine 2024;76:102842.
6. Taquet M, Skorniewska Z, De Deyn T et al. Lancet Psychiatry 2024;11:696-708.
7. Wood GK, Sargent BF, Ahmad ZU et al. Nat Med 2025;31:245-57.
8. Denno P, Zhao S, Husain M et al. Trends Neurosci 2025;48:330-48.
9. Greenwood DC, Mansoubi M, Bakerly ND et al. Lancet Reg Health Eur 2024;46:101082.

DOI:10.1002/wps.70027

Public health impacts of legalizing recreational cannabis use in Canada and the US

In 2012, the citizens of the US states of Colorado and Washington passed popular ballots to legalize adult non-medical cannabis use, and this policy was implemented in 2014[1]. Uruguay legalized adult cannabis use and production in 2013; Canada did so in 2018; and approximately half of US states have since done so[1,2]. Other countries in Europe, Asia, and Central and South America have implemented, or are considering, the legalization of adult cannabis use[1].

How has cannabis legalization fared in Canada and the US, where it has been in place the longest and where data have been collected on its impacts?

Most Canadian provinces and US states have adopted a modified form of alcohol regulations for legal cannabis frameworks[1-3]. These set an age threshold for legal use (21 years in US states and 19 years in most Canadian provinces), restrict conditions of use and possession, and licence for-profit companies to produce and sell legal cannabis products[1-3]. They place more restrictions on advertising cannabis than alcohol[1,3,4], but compliance with these restrictions has been variable[5].

Legalization has produced large reductions in arrests for cannabis use offences, although this has not been accompanied by a reliable reduction of relevant racial disparities in the US[1]. Legalization has increased adults' access to cannabis products that are quality-regulated and labelled for potency[1]. It has also increased the diversity of cannabis products; greatly reduced their prices[1,2]; increased the Δ9-tetrahydrocannabinol (THC) content of herbal cannabis and edibles, extracts and vape products[1-3]; and appears to have reduced the size of the illicit cannabis retail market in Canada[1-3]. Its impact on illicit markets in US states has varied, depending on the size of the illicit market before legalization, the barriers faced by new entrants to the legal market, and the level of enforcement against the illicit market[1].

The prevalence of daily cannabis use has increased markedly among adults in the US[1,6] and more modestly in Canada[1,3,4]. There are now more daily cannabis users than daily alcohol users in the US[6]. There has been a small increase in the proportion of adults who have used cannabis, including older adults, in the US[1,2]. There is limited evidence that adult legalization has increased cannabis use among adolescents[1-3], possibly reflecting a general reduction in the use of tobacco and alcohol by young adults in many high-income countries, and perhaps variations in age-of-purchase laws in Canada[2].

There has been an increase in emergency department attendances for the acute adverse effects of cannabis use, that probably reflects increased regular use of more potent cannabis[1,2,7-9]. These presentations include psychiatric symptoms, psychoses, anxiety and depression, and the poisoning of children who ingest edible cannabis products that look like confectionary[1,2].

It is unclear how adult legalization has affected the population prevalence of cannabis use disorders[2]. Some national US and provincial Canadian surveys suggest that the prevalence of symptoms of these disorders has increased, but other surveys do not[2]. Fewer people have sought treatment for cannabis use problems in addiction services in the US, probably because fewer persons are referred to treatment by courts as an alternative to criminal charges[1-3]. Data in Ontario suggest that more people are presenting to emergency departments for problems related to their cannabis use after the number of cannabis retail outlets has increased[7,8].

The evidence on the impact of legalization on car crashes in impaired drivers is mixed[1-3]. Some Canadian studies have found higher blood THC levels in persons injured in road accidents[4], but the overall trends in accident fatalities in both the US and Canada have not been clearly related to the implementation of cannabis legalization[1-3].

In the US and Canada, there have been increased rates of cannabis use reported among women during pregnancy, probably to manage nausea[1]. Cannabis hyperemesis syndrome has increased in very heavy cannabis smokers[2].

There are increasing concerns that adults who smoke cannabis frequently may have an increased risk of cardiovascular disease. The risk may be higher in older adults who use cannabis to treat chronic pain or sleep problems[1,2].

These adverse impacts of cannabis legalization may be greater in socially disadvantaged communities[1]. In the US, there are more retail outlets in low socioeconomic status neighborhoods, and daily cannabis use has increased more among people in these areas[1]. These trends could amplify social disadvantage, especially if they reduce educational attainment and impair work performance[1].

A major public health concern is about future reductions in the regulation of cannabis sales[2,5]. The legal cannabis industry has been campaigning in Canada for the right to use cannabis brand names to promote their products[2]. Along with the US industry, they are campaigning for lower taxes and less regulation, allegedly to compete more effectively with the illicit market[2]. In many US states, the cannabis industry has been involved in designing regulations[1], and has resisted proposals to regulate or differentially tax higher potency cannabis products[2]. A major concern in the US is the public health impact of an end to federal cannabis prohibition, because this would enable the creation of a large national cannabis market with greatly reduced prices and a capacity to invest in other countries planning to legalize cannabis[2].

We need more rigorous studies of the effects of legalization of cannabis use in higher-risk populations[1-4]. These include adolescents, young adults with mental health disorders, pregnant women, and older adults who use cannabis for medical reasons, such as to treat chronic pain[1]. Unfortunately, most US states that have legalized adult cannabis have not invested in the public health research infrastructure needed to evaluate the impacts of the policy changes[1].

We also need better studies of the impacts of legalization on the prevalence of cannabis use disorders, and greater research investment in developing more effective interventions to assist people who want to stop using cannabis[1,2]. The impacts of legalization on illegal cannabis production and supply are also under-investigated.

The challenge for policy makers will be to design regulations that balance the competing goals of cannabis legalization, i.e., reducing illicit cannabis markets, minimizing the adverse effects of criminalization, and protecting public health[1,5]. A reasonable concern, given historical experiences with the tobacco, alcohol and gambling industries, is that governments will give a higher priority to maximizing tax revenue from cannabis sales than they do to protecting public health, and so they will be receptive to cannabis industry lobbying to reduce public health-oriented regulation[1,5].

Wayne Hall[1], Benedikt Fischer[2-7]
[1]National Centre for Youth Substance Use Research, University of Queensland, Brisbane, QLD, Australia; [2]Faculty of Health Sciences, S. Fraser University, Vancouver, BC, Canada; [3]Research and Graduate Studies, University of Fraser Valley, Abbotsford, BC, Canada; [4]Department of Psychiatry, University of Toronto, Toronto, ON, Canada; [5]Department of Psychiatry, Federal University of Sao Paulo, São Paulo, Brazil; [6]School of Population Health, University of Auckland, Auckland, New Zealand; [7]Waypoint Centre for Mental Health Care, Penetanguishene, ON, Canada

1. National Academies of Sciences, Engineering, and Medicine. Cannabis policy impacts on public health and health equity. Washington: National Academies Press, 2024.
2. Yimer T, Hoch E, Fischer B et al. Lancet Public Health 2025;10:e148-59.
3. Fischer B, Jutras-Awad D, Hall W. Can Med Assoc J 2023;195:E1648-50.
4. Hall W, Stjepanović D, Dawson D et al. Addiction 2023;118:2062-72.
5. Fischer B, Myran D, Jutras-Aswad D et al. World Med Health Pol 2024;17:167-75.
6. Caulkins JP. Addiction 2024;119:1648-52.
7. Myran DT, Gaudreault A, Konikoff L et al. JAMA Netw Open 2023;6:e2336113.
8. Myran DT, Gaudreault A, Pugliese M et al. JAMA Netw Open 2023;6:e2331551.
9. Myran DT, Pugliese M, Roberts RL et al. Mol Psychiatry 2023;28:4251-60.

DOI:10.1002/wps.70030

Why climate action is an opportunity multiplier for mental health

Climate change is increasingly recognized as a risk multiplier for mental health. Escalating climate hazards induce compounding stressors that destabilize the foundations of good mental health and well-being. This systemic threat ripples across geographies and generations[1].

Less appreciated is how climate action – cutting emissions and adapting to change – is an opportunity multiplier for mental health. Actually, the climate and mental health fields share synergistic goals, with overlaps in conditions that foster healthy minds and environments. In spite of this, mental health is rarely embedded in climate policy. Only 17% of national adaptation plans include actions addressing the mental health consequences of climate change, though the Intergovernmental Panel on Climate Change stresses that successful climate action must build resilience, not just of infrastructure, but of people and societies (www.ipcc.ch/report/ar6/wg2).

Preventive psychiatry identifies key mental health determinants to foster people's resilience[2], such as stable early development, income equality, food security, community cohesion, and social support in the context of environmental hazards. Climate change threatens these determinants, while climate action relies on and can reinforce them.

Minimizing fossil fuels and biomass burning lowers air pollution and its mental health toll. Even relatively low levels of air pollution can increase anxiety, depression and mental health service use, and high air pollution days carry increased suicide risk[3]. It is estimated that China's air pollution policies prevented 13,000 to 79,000 (95% confidence interval) deaths from suicide between 2013 and 2017[4].

Urban design matters for climate as well as mental health. Infrastructure promoting active travel (walking and cycling), connected communities, tree cover, and local biodiversity access can reduce fossil-fuel based transportation, and buffer climate change-related hazards such as floods and heatwaves. Accompanying this, physical activity can reduce anxiety and depression symptoms, while greenspace access and heightened nature connectedness can improve mental health. More links could be made: initiatives such as "green social prescribing" (prescribing nature connection to people experiencing mental health challenges) could facilitate community-based climate actions.

Building design is also central to climate action and mental health. Australian and Irish schemes to improve home energy efficiencies reduced anxiety and depression while improving emotional and social well-being. Vitally, governmental cost savings were more clearly evident when accounting for health. In Australia, for every AUD of energy cost savings, 10 AUD were saved in health care[5].

Education is another essential system-level action. Young people call for education that tells the truth about climate change while building psychological resilience and agency – skills that benefit mental health beyond the climate context.

Community cohesion is a powerful protective buffer against climate stressors, and climate action requires preparing communities to cope with escalating climate hazards. Collective climate action confers mental health benefits, and bridges individual and systemic transformation while building social connection. This is vital for good mental and physical health, and tackling the loneliness "epidemic".

Local knowledge and cultural practices are key. Initiatives that strengthen care for local environments through traditional cultural practices can synergistically confer mental health and well-being benefits, as shown in the Caring for Country initiatives with First Nations communities in Australia (https://soe.dcceew.gov.au).

Global mental health advocates for expanding mental health care into community-level services. Global mental health tools, such as task sharing, can benefit climate resilience approaches, and simultaneously strengthen the ability of a community to cope and to spread proven adaptive strategies. At the same time, scaling the social infrastructures of climate action could provide an enabling opportunity for community-based mental health capacities.

Workplace mental health and well-being is at risk. Extreme temperatures impair cognition and productivity. Poor youth mental health, linked to global megatrends including climate change, contributes to unemployment. Maintaining a healthy workforce in a changing climate and global energy transition requires designing for psychological resilience. Synergistic benefits for climate action and mental health can flow from appropriately designed climate-aware workplace mental health strategies.

Thriving in the climate crisis and sustaining climate action requires psychological abilities: tolerating uncertainty, complexity, and uncomfortable emotions. Building these skills in individuals and communities (e.g., schools) can strengthen psychological determinants of good mental health. For instance, adolescents who can tolerate uncertainty have better mental health outcomes[6].

Positive psychology highlights meaning, engagement and social relationships as keys to well-being. Meaning-focused coping is among the most well-researched approaches to protect mental health while encouraging climate action. This requires and encourages emotional flexibility and values-based behaviors. Individual climate actions can follow a similar virtuous cycle to behavioral activation techniques in protecting mental health, especially when boosting agency, social connection and purpose.

Individual-, community- and system-level actions interconnect. Realizing climate-mental health co-benefits requires systems-thinking that recognizes the cascading and interacting pathways connecting healthy environments and minds. It also requires decision-making spanning traditional siloed sectors, and transdisciplinary approaches crossing fields and cultures. Climate and mental health communities must embrace mechanisms to share knowledge and foster mutual understanding. Initiatives such as Connecting Climate Minds (www.connectingclimateminds.org) provide examples. Supportive infrastructure for such connective bridging requires critical investment.

Prevention is cheaper than cure, for both psychiatry and climate. The world is on track for nearly 3°C of global boiling by the late century – when today's children will still be working – slashing up to 34% off the global economy. The net cost of inaction is estimated to be "three times global health care spending"[7]. The true cost is likely far greater, with many impacts – such as on mental health – under-accounted. The extra mental health burden from climate hazards, air pollution and insufficient green space access could cost US$ 537 billion/year by 2050[8]. On the other hand, mental health returns on climate action investments are rarely included in cost-benefit analyses.

A word of caution: a systems perspective must recognize the possible mental health risks and unintended consequences of climate actions. For instance, transitioning away from fossil fuels may affect jobs. Climate action design must include diverse lived experiences of mental health needs and psychologically-informed, participatory decision-making, to mitigate unforeseen harms.

Psychiatry can inform and benefit from synergistic climate actions. As a trusted profession, it can raise awareness among decision-makers and the public of the potential to create a mentally healthier future, and provide mental health expertise to bolster climate resilience efforts. Support for population-level climate resilience aligns with the field's growing emphasis on prevention and positive mental health.

Training on climate-mental health links should be embedded in psychiatric education, and psychiatrists should be equipped to support, design and implement co-beneficial climate actions. Psychiatry researchers can help understand and quantify climate actions' mental health benefits (and possible risks).

At the heart of responding to the climate crisis lies a profound opportunity to create "environment[s] that support mental health for all"[9]. Rapidly phasing out fossil fuels and protecting biodiversity is not just climate-smart; it is brain-saving. Recognizing and acting on the climate action benefits for mental health can spark a virtuous cycle, where more people thrive.

Emma L. Lawrance
Climate Cares Centre, Institute of Global Health Innovation and Grantham Institute for Climate Change and the Environment, Imperial College London, London, UK; Department of Psychiatry, University of Oxford, Oxford, UK

1. Lawrance EL, Thompson R, Newberry Le Vay J et al. Int Rev Psychiatry 2022;34:443-98.
2. Kirkbride JB, Anglin DM, Colman I et al. World Psychiatry 2024;23:58-80.
3. Radua J, De Prisco M, Oliva V et al. World Psychiatry 2024;23:244-56.
4. Zhang P, Carleton T, Lin L et al. Nat Sustain 2024;7:260-9.
5. Page K, Hossain L, Liu D et al. BMJ Open 2025;15:e082340.
6. Ye H, Li Y, Huang Y et al. Child Adolesc Psychiatry Ment Health 2025;19:54.
7. Benayad A, Hagenauer A, Holm L et al. Why investing in climate action makes good economic sense. Boston: Boston Consulting Group, 2025.
8. Kumar P, Brander L, Kumar M et al. Ann Glob Health 2023;89:49.
9. Patel V, Saxena S, Lund C et al. Lancet 2018;392:1553-98.

DOI:10.1002/wps.70029

Social inclusion of people with severe mental illness: a review of current practices, evidence and unmet needs, and future directions

Claire Henderson[1,2], Yasuhiro Kotera[3,4], Brynmor Lloyd-Evans[5], Gerald Jordan[6], Matthew Gorner[7], Anthony Salla[8], Jasmine Kalha[9], Peter A. Coventry[10,11], Laura Bojke[12], Sebastian Hinde[12], Mike Slade[3,13]

[1]Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; [2]South London and Maudsley NHS Foundation Trust, London, UK; [3]Institute of Mental Health, School of Health Sciences, University of Nottingham, Nottingham, UK; [4]Center for Infectious Disease Education and Research, Osaka University, Suita, Japan; [5]Division of Psychiatry, University College London, London, UK; [6]School of Psychology, Institute for Mental Health, Centre for Urban Wellbeing, University of Birmingham, Birmingham, UK; [7]Institute of Psychosynthesis, London, UK; [8]School of Health Sciences, City University of London, London, UK; [9]Centre for Mental Health Law and Policy, Indian Law Society, Pune, India; [10]Department of Health Sciences, University of York, York, UK; [11]York Environmental Sustainability Institute, University of York, York, UK; [12]Centre for Health Economics, University of York, York, UK; [13]Faculty of Nursing and Health Sciences, Health and Community Participation Division, Nord University, Namsos, Norway

Social inclusion means being able to participate in activities valued within one's community or wider society as one would wish. People with severe mental illness (i.e., psychoses, bipolar disorder, and severe depression) experience some of the highest rates of social exclusion compared to people with other disabilities. This is the case regardless of the availability of specialist mental health services. Therefore, questions arise about the extent to which mental health services can and do prioritize social inclusion as a goal of service provision, and what strategies are needed outside of mental health services, at the levels of legislation and policy, statutory services, and civil society. In this paper we consider what social inclusion means in different cultures and contexts, since the value attached to different activities varies by culture and by life stage and gender. We discuss the subjective impact of low levels of social inclusion in terms of loneliness, and the evidence base for interventions to address it. We then turn to strategies to increase observable forms of social inclusion, considering them at the levels of legislation, services and other community assets. While evidence for some interventions is largely based on the Global North, we use evidence and examples from the Global South to the extent that we have found them. We also consider the predominant frameworks for social inclusion used in health services, followed by alternatives that may offer a more empowering approach to social inclusion for some people. We then describe strategies to reduce social exclusion through interventions to address stigma and discrimination, directed at key target groups or at population level. We make recommendations for policy makers, researchers, health professionals, and advocates based on the evidence and examples we have found, covering various forms of legislation, services and mental health research. Our conclusions identify the next steps for interventions, including development, evaluation, implementation or modification for better contextual adaptation.

Key words: Social inclusion, severe mental illness, social roles, loneliness, employment, community engagement, stigma, discrimination, social prescribing, advocacy

(World Psychiatry 2026;25:56–82)

Social inclusion means being able to participate in activities valued within one's community or wider society as one would wish. People with severe mental illness (i.e., psychoses, bipolar disorder, and severe depression) experience some of the highest rates of social exclusion in terms of both its subjective and observable aspects. For example, they report very high levels of feeling lonely[1] and experience higher rates of unemployment than the average for people with a disability. Unemployment, social isolation and the resulting poverty and loneliness have severe consequences for both quality of life and life expectancy[2,3]. Therefore, increasing social inclusion should be of the highest priority for health services, policy makers, and the voluntary and community service sectors.

There is no evidence that social inclusion is greater in countries with extensive mental health services compared to those without. Indeed, using employment as one indicator suggests that, in some countries, this is better in rural areas, which tend to have less service provision, than in urban areas, due to the availability of employment within the agrarian sector[4,5]. However, rapid urbanization around the world is reducing access to this way of life, and rural areas are not free of other forms of social exclusion.

The finding that over 80% of people with psychosis reported loneliness in an Australian study[1] emphasizes the insufficiency of keeping people out of hospital as a service goal, and the lack of effective use of community assets besides health services to promote social inclusion. At a time of widespread scaling-up of mental health services, for example through primary care, and of mental health professional workforce shortages, it is important to question the efficiency, in relation to social inclusion, of mental health care provided via either primary or specialist health services, and to consider both the role of other community assets and their relationship to organizations providing mental health care. It is also important to identify what interventions require tailoring to people with severe mental illness, and to establish an evidence base for social inclusion-enhancing interventions.

One response to low levels of social inclusion could be to work to reduce structural discrimination and interpersonal stigma. There is some evidence to support this strategy. For example, over the course of the first six years of England's Time to Change programme to reduce mental health-related stigma and discrimination, serial surveys of mental health service users indicated a fall in the median number of life areas in which they experienced discrimination in the last 12 months[6]. Carefully designed, multi-year stigma reduction programmes have been conducted or are currently running in a number of countries[7].

However, we do not believe that stigma reduction alone would be sufficient, for several reasons. The first is the lingering effect of anticipated discrimination. Studies in countries of all income levels highlight the extent to which people avoid seeking employment opportunities due to their anticipation of discrimination, even if they have not directly experienced it. Anticipated discrimination affects many other life areas[8], preventing people from taking up social, educational and economic opportunities, from pursuing leisure activities, and from using needed services such as physical health care [9]. On the other hand, evidence supports the protective role of employment in relation to overall levels of discrimination[10]. Thus, active strategies to increase people's ability and confidence to manage both anticipated and experienced discrimination are needed in addition to stigma reduction[11,12].

Second, even in the absence of stigma or its anticipation, the impact of severe mental illness, with its symptoms and associated functional impairment, means that many people need active support to attain valued social roles, whether this be employment, education, intimate relationships or parenting. Third, reducing stigma will not address some issues that hinder effective mental health care, such as low public spending on mental health, limited development and implementation of mental health policies, workforce shortages, and lack of professional training in social inclusion activities[13].

Fourth, people with severe mental illness belong disproportionately to a number of minoritized groups[14,15], and a high proportion of them experience poverty[16] and substance use disorders. These groups are subject to social isolation on the basis of these intersecting characteristics. We must therefore consider not only strategies to reduce social exclusion, but active social inclusion strategies at all levels and across all settings, with their different culture and service contexts, and with a view to implementation equity[17], so that intersectionality does not lead to continued or widening levels of exclusion. For researchers, addressing the aim of implementation equity requires that the design and conduct of studies fosters the involvement – as participants, advisors and peer researchers – of people with severe mental illness with such intersecting characteristics.

In this paper, we first consider what social inclusion means in different cultures and contexts. We then discuss the subjective impact of low levels of social inclusion in terms of loneliness, and the evidence base for interventions to address it. We subsequently describe strategies to increase objective forms of social inclusion, considering them at the levels of legislation, services and other community assets, with examples of each and their evidence base. We also consider the predominant frameworks for social inclusion used in health services, as well as alternatives that may offer a more empowering approach to social inclusion for some people. We then outline strategies to reduce social exclusion through interventions to address stigma and discrimination, directed either at key target groups or at the population level. Finally, we make recommendations for policy makers, researchers, health professionals, and advocates covering various forms of legislation, services and mental health research.

THE MEANING OF SOCIAL INCLUSION IN DIFFERENT CULTURES AND CONTEXTS

Social inclusion encompasses social connectedness, meaningful participation in community life, and freedom from stigma and discrimination[18,19]. However, its interpretation and practice are different across cultures[20,21]. This section examines how social inclusion is understood and practiced in different cultures and contexts.

Individualism

Individualism is dominant in Western countries such as the US, the UK and Australia. It emphasizes personal autonomy, self-reliance, and the importance of individual rights and goals[22]. Social inclusion programmes in this context place strong emphasis on individual achievement and independence[23,24]. Success is often defined by personal milestones, such as securing independent housing, obtaining competitive employment, and engaging in self-advocacy[25-27].

For instance, the Americans with Disabilities Act focuses on ensuring individual rights and providing accommodations in public spaces, underscoring the importance of personal autonomy and equal opportunities[28]. The UK is pioneering a mental health innovation called Recovery Colleges[29], which are learning-based mental health recovery support systems offering information, social support and skill development for people with mental health symptoms, carers and staff[30]. The Clubhouse Model in the US emphasizes member-driven recovery through work and community, where individual strengths and choices are central[31]. Australia's National Disability Insurance Scheme, a major initiative providing support to people with disabilities and their families and carers[32], emphasizes individual choice and control, enabling participants to set their own goals, and access services that promote independence, such as assistance with employment, education and daily living. The focus is on personal achievement in terms of living more independently and integrating into the community[32].

In Scandinavian countries, such as Denmark, Norway and Sweden, social inclusion reflects a hybrid approach to balance individual rights with strong social welfare systems[33,34]. Both personal autonomy and collective responsibility are emphasized, with success measured through both individual well-being and societal participation. For example, Norway's Individual Care Plan is a legally mandated, personalized plan designed to coordinate health and social services for individuals who have complex, long-term needs[35], including people with mental health conditions. It aims to provide comprehensive personal support planning with strong service integration[36]. In Sweden, Supported Employment is a well-known social inclusion scheme, supporting people with severe mental illness to obtain an employment[37]. A job coach offers support not only for the person with severe mental illness and the employer, but also for the person's colleagues, emphasizing collective responsibility[37].

Self-effacing collectivism

Self-effacing collectivism is dominant in East Asian countries, including Japan, South Korea and China. It values strong commitment to social harmony, interpersonal obligations, and adjustment to social norms and expectations. Conflict avoidance is the primary way to maintain social relationships. Social inclusion in these countries is deeply embedded in family and group contexts[38-40]. Success is often measured by how well someone maintains family harmony and fulfils social roles[38,41]. For instance, in Japan, the condition called *hikikomori* (a severe form of social withdrawal) is not only seen as problematic for the individual, but also as disrupting family harmony and social obligations[42,43].

Social inclusion programmes in Japan often prioritize social harmony through interventions such as community-based integrated care systems[40]. Singapore's National Mental Health and Well-Being Strategy emphasizes family and social support[44], including mental health education. In China, the 686 Programme actively involves family members in treatment and rehabilitation plans, offering psychoeducation and support to enhance understanding of mental health conditions. Additionally, community-based rehabilitation centres provide a platform where individuals with severe mental illness and their families engage in social and vocational activities, fostering a supportive network within the community[45].

Argumentative collectivism

Argumentative collectivism values social harmony, but through active engagement in argumentation. This type of collectivism is dominant in regions such as South Asia. Social inclusion in this context tends to prioritize community engagement and open dialogue. In India, health care workers who are involved in social inclusion programmes for people with severe mental illness are often viewed as extended family members, and participate in open discussions in families and communities[46].

In a peer-led, community-based, participatory group intervention for young people with psychosocial disabilities in Uttarakhand, India, outcomes such as forming new friendships, community involvement, and confidence in communicating were highlighted[47]. Likewise, pregnant women suffering from anxiety in Pakistan reported that family connection and their ability to open up and discuss their mental distress were key components to address their condition[48].

Self-assertive collectivism

Self-assertive collectivism is a cultural orientation in which individuals maintain strong group ties and collective identity, but are also encouraged to express personal opinions, assert themselves, and take initiative to protect and strengthen their group. This approach tends to prioritize safeguarding the ingroup by using individual resilience and strength through self-assertiveness[49]. This type of collectivism can be observed in Arabic countries.

In these countries, social inclusion is often interpreted through religious participation and adherence to religious values[50]. Being "included" encompasses active participation in various aspects of community life, including religious, family, and broader social networks, and following prescribed social norms[51,52]. A common approach to mental health support involves engaging religious leaders and incorporating faith-based practices[53].

In United Arab Emirates, despite the well-invested and highly accessible medical services, religious counsellors (*Mutawa*) remain highly in demand[54]. In Qatar, recent national mental health strategies were implemented to shift from hospital-based psychiatric care to a community care based on the Islamic faith[55,56]. In Saudi Arabia, social inclusion for people with mental health issues combines religious and professional care. Mosque-based support groups and regular consultations with psychiatric professionals and religious leaders play a central role[57-59].

In many Arabic cultures, strong family and tribal ties provide vital emotional and practical support for individuals with mental health conditions, with family members often actively participating in caregiving and community engagement. Support from tightly connected communities can have an important role in resolving mental health crises, including suicidal behavior[60].

Expressive collectivism

Expressive collectivism aims to achieve social harmony through personal expression[49]. This cultural orientation maintains that personal expression and sharing one's authentic self can enhance social cohesion and mutual understanding, rather than threaten group harmony[49]. Latin American countries often exhibit this cultural orientation.

For example, Brazil's *Programa De Volta Para Casa* exemplifies this approach through its integration of theatrical or musical elements as therapeutic tools, where emotional expression and family participation in celebratory gatherings are regarded as central to recovery[61,62]. Similarly, Colombian educational organizations aiming at social inclusion for young people with mental health issues often employ expressive programmes[63].

Connection to ancestral traditions

Traditional Indigenous communities, such as the Maori in New Zealand or First Nations in Canada, often interpret social inclusion through connection to ancestral traditions[64].

For example, *Te Whare Tapa Whā* in New Zealand is a holistic social inclusion model, rooted in Maori cultural values, focusing not only on mental and physical health, but also on family and spiritual health. Health is based on connection to the environment, ancestors and heritage[65]. Similarly, Canada's First Nations Mental Wellness Continuum Framework integrates traditional healing with modern care[66], regarding culture as the foundation for a good life, and prioritizing Indigenous people's cultural knowledge (e.g., connection to the land and community) and language.

THE ROLE OF LONELINESS

Loneliness, the negative affective state resulting from a subjectively experienced gap between someone's desired and actual social relationships[67], is common among people with mental health conditions. Over 80% of individuals with psychosis reported feeling lonely in one large Australian study[1]. Loneliness is negatively associated with both social inclusion and quality of life in people with severe mental illness[68].

Loneliness is typically only weakly or moderately correlated with the amount of social contact that someone has[69]. Rather, it is related to the development or sustenance of meaningful social connections, which provide emotional support, understanding, acceptance, and a sense of belonging[70,71]. Addressing loneliness is an important element of improving social inclusion for people with mental health problems.

In the general population, a wide range of interventions can reduce loneliness[72,73], including social approaches such as community linkage or befriending, and psychoeducation. But the evidence base for how to help reduce loneliness for people with severe mental health conditions is thinner and less promising. A systematic review published in 2020[74] included nine trials in people with severe mental illness, with subjective social isolation or loneliness as main outcomes. The interventions tested in these trials, all in high-income countries, included psychoeducation, social skills training, and supported socialization, or combinations of these. Despite positive findings in some studies regarding the amount of social contact or support received, none yielded positive results on the main measure of loneliness or subjective social isolation[74]. An update of this review (in preparation) indicates that the field has not moved on substantively.

Why might it be harder for people with severe mental illness to develop meaningful social relationships and reduce loneliness? Two recent systematic reviews collate findings from qualitative studies about the subjective experiences of loneliness among people living with psychosis[75] and across a range of mental health conditions[76]. Contributing factors identified in these reviews are consistent with quantitative and theoretical literature, and are summarized below.

First, people with severe mental illness have smaller social networks than the general population[77], and social network size does not typically increase over the course of contact with mental health services[78]. Existing friends and family provide companionship and can introduce us to their friends and acquaintances. Going to new groups and social activities can be less daunting with a friend. A small social network is a difficult starting point for addressing loneliness and developing new social relationships.

Second, as already noticed, people with severe mental illness experience high levels of stigma, and this is independently associated with loneliness[79]. They report experiencing hostility, ridicule and fear from others[75,76]. Negative attitudes may extend to sexual stigma, with these people being viewed as less suitable romantic partners[80] and more sexually exploitable[81]. While these attitudes are not universal, they make it harder to navigate social relationships. Moreover, in the context of realities of stigma and discrimination, people with severe mental illness may anticipate negative reactions from others and avoid social contact rather than risk rejection[75]. People may also absorb the negative attitudes of others, and come to doubt their own likeability or ability to forge relationships[77]. This may result in "self-stopping behaviors"[82] which limit opportunities to develop social connections that might reduce loneliness.

Third, symptoms of illness may be direct barriers to social interaction. For example, anhedonia and blunted emotional response reduce pleasure from social interaction, and social anxiety, exhaustion or acute psychotic symptoms make it harder to initiate it[75,76]. Some people with severe mental illness have described the need to balance their desire for social contact with the demand to limit stresses to maintain health, which could deter them from social contact. This was a recurring theme in a recent clinical trial, in which participants emphasized the emotional burden of taking part in a programme to reduce loneliness, even though the extra support was wanted[83].

Finally, barriers to social connection for people with severe mental illness are not all psychological. Lack of money to join social activities, transport and physical access challenges, and lack of information about available local groups all make it harder to take action to extend social interaction and reduce loneliness[75,83].

When asked, people with severe mental illness typically say that they would like help to enhance their social relationships[84], including romantic and sexual ones[85]. But they often find it hard to talk to staff in mental health services at all about their needs and wishes for social connection and reducing loneliness, and are rarely offered the help they want[86-88]. This may be partially explained by the lack of established models of support to help with loneliness in mental health care. Yet, a wide range of ways by which services could help these people have been developed. Four broad groups of interventions have been proposed[89]: changing cognitions; social skills training and psychoeducation; supported socialization or having a "socially-focused supporter"; and wider community approaches. However, all require further development and evaluation.

Recent years have seen increasing interest in supporting people to reduce loneliness, in clinical and public health contexts. Two current randomized controlled trials will add substantially to the evidence base for social interventions on loneliness in psychosis[90] and treatment-resistant depression[91]. Nonetheless, more research is needed. While the most effective intervention models will have to be established through clinical trials, creative collaborative initiatives in mental health practice are warranted to address the common unmet need for support with loneliness among people with serious mental health conditions, thus improving their social inclusion.

LEGISLATION

We identify four types of legislation that should be scrutinized for its impact on social inclusion of people with severe mental illness: equality legislation; legislation that includes discriminatory content specific to people with a mental health problem; criminalization of behaviors that may be associated with mental disorders, such as suicide and suicide attempts or use of illicit substances; and mental health legislation and policy.

Equality legislation

In the European Union (EU) and the UK, the European Employment Equality Directive and the subsequent EU Charter of Fundamental Rights have led to harmonization of legislation for people with disabilities along with other protected characteristics (age; gender reassignment; marriage and civil partnership; pregnancy and maternity; race; religion or belief; sex; and sexual orientation). In Germany, both general equality and disability legislation exists. In the UK, the Equality Act 2010[92] superseded the previous Disability Discrimination Act and covers all protected characteristics. We discuss this Act here as a comprehensive piece of legislation, to exemplify how disability can be defined; types of discrimination to be covered; coverage of pre-employment questions about health and disability; and consideration of when disclosure of a disability is needed for aspects of legislation to be implemented.

The Equality Act 2010 defines disability as a "physical or mental impairment which has a substantial and long-term adverse effect on the ability to carry out normal day to day activities"[92]. The Act prohibits several types of conduct. First, it prohibits direct discrimination, in which someone discriminates against a disabled person because that person is disabled. Second, it covers indirect discrimination: a person with a disability can claim that a particular practice or provision disadvantages persons sharing his/her same disability. Third, discrimination arising from disability occurs when an organization treats a disabled person unfavorably because of something connected with that person's disability (for example, an employer dismisses a worker because she has had three-month sick leave). The Act also refers to third-party harassment due to disability. Employers are liable for harassment of their employees by a third party (e.g., a customer) when: the employer knows that the employee has been harassed; harassment occurred at least twice; and the employer did not take reasonably practicable steps to prevent harassment recurring.

A significant feature of the Equality Act is that it makes it unlawful for employers to enquire of an applicant's disability or health, until that person has either been offered a job or been included in a pool of candidates to be offered a job when a suitable position arises. This restriction is qualified by several exclusions: questions required for national security vetting; making reasonable adjustments to enable the disabled person to participate in recruitment; establishing whether a job applicant would be able to undertake a function intrinsic to the job, with reasonable adjustments in place as required; monitoring diversity in job applications; supporting positive action in employment for disabled people; and, if the employer applies a requirement to have a particular disability, establishing whether the applicant has the disability. Nothing in the Act prevents employers asking about health-related questions once recruitment decisions have been taken.

While the Equality Act does not obligate disclosure of disability, a claim for direct discrimination or discrimination arising from disability can only be made when the employer/organization knew or ought to have known that the person was disabled; and no duty arises to provide "reasonable adjustments" if the employer/organization does not know or could not reasonably be expected to know that a person has a disability. However, in some circumstances, disclosure may be obligatory – for example, if a job environment is such that one's disability could present a risk to one's health and safety or that of colleagues.

Legislation with specific discriminatory content

In theory, legislation that covers any area of life could specify an exclusion of some people with mental health problems from valued social roles, particularly if it predates equality or disability legislation. The exclusionary criterion may for example apply to anyone previously and/or currently detained in hospital for treatment under mental health legislation. Identifying whether such exclusions exist is no small task. Doing so has taken either of two approaches; we present an example of each below. One involves the scrutiny of all legislation within one country, with a view to changes within that country across multiple pieces of legislation; the other examines legislation from multiple countries covering a specific life area to inform international action to promote national level change.

Scrutiny of all legislation in one country

The UK Mental Health (Discrimination) Act 2013[93] brought about changes to help protect individuals against discrimination on the grounds of mental health, with the broader aim of destigmatizing mental illness. It abrogated provisions in several pieces of legislation which could prevent people with mental health conditions from serving as members of Parliament, members of the UK's devolved legislatures, jurors, or company directors.

Members of Parliament had previously been disqualified if they had been detained under the Mental Health Act 1983 for more than six months. The Juries Act 1974 disqualified people from jury service if they were "liable to be detained under the Mental Health Act 1983" or were resident in a hospital due to mental disorder. Companies Regulations for England and Wales from 2008, 2009 and 2011 provided for the termination of a director's appointment on grounds of mental health problems.

Scrutiny of legislation across multiple countries regarding one life domain

In 2010, the EU Agency for Fundamental Rights published a report entitled "The right to political participation of persons with mental health problems and persons with intellectual disabilities" [94]. The project was started after the entry into force of the United Nations (UN) Convention on the Rights of Persons with Disabilities (CRPD)[95] in 2008, and in anticipation of the EU's ratification of it, which took place in December 2010. At the time of the project, the right to political participation was already legally protected by international and European instruments. However, the Agency found that 15 member states excluded people with mental health problems and/or intellectual disabilities from political participation.

In many countries, deprivation of the right to vote was often directly, and sometimes automatically, linked to the loss of legal capacity, in spite of a 1999 recommendation by the Council of Europe Member States that the deprivation of the right to vote should not be automatically linked to the loss of legal capacity or any other protecting measure, such as guardianship. In other countries, individual assessments were made of a person's capacity to vote, either starting from a policy of exclusion or one of full participation. Notably, in several countries with no limitations, restrictions had only recently been lifted. For example, the UK's Electoral Administration Act 2006 abolished a common law rule that a person lacks legal capacity to vote by reason of mental health problems.

An update to the EU report in 2024 showed that considerable progress had been made, such that 14 member states allowed full participation and several others had moved from blanket exclusions to those based on assessments[96]. However, seven countries continue to automatically exclude people under legal guardianship from the voting process.

Criminalization of behaviors that may be associated with mental disorders

Suicide and suicide attempts

The majority of people who die by suicide have a diagnosable mental health problem. As of 2025, suicide and attempted suicide are criminal offences in 25 countries worldwide, such that survivors of attempts are punishable by imprisonment or fines, while family members of those who die by suicide face fines. In another 27 countries, the legal status of suicide is unclear[97]. The situation has recently shifted in both directions. In 2022, Pakistan decriminalized suicide, while Jordan passed a new legislation imposing a fine and six-month prison sentence on those who attempt suicide.

The threat of criminalization may deter people from seeking treatment after a suicide attempt; and criminalization is likely to exacerbate an attempter's mental ill health and increase social exclusion through imprisonment and the stigma of criminality. Further, there is no clear evidence that criminalization deters people from suicide[98]. Campaigns such as Decriminalize Suicide Worldwide highlight these problems and support people in the relevant countries to speak out against this legislation[97].

Substance use

In 2022, Harm Reduction International[99] reported that, out of 128 countries, 115 criminalized the use and/or possession of drugs for personal use. For those with a substance use disorder, this can reduce access to treatment and increase social exclusion due to stigma and imprisonment, and there is no evidence that the threat of imprisonment deters people from drug use. In some countries, human rights violations occur at inpatient centres for treatment of substance use dependence, such as beatings and forced labor, denial of health care, and poor sanitation[99].

Mental health legislation and policy

Historically, mental health legislation has led to social exclusion resulting from institutional care which segregated people from society and frequently failed to provide treatment of sufficient quality to promote re-inclusion. Instead, custodial care impaired people's skills for everyday living and sense of identity[100]. Modern legislation seeks to avoid this by ensuring effective treatment in the least restrictive setting possible.

An important example is India's Mental Healthcare Act 2017[101], which represents a full-scale rewriting of that country's mental health legislation with the aim of consistency with the UN CRPD[95], that seeks "to promote, protect and ensure the full and equal enjoyment of all human rights and fundamental freedoms by all persons with disabilities, and to promote respect for their inherent dignity". The Act covers rights to good quality, geographically accessible treatment regardless of ability to pay, but also social rights such as housing when people have been abandoned by their family, as part of a commitment that "every person with mental illness shall: a) have a right to live in, be part of and not be segregated from society; and b) not continue to remain in a mental health establishment merely because he does not have a family or is not accepted by his family or is homeless or due to absence of community based facilities". However, there is the obvious risk that, without extensive implementation resources and effective destigmatization of mental illness, it will be a long time before the ambition reflected in the Act is realized.

India's Mental Healthcare Act and several recent mental health legislative reforms elsewhere provide for the expression of advance wishes in the event of loss of decision-making capacity, including preferences and specific refusals for treatment. Research shows high levels of consumer demand for these advance statements[102,103]. They offer significant benefits and opportunities to patients with severe mental illness, especially those most at risk for involuntary hospitalization[104-106]. Empowering individuals to express their treatment preferences and to promote early intervention can enhance autonomy[107], improve therapeutic relationships[108,109], reduce compulsory admissions[104-106], and facilitate social re-integration by mitigating the disruption to daily life caused by admission.

A common concern among clinicians is that advance statements may contain refusals of all psychiatric treatment[110-112] or that preferences will not meet clinical practice standards[113-115]. However, studies show that blanket treatment refusals are very rare, and that the contents are mostly compatible with standard practice[116,117]. Moreover, advance statements provide acute care clinicians with valuable information about what has or has not worked for the statement holder before, and what treatment that person will accept[116,117]. Nevertheless, potential issues such as legal complexities, communication challenges, and the risk of exacerbating rather than mitigating racial inequities in access, experiences and outcomes, as well as resource constraints, must be addressed to ensure the effective and ethical use of these documents[118].

A further implementation challenge identified in India is that mental health care is often oriented to what is best for the family, such that decision-making is done by families rather than the individual service user[119]. Therefore, research efforts must shift towards effective implementation, particularly for those who can benefit the most from advance statements[120,121].

SOCIAL INCLUSION FRAMEWORKS

Explanatory frameworks in psychiatry lie on a continuum, from those which provide explanations for mental health-related experiences at the individual level through to those locating the experiences within wider social processes.

The explanatory framework influences the importance attached to social inclusion. When mental health issues are understood as entirely decontextualized and internal experiences, system responses are oriented towards resolving the underlying issues in the individuals rather than supporting access to, or changing, their wider context. This can result in a primary focus on treating the individuals with evidence-based interventions, including compulsion in their best interests when needed, so that they can be restored, rehabilitated and made ready for future engagement in society. Some dangers of this approach are the sharp distinction between "well" and "ill", which may create secondary harms of stigma [122], rights violations especially within inpatient and institutional care[123], secondary traumatization arising from compulsion[124], and a failure to address the underlying social, economic and environmental determinants of health[125].

By contrast, if the mental health issue is understood as entirely social, then system responses are oriented towards changing society to make space for people with mental health issues to be valued, and to lead a contributing and satisfying life. Some dangers of this approach are that people may not receive effective treatments [126]; insufficient support may be given at the individual level to help people engage in societal institutions[127]; the global under-investment in mental health services may be exacerbated[128]; and people with severe and enduring mental health issues may be left to "rot with their rights on"[129].

So, explanatory frameworks matter for social inclusion. A quasi-systematic review identified 34 explanatory frameworks, organized into five types: biological, psychological, social, consumer, and cultural[130]. We group these five types into three broad categories of model: clinical (biological and psychological), disability (social), and diversity (consumer and cultural)[131].

The first category of explanatory frameworks in mental health systems, and the most widely used, is clinical models. Examples include biomedical, biopsychosocial and cognitive models. Each have a number of limitations. Biomedical models are based on the assumption that a biologically-grounded science of psychopathology is possible[132], although ongoing nosological debates[133] indicate that this assumption is not yet empirically justified. Biopsychosocial models have been criticized for prioritizing the biological[134] – as "foundational", in contrast to the psychological and social "correlates" of mental illness – and for purporting to offer, but not actually delivering, a holistic and contextualized understanding. Specific concerns include the lack of importance ascribed to subjectivity and personal meaning[135]; the epistemic weakness of these models, meaning that they should not be used as scientific frameworks with explanatory power[136]; and their focus on diagnosis over case formulation[137,138]. Finally, cognitive models place a stronger emphasis on interpretation mediating experiences. Although these models have more potential to work outwards from meaning to the social world, in practice most psychological therapy is based on similar assumptions to biopsychosocial models[139]: psychopathology differs in kind, not just degree, between clinical and non-clinical populations; psychological disorders reside *inside* the individual; and the clinician's task is to identify the disorder inside the person and provide a psychological intervention to eliminate the internal disorder. More recent psychological models, such as salutogenesis[140] and the power-threat-meaning framework[141], attempt to orient more towards societal influences on mental health and well-being, but have not yet gained international traction.

The second category of explanatory frameworks is disability models, the most widely used of which is the social disability model[134]. Disability models highlight the social foundations of disabling constraints placed on people with mental health problems. If mental distress is a socially situated response to social circumstances[142], then societal rather than individualized solutions are indicated. An example is the capabilities approach, which emphasizes the role of agency for individuals to achieve well-being. This approach was first articulated by Nobel Prize winner A. Sen[143], and then applied to health by M. Nussbaum, who explored its implications for justice, social inclusion, and citizenship[144]. The approach has relevance to disadvantaged groups[145], including those with significant mental health challenges[146]. For example, qualitative research using the theoretical lens of a capabilities approach concluded that "systems and professionals tend to shape social outcomes for people with mental distress through regulation and containment; however, the application of capabilities draws out the complexity surrounding this, the agentic, social and structural working in tension, and the power of the mental health system not removing peoples' agency"[147], which captures the intricacies many clinicians are aware of when confronted with socially situated mental health problems. Social models of disability have evolved with different emphases – e.g., the Scandinavian emphasis on social regulation and societal participation[148] contrasts with the North American focus on civil rights[149]. An influential framework developed at Yale University emphasizes the five Rs of citizenship: rights, responsibilities, roles, resources and relationships[150]. However, the evidence is that social models have not significantly impacted on public mental health[151]. As the British Medical Association put it, "Doctors struggle to support patients' mental health in a society which has not addressed social determinants, including poverty and racism"[152].

The third category of explanatory frameworks is diversity models, the most widely used of which is mental health recovery[153]. Other examples include Mad Pride[154] and spiritual emergence[155]. These frameworks intersect with new ways of doing research, such as survivor research[156], Mad Studies[157], and citizen science[158]. Diversity models use standpoint epistemologies to give primacy to the lived experience of individuals and groups, and criticize systems developed around professional priorities. They place an emphasis on inclusive and participatory approaches to both research and practice: "Nothing about us without us". A recovery orientation is the most incorporated – although some argue institutionalized[159] and co-opted[160] – diversity approach within mental health systems, and has underpinned system transformation towards approaches to improve social inclusion, such as shared[161] and patient-led[162] decision-making, a focus on citizenship[163] and human rights[164], and the development of new approaches including mental health peer support work[165] and Recovery Colleges[29]. In relation to social inclusion, a recovery approach highlights the impact of social and environmental conditions[166]. This leads to foregrounding of social and community aspects, including social relations[167], social movements[168], the influence of politics on experience[169], the role of activism[170], and the imperative of social justice[171].

Explanatory frameworks as a conceptual resource to improve social inclusion are available but have not been widely used. The dominance of clinical models in relation to resource allocation and institutional power structures may favor social exclusion, both directly by responsibilization (making the individual responsible for societal issues[172]) and indirectly by channelling resources away from societal change towards individual treatment. It may be argued that addressing social inclusion will require a mental health system and workforce with conceptual competence. For example, clinicians need training in epistemic pluralism – actively cultivating a plurality of "systems of knowing"[173] – in order to develop the epistemic humility[174] to apply different models.

INCREASING ACCESS TO VALUED ROLES

Employment

The ability to provide for oneself and others is key to social inclusion across most societies[175,176]. Not only does it offer the material means needed for many aspects of community participation; it also confers social status. Consistent with this importance, employment is associated with fewer experiences of discrimination among people with severe mental illness[10], and is an aspiration held by most of these people[177]. Here we discuss increasing access to employment in terms of interventions delivered through mental health services, and actions on the part of employers.

A wide range of strategies can be used by mental health services, including: a) pre-vocational strategies (simulated work, work in protective factories and sheltered workshops); b) systematic involvement of families and wider social networks to help with job finding and facilitate work in family business; c) supported employment strategies (job analysis and matching, job finding, job coaching, trial placement, work visits to observe real work and assist with performance appraisals); and d) entrepreneurship and self-employment initiatives[178].

Supported employment strategies include a highly specified model known as Individual Placement and Support (IPS), in which employment specialists embedded in clinical teams aim to support participants who would like to work in a rapid search for competitive employment, and then provide time-unlimited and individualized support to participants and employers. Membership of clinical teams facilitates identification of people who wish to work, while liaison with the work environment allows specialists to identify supportive employers and ensure compliance with equality legislation, for example in provision of reasonable adjustments to help people perform their job.

Several recent trials of supported employment, including the IPS, have tried to improve the success of the model through augmentation with various interventions, including cognitive training/remediation[179-183], cognitive therapy[184], job-related skills training[185], and the use of the CORAL (COnceal or ReveAL) decision aid regarding disclosure to a prospective or current employer[11].

While the above strategies are in use in several countries, and many have a good evidence base[186], many people with severe mental illness spend long periods with only access to primary health care, including in high-income countries. A scoping review published in 2018 identified locating employment interventions in primary care as a promising approach, although facing multiple barriers to implementation[187]. Vocational rehabilitation through primary care may be targeted to people with common mental health problems[188], but less accessible or ill-suited to people with severe mental illness.

A limitation of the IPS is that it is better suited to countries in which working for an employer is the norm. Self-employment strategies may need to be emphasized where unemployment rates are high, such as in many low- and middle-income countries (LMICs). Implementation strategies also need to vary in urban compared with rural areas. For people with severe mental illness, employment rates have been found to be higher in rural areas[4,5], despite relatively poorer access to treatment. These studies identified that the agrarian sector (farming or fishing), in which the great majority of survey participants worked, is more flexible than most other sectors, and more often involves other family members, allowing for periodic disability or a degree of long-term impairment.

Employers in many countries have become increasingly aware of the impact of mental ill health on absenteeism, presenteeism, productivity and financial outcomes. However, workplace interventions usually focus on common mental disorders, as does research on such interventions[189]. The lower prevalence of severe mental illness, and the lower employment rate of people with such illness, make it less likely that employers will identify the need for interventions for this group. This may compound the difficulties faced by these people, and increase their reliance on mental health services to support them into employment. This suggests an important role for supported employment specialists: while they work with employers to support individuals, they may be able to effect changes in employer behaviors in relation to potential employees with severe mental illness. However, studies of supported employment only evaluate individual level outcomes of trial participants rather than including employer level outcomes[190].

While interventions delivered by mental health services and action by employers can promote employment, other factors contribute to the ability of people with severe mental illness to obtain work, such as the general unemployment rate, the nature of the labor market, and any welfare benefits system[191]. As a form of income replacement, welfare payments contribute to social inclusion by allowing a degree of community participation, and may facilitate fulfilment of unpaid but valued social roles such as caring for dependents or voluntary work. Lack of access to welfare benefits can lead to great financial strain on family members, destitution in the absence of paid employment[192,193], or a sense that people with mental illness are discriminated against in relation to the benefits system[194,195]. On the other hand, the impact on benefits of working and/or losing work can deter people from seeking employment[191]. While there are studies of separate services to increase the uptake of welfare entitlements[196], there is little research on how the welfare system itself can best provide both income support and support to gain employment for people with severe mental illness.

Housing

Severe mental illness can lead to homelessness even in countries with welfare systems, for example when illness and hospital admission lead to eviction for non-payment of rent or a mortgage. People with comorbid substance use disorders are particularly at risk, due to the impact of these disorders on personal finances and on social networks[197]. One way to avoid these problems is through direct rent payments to landlords, for example when someone is already behind in rent payments. This requires legislation, which has to consider what process for consulting with the tenant there should be before this is done.

The Housing First intervention provides a tenancy on condition of community mental health service engagement, as part or all the rent is covered at the start of the intervention. Several trials of this in North America and France have shown positive results on housing stability and other outcomes important in terms of social inclusion. For example, at 4 years follow-up, the French Housing First participant group had better quality of life in two respects (autonomy and intimate relationships), lower symptom levels and lower use of hospital services[198].

In countries with little or no disability welfare payments, lack of employment creates dependency on family members who may or may not be able and willing to support their relative. This dependency and the risk of homelessness may be exacerbated in countries which also have low coverage of treatment for severe mental illness.

Education

Education can facilitate social inclusion through a wide range of opportunities for paid employment, self-employment or voluntary work, and by acquisition of skills and knowledge that facilitate choosing and developing leisure pursuits.

However, there is less research on interventions to increase access to education as compared to employment. A recent review[186] identified five randomized controlled trials (RCTs) which reported education outcomes in people with severe mental illness, though only one intervention was aimed specifically at educational outcomes rather than employment[199]. This skills training-based intervention – which taught various skills, including study, time management and basic computer abilities – was the only one to report significant benefits compared to usual care in successful enrolment in education at 6 months.

A pattern emerged from two studies using the IPS model[200,201] such that this intervention was associated with short-term benefits in getting participants into education. However, treatment-as-usual control groups caught up, such that similar proportions were studying at longer-term (12-24 month) follow-up. Two other pre-vocational skills training interventions which reported education outcomes, including one that added cognitive therapy[202] and another involving job-related skills training[203], did not find improved education outcomes in the medium or long term.

Recovery Colleges provide adult education tailored to people with lived experience of mental illness, while also being open to their informal supporters, mental health staff, and in many cases the public. They are based on principles of mental health recovery, co-production between people with lived experience of mental health problems and professionals, and adult learning[204-206]. The first college opened in 2009 in London, and since then numbers have grown: in 2021 there were 88 colleges in England[207], and in 2022 there were 221 colleges globally, spanning 28 countries[208]. Most colleges around the world exhibit high fidelity[209], though they operate differently. For example, relational and long-term aspects of recovery are emphasized in Japan, compared with a focus on personal learning and skills acquisition in England[210].

Recovery Colleges have potential to support social inclusion in three ways. First, intended outcomes for students with mental health issues who attend a college include improved occupational opportunities, expanded social networks and strengthening of existing relationships, less social isolation, and attainment of socially valued roles such as partner or parent[211], in addition to that of student. Second, a cluster analysis of Recovery Colleges in England identified three distinct types of college: strengths-oriented, with a health service focus; community-oriented, with a community and social connection focus; and forensic[207]. The community-oriented colleges work closely with local community networks, encourage local people with no existing connection to the mental health system to be students alongside people who use mental health services, thus addressing community stigma, and create routes into accessing community resources, such as mainstream educational and employment opportunities. In pursuit of stigma reduction and access to mainstream education, some Recovery Colleges are part of, or affiliated with, mainstream tertiary education providers.

Finally, Recovery Colleges provide a place for students to experience doing, being, becoming and belonging[212], and the latter two mechanisms create social inclusion outcomes. For example, the role of peer trainer is transformative for individuals in identifying their lived experience as an asset providing a route to employment rather than a deficit requiring treatment, and some students transition to paid or voluntary roles within the college[213].

Caregiving and parenting

A recent evidence synthesis on interventions to improve the social circumstances of people with mental health conditions did not find any systematic reviews or RCTs directly addressing the achievement or sustainment of intimate partner or family member roles, or maintenance of informal caring roles or custody of children[186].

Caregiving for adults as a valued social role has particular cultural importance in societies which emphasize the responsibility of members of younger generations to care for those who are older, such as those in which the influence of Confucianism is strong; and where access to formal services for support for frail or disabled people is limited. Research into the experience of family members of people with severe mental illness has shown that, while there are some negative aspects to this experience, there are also positive ones, including reciprocal caregiving[214]. It is, therefore, important that people with severe mental illness are not excluded from interventions to support caregivers, whether inadvertently or intentionally.

Available data suggest that around two-fifths of people with severe mental illness become parents, with a higher rate for women than for men. Similarly, a higher proportion of women have either their own children or stepchildren living with them[215]. There is some indication that these rates are increasing, likely due to increasing proportions of time living in the community and less time taking antipsychotics, which reduce fertility by increasing prolactin levels[216].

People with severe mental illness experience a range of difficulties as parents, due to symptoms, medication side effects, comorbid physical or substance use disorders, and internalized, interpersonal and structural stigma[217,218]. As a result, a range of recommendations have been made to create a system-wide, strengths-based, approach to supporting such parents, commonly referred to as family-focused practice. These include policy recommendations to reduce stigma and socioeconomic adversity and increase provision of trained staff; training to health and social care staff working with parents and children; monitoring, psychosocial support and respite care for children; and psychoeducation, practical and psychological support for parents[217]. Currently, implementation of family-focused practice is variable and challenging, not least because of the dual focus on adult and child family members required from service providers[219].

Overall, the evidence from a range of countries suggests the potential effectiveness of parenting programmes tailored to people with severe mental illness. However, a recent systematic review found that, while such interventions have been developed, only one small trial (N=50), from which no data could be extracted, has been published[220].

Romantic and intimate relationships

Intimate relationships are those involving romantic love, physical intimacy or sexual activity. These relationships are "a central aspect of being human"[221]. They are valued by most people with severe mental health problems as a key facilitator and indicator of recovery[85]. Yet, in clinical contexts, about two-thirds of these people are single[222,223]. They often report struggling to form and maintain romantic relationships[224]. For people with psychosis, satisfaction with their sexual life was the lowest rated of all life domains[225].

People with mental health problems commonly experience sexual stigma. Surveys of the public suggest that, for many people, mental illness is seen as a "dealbreaker", leading them to reject a potential romantic partner[80]. At the same time, people with mental health problems are viewed as more "sexually exploitable" than others[81], leaving them vulnerable to unwanted or upsetting sexual contact. People with mental health problems often absorb these attitudes and experience sexual stigma, e.g. believing that they are not viewed as acceptable romantic partners[223].

Relationship status satisfaction is inherently important, and is associated with higher well-being[226]. Romantic loneliness, more than family or social loneliness, is associated with suicidal behaviors[227]. Despite the importance of positive romantic/intimate relationships for many people who use mental health services, and their challenges in achieving them, these people often experience staff as uninterested in their problems in this area[87]. This has been described as the "institutional silencing of sexuality" in mental health care[228]. Mental health staff report numerous barriers and reservations to discussing people's wishes and needs regarding romantic/intimate relationships, and a lack of resources or guidance to support them in this respect[88,229-232].

We identified two small pilot studies of group interventions in mental health settings to help people with severe mental illness develop intimate relationships[233,234]. Both involved only men, with first-episode psychosis, and used psychological approaches. One brief paper from 2006[235] described an innovative social relationship agency in a voluntary sector organization in England dedicated to helping people recovering from a mental illness find and sustain social relationships. The programme comprised three elements: regular social events; group training about how to initiate and manage friendships and romantic relationships; and individual coaching to discuss past or present relationships and offer practical suggestions about finding a partner. However, there was no formal evaluation, and the service is no longer running. There is, therefore, an absence of established models of support with needs for romantic/intimate relationships suitable for mental health care contexts, although fulfilling these relationships is a cornerstone of feeling socially included and belonging for many people.

Community engagement

A broad approach to community engagement is to consider aspects of citizenship, as exemplified by the Citizenship Project[236], developed in the US for people with severe mental illness, whose aim is to support personal recovery by fostering the five Rs of citizenship described above (i.e., roles, resources, responsibility, relationships and rights).

The intervention involves peer mentorship, a citizenship-based curriculum, and "valued role projects". Peer mentors help participants identify and achieve goals, share strategies for supporting recovery, and advocate for participants' access to important social determinants of health, such as employment, housing, social services and education. The citizenship-based curriculum is taught by a community advocate and supports problem solving, life skills acquisition, knowledge of community resources, and social network development. Specific classes focus on self-advocacy, housing, relationship building, and social integration. In valued role projects, people draw on their lived experience and curriculum to develop, lead and participate in projects aimed at supporting others in their community. Participating in this intervention was associated with a decrease in substance use and an increase in satisfaction with quality of life, employment, finances and social activity[236].

Turning to specific activities, engagement in community arts, volunteering or social groups offers critical opportunities for individuals to build social connections, enhance their coping strategies, and develop a sense of belonging. Participants in community programmes are often motivated by the opportunity to connect with others and the chance to experience positive emotions through shared activities[237].

For example, the "Art Lift" intervention, which offered ten weeks of art delivered by an artist in UK general practice, showed significant improvements in well-being among participants with mental health problems[238]. This intervention provided a safe space for creative expression through various art forms, such as painting, ceramics and poetry, facilitating the development of social networks and reducing feelings of isolation. However, this programme was not focusing on people with severe mental illness, and there are likely to be barriers – such as lack of motivation, opportunities, confidence, and social skills – to participation of these people in programmes of this kind. So, there is a need to develop specific projects that can be successfully implemented across a range of settings, and to identify enablers to participation and address the above-mentioned barriers[75,76].

There is some evidence[239] that group and facilitated nature-based interventions – including green exercise, therapeutic horticulture, and therapeutic offers such as forest bathing (i.e., immersing oneself in the forest environment through mindful, sensory engagement) – can improve mental health. While there is limited evidence for these interventions in people with severe mental illness, their focus on low-pressure, structured exposure to the natural environment makes them possible candidates for further development and testing.

Overall, this preliminary evidence suggests that social prescribing, arts-based and nature-based interventions, integrated into a structured multi-component programme, may be effective in fostering social inclusion in people with severe mental illness. Additional research is needed to refine their design and break down barriers such as low motivation and confidence, leading to more accessible and sustainable models for these people. Future studies should prioritize optimizing delivery models, evaluating feasibility and acceptability, and identifying the core mechanisms that can support sustained participation.

THE ROLE OF MENTAL HEALTH PROFESSIONALS

What can clinicians and other front-line practitioners do to support social inclusion? We identify example approaches relating to knowledge, attitudes and behavior.

At the knowledge level, clinicians can develop an understanding about the problem. Several UN reports[240-242] have identified rights violations as still frequent in mental health systems internationally. Global issues include institutionalization, isolation, segregation, and control through involuntary and compulsion-based approaches to management of people with mental health issues, especially those in crisis[243,244]. In relation to human rights legislation, the CRPD[95] was adopted in 2006, and has since been ratified by 185 of the 193 UN member states. The Convention comprises 50 articles describing the rights of persons with disabilities, including those arising from mental health issues, to independent living, education and employment, health, habilitation and rehabilitation, food, clothing, housing, justice, transportation, information technology, and voting. Articles 12 (being allowed to exercise legal capacity) and 14 (not being deprived of liberty unlawfully or arbitrarily) are particularly challenging to current mental health practice.

To address widespread non-compliance with CRPD at national level, the World Health Organization (WHO) developed in 2012 the QualityRights framework[245], which provides a range of resources to monitor and improve quality and respect for human rights. Of specific relevance to clinicians is the e-training toolkit published in 2022[246], which is intended for use by all mental health stakeholders, including clinicians. The training is available in multiple languages, and the toolkit comprises core and specialized modules. Core training covers human rights, legal capacity, recovery and freedom from coercion, violence and abuse. Specialized training covers recovery practices, strategies to end seclusion and restraint, and supported decision-making and advance planning.

The QualityRights approach has been implemented in many countries, including Afghanistan[247], Brazil[248], Czech Republic[249] and Lithuania[250]. There is emerging evidence from Ghana[251], Iceland [252] and India[164] that completing QualityRights e-training leads to beneficial staff attitudinal shifts. Integration with the World Psychiatric Association (WPA) programme on implementing alternatives to coercion in mental health care is underway[253]. In India, a pragmatic trial, involving implementation of QualityRights at six public mental health services, showed that, over a 12-month period, the quality of the performance of those services receiving the QualityRights intervention improved significantly. The mental health professionals at the sites showed substantially improved attitudes towards service users, and these users reported feeling significantly more empowered, and satisfied with the services offered. Caregivers at the intervention services also reported a moderately reduced burden of care[164].

At the attitude level, clinicians can develop an orientation towards supporting people's personal recovery (i.e., living a meaningful life in the context of mental illness)[153,254]. An international consensus has emerged about orienting mental health systems towards personal recovery and associated values such as rights-based and person-centred care. This orientation is now recommended by national policies in many countries, for example Australia[255], Canada[256], Hong Kong[257], India[258] and the UK[259], as well as in multinational guidance[260-262]. Cultural adaptations of the concept of personal recovery have been investigated globally, for example in Brazil[263], Japan[264], Poland[265], Spain[266], South Africa[267] and Taiwan[268].

A recovery orientation improves social inclusion: "People do not recover in isolation. Recovery is closely associated with social inclusion and being able to take on meaningful and satisfying social roles within local communities, rather than in segregated services"[269]. Indeed, facility-based mental health care is on its own not equipped to meet social needs, such as addressing poverty and social isolation. It is, therefore, important to map resources that already exist in the community, and to maximize their accessibility by people with severe mental illness, also by establishing good working relationships with key people in the relevant sectors[261].

The impact of a recovery orientation on psychiatric professional practice and education has been explored in Austria[270], New Zealand[271], the UK[272] and the US[273]. Implementation approaches – and transformations from traditional practice – identified in systematic and umbrella reviews[274-276] include developing an organizational commitment to recovery[277], centering organizational culture around lived experience[278], facilitating access to community-based participatory arts[279] and leisure activities[280], supporting the social relationships which drive recovery[281], and political engagement to address structural discrimination[282].

At the behavior level, an important approach to improving social inclusion is focusing on decision-making style in clinical practice. A 2023 umbrella review found that decision support tools addressing social inclusion (e.g., social prescribing, work, lifestyle, housing, social/leisure activities) are needed, since most existing decision aids focus on psychopharmacological treatment[283]. One exception to this is the CORAL decision aid regarding disclosure of a mental illness in the employment context, relating to either current or potential future employment[11].

A promising development is peer-facilitated decision-making, in which peer support workers assist with decision-making as part of their wider role[284]. Peer support workers are oriented towards community engagement and integration, being well-placed to support social inclusion goal-setting and goal-striving.

PEER ROLES

Peers are a new resource emerging internationally to support social inclusion. A peer is someone with direct, first-hand past or present experience of an issue[285]. In a mental health context, a peer will typically have personal experience of mental health issues, whether formally diagnosed or not, and/or using mental health services.

This lived experience provides one type of knowledge. Other types of knowledge arise from loved, labored or learned experience [286]. Loved experience emerges from a role as a carer, family member, friend or colleague of a person with mental illness. In mental health, sometimes the term "peer" is also used to include loved experience. Labored experience is gained through work roles, such as clinician, police officer or teacher. Learned experience is obtained through researching or studying mental health and associated systems.

These four types of knowledge are not distinct. Many clinicians and researchers have a dual identity of both labored/learned and lived/loved experience[287]. For example, a national survey in the UK found that 40% of clinicians also have lived experience, and 75% also have loved experience[288]. The integration and use of this lived and loved experience within clinical practice can be challenging[289,290]. However, therapist self-disclosure supports recovery[291,292], and decision-making frameworks for staff with dual identity are emerging[293].

A recovery orientation tends to emphasize loved and especially lived experience. One benefit of this re-orientation is an increased emphasis on social inclusion. Indeed, there is a growing body of evidence showing a positive impact on social inclusion for people receiving peer support, including increased social functioning[294], higher satisfaction with family life and sense of community belonging[295], improved social network support[296], and stronger community integration[297]. The peer support worker also benefits: an umbrella review found that this role provides a route back into employment and improved social inclusion for the worker[298].

The Indian state of Gujarat used the WHO's framework[245] to bring reform of mental health services since 2014-2016. One of the key developments was to introduce peer support volunteers in these systems to practice a recovery-oriented approach. These were people with lived experience of severe mental health conditions seeking care and treatment at the six intervention sites, volunteering part-time to support other persons with lived experience to fill out their recovery plans, and to organize and conduct monthly peer group meetings. One of the significant policy shifts towards sustaining this project was the provision of resources by the government of Gujarat since June 2016. The current funding provides for 35 peer support volunteers with a plan to increase their numbers over time[299].

A model of peer-like support that promises to be acceptable, feasible and scalable comes from rural India[300]. In this model, called *Atmiyata* (which means shared compassion and empathy in local language), community volunteers are trained to become "champions" or "friends", providing support and basic counseling to people with mental health problems, connecting them to social resources, and referring those with severe mental health conditions to the public health system.

Despite the growing interest in peer support, several challenges remain for integrating this support within formal health systems and for it to be seen as a legitimate intervention. In a primarily biomedical model, where people with lived experience have the least power, a peer support intervention requires an ecosystem change to a rights-based and recovery-oriented perspective. Further challenges are the need to develop peer support models that are co-designed with the communities, that really follow peer support principles in spirit and practice, that are evaluated for their effectiveness, and that have sustained funding pathways.

ADVOCACY

Advocacy has long been recognized internationally as a central component of mental health policy[301]. With a view to social inclusion, it is important to distinguish between advocacy which is part of the role of health and social work professionals[302], and the designated role of a patient advocate acting independently[303].

Taking the former, the potential impact that physicians' advocacy can have in reducing discrimination[304] has been acknowledged, agreeing that professionals could champion much needed structural changes through health care quality improvement and development of new policies. Mental health professionals can highlight service users' barriers to seeking and engaging with treatment, obstacles to rehabilitation due to discrimination in employment and within social networks, reluctance to pursue economic and social opportunities due to the anticipation of discrimination, and negative self-evaluation due to internalized stigma[305].

In other fields of medicine, especially primary care, there is an increasing focus on physicians' social accountability and advocacy. Several North American organizations have expressed a pressing need for advocacy training in medical education[306]. The Royal College of Physicians and Surgeons of Canada published a Physician Competency Framework, introducing health advocacy as one of six main competencies. The role of health advocate was described as "to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change"[307]. These competencies have been adopted for psychiatry training in several countries, such as for instance Ethiopia[308], where psychiatrists are likely to be called upon to develop policy, services and training, and to join with service users to advocate for better services.

Across many countries in the Global North, including the UK and Ireland[309], New Zealand, Australia and Canada[310], advocacy is also provided independently from statutory and mental health services, an approach identified as a foundational principle. Independent advocacy has been characterized by its potential to empower people through social inclusion, equality and social justice[311]. Moreover, the emphasis on advocacy's independence has been to mitigate against the potential for conflicts of interests, as the best interests of health professionals will not always align with those of service users[303].

Other forms of advocacy have a role in fostering social inclusion[312]. Citizen advocacy is centred on the involvement of unpaid volunteers trying to ensure that the voice of vulnerable people is heard. Peer advocacy involves somebody with lived experience functioning as an advocate by virtue of sharing a similar experience. Collective advocacy can include lobbying for improved access to mental health services, housing, work, education, and basic resources. Research documents the role of mental health service user organizations involved in collective forms of advocacy, as well as the precarity of this work due to resource limitations[312].

When considering the role of advocacy, understanding how culture can influence expectations and activities is part of developing a stronger evidence base. In a recent review[313], drawing mainly on collective advocacy, it was found that, within the Argentinian context, civic participation was a central part of belonging and identity, offering a fertile ground for involvement in mental health activism. Similar facilitators to involvement in mental health advocacy were noticed in South Africa, in relationship to the Treatment Action Campaign. These cultural conditions were found to contrast with the situation in Ethiopia, where civic participation is less common, making it challenging for advocates to negotiate the terrain and influence change.

STRATEGIES TO REDUCE STIGMA AND DISCRIMINATION

At the structural level, changes to discriminatory laws and implementation of equality legislation that includes people with mental illness have been discussed above. Structural level discrimination can in addition be addressed through interventions targeted to key occupational groups with the aim of creating organizational change. This includes both groups who have societal influence such as media professionals, and groups with professional contact with people with severe mental illness, such as health care, emergency service and criminal justice professionals. Finally, interventions can be aimed at the general population.

Media professionals

Mass communication sources, including the news media, provide fundamental frameworks through which most people come to perceive and understand the contemporary world. When mass media frame a group in a negative light, this propagates prejudice and discrimination. Media often reinforce common stereotypes of people with severe mental illness by providing a negative image of such people, who are labelled as dangerous or unpredictable [314-316]. Hence, whether intentionally or not, they may become social structures for perpetuating stigma[317].

Media professionals have therefore been a target group for behavior change interventions, most commonly the provision of guidelines on reporting, with or without monitoring to allow media outlets to be held accountable when guidelines have not been followed[318]. Other interventions have comprised contact-based education for journalists and journalism students.

Given the effectiveness of guidelines for reporting on suicide[319], and of contact-based education for stigma reduction among other groups[190], these approaches are promising and worth considering, though a systematic review of research on such interventions found limitations with respect to small sample sizes and short-term follow-ups[318].

Health professionals

A recent umbrella review[320] found that 68 reviews have been published since 1994 on stigma reduction interventions among health care staff and students. These focused on pre-qualifying stigma reduction programs for trainees, such as nursing and medical students, and in-service programs for qualified staff. More recent reviews have covered community pharmacy staff and students[321], and physiotherapy professionals and students[322], reflecting the recognition that stigma reduction is important for the provision of good quality care by all professionals. The stigma-related outcomes included changes in knowledge, attitudes, and clinical skills, as well as clinical confidence and self-efficacy[323,324]. Six meta-analyses reported small to medium effect sizes in improved attitudes; a range in effects on knowledge from negligible to large; and medium to large effects sizes in clinical skills[325-330].

A consistent finding is that interventions for health care professionals are more effective when tailored to the professionals' clinical setting and training requirements, for instance by covering specific diagnoses or providing tailor-made contact interventions[331]. Another is that the evidence for improving attitudes is greater for students in clinical settings where patients demonstrated recovery[332]. Two reviews suggested that interventions should be repeated regularly to sustain changes over time[330,333]. Many reviews recommend including people with lived experience in the design and evaluation of stigma interventions, in addition to providing contact through live or filmed recovery testimonials[334,335]. Some studies reported that both live and filmed contact were more often associated with better outcomes on stigma-related knowledge and attitudes than were educational interventions alone[326] or interventions with only one form of contact[336].

Two reviews focused on e-interventions for professionals, both reporting improved knowledge and attitudes, more humane treatment of service users, and reduced use of coercive methods[337,338]. Fully online interventions are effective at stigma reduction when they are multi-component, including educational tutorials, case-based instruction, and practice-based learning[337]. Internet-based anti-stigma campaigns have also been reported to reduce stigmatizing attitudes among health care staff[339].

The use of digital interventions and simulations – e.g., "serious games" or standardized role plays with actors or virtual patients – has increased in part due to COVID-19 pandemic restrictions. In all the studies reviewed, there was a benefit of simulations on stigma reduction[328,339-342]. A meta-analysis showed a small to medium effect size on learners' attitudes, and a large effect size on clinical skills at immediate follow-up for simulation interventions, as well as sustained benefits three months later[328]. Another review reported that staff empathy improved with narratives of students' personal experiences, exposure to individuals with lived experience, and reflective sessions, but did not improve with simulations, suggesting that direct contact and practice-based components are necessary for more positive effects on stigma reduction[343]. Similarly, the authors of a review on virtual reality interventions for health care and other students recommended that, while these have some potential, they should not be used in isolation and instead be combined with direct contact and education[344].

Few such studies have been conducted in LMICs[345-347], with China being the most frequently represented middle-income country[326,332,348]. It is clear that greater emphasis is needed for long-term collaborations between LMICs and high-income countries to pool resources and data[347]; assess the sustainability of impacts or effectiveness[339]; and develop cultural adaptations of the anti-stigma programs[347,349]. A further key challenge is that not all studies have used well-adapted outcome measures for stigma and discrimination, particularly in LMIC settings[345,346,350-353]. Researchers recommend more mixed methods with qualitative components[334]. Cost-effectiveness was also a common research gap [334,347,354], as were meta-analyses[334,354].

Stigma reduction interventions aimed at health professionals rarely address issues such as access of people with severe mental illness to screening for and management of physical health conditions. However, health professionals have a key role in preventing and addressing discrimination of these people regarding physical health care.

For instance, one contributor to poorer survival rates of people with severe mental illness after cancer diagnosis is unequal access to cancer screening[355,356]. A Western Australia data linkage study found that these people are more likely to present with metastases at diagnosis than the general population. This and other studies have found that these patients are less likely to get surgery and radiotherapy, and receive fewer chemotherapy sessions[357]. Among women, delays in help-seeking are particularly problematic, because of their increased risk of invasive cervical cancer, due to the higher prevalence of risk factors such as sexual abuse and risky sexual behavior. As routine cancer screening becomes more widespread, programmes to ensure its equitable implementation in people with severe mental illness are needed, requiring collaboration among mental health, primary care and radiology professionals[358].

A review of cancer screening, prevention and treatment[359] identified three factors which may play a role in reduced rates of oncology treatment uptake in people with severe mental illness: fragmented health services (primary, oncology and mental health care), health professionals' stigmatizing attitudes and behavior, and diagnostic overshadowing (i.e., the attribution of symptoms to the mental condition, which may delay appropriate diagnosis and treatment)[360].

Strategies to promote equitable access to and uptake of effective screening and early treatment of physical health conditions in people with severe mental illness are key priorities, and should make use of existing evidence such as that on informed choice tools[361] and implementation science[362]. Prejudicial assumptions by health professionals concerning, for instance, non-attendance at appointments or poor adherence to treatment[363] should be acknowledged as forms of discrimination and become the target of specific anti-stigma interventions.

Mental health professionals

While some evidence on mental health service users' experiences of discrimination[364,365] suggests mental health professionals as a target for stigma reduction intervention, any such intervention needs also to take into consideration these professionals' potential role in helping service users respond to discrimination, or acting in other ways as an anti-stigma change agent[366]. For example, qualitative interviews of a sample of the CORAL intervention group showed that many participants wanted to discuss their decision with a mental health professional in conjunction with working through the decision aid[367].

A 2024 systematic review[368] of the feasibility and effectiveness of training for health professionals in anti-stigma competency or related skills retrieved 39 studies, four of which reported interventions for mental health care professionals[305,369-371]. The content of programmes varied: some covered mainly interpersonal stigma reduction, others focused on social determinants of health, and some included advocacy at the structural level. While there was some evidence of effectiveness, it proved difficult to compare effectiveness across programmes, given the wide variety in content, duration, teaching methods, and outcome measures. Most studies were carried out in high-income countries, making it difficult to assess feasibility for LMICs. The authors concluded that, to maximize its relevance to the communities served, any intervention for mental health care professionals needs to link to the professionals' roles; be developed following a situational analysis; and include local people with lived experience of mental health problems in the delivery. Training should use interactive delivery methods, and evaluation should examine behavioral change.

Following this review, members of the INDIGO Partnership research team developed Responding to Experienced and Anticipated Discrimination training for health professionals working in mental health services (READ-MH)[12] in China, India, Ethiopia, Nepal and Tunisia. A cultural adaptation matrix was applied to create site-specific content relevant to the socio-cultural context, with specific examples of adaptation to each site. Delivery methods included facilitated group discussions and testimony from an expert by experience, and didactic content. Evaluation used a knowledge quiz tailored to the course content; a measure of attitudes to addressing stigma as part of one's professional role; and an objective structured clinical examination comprising a simulated mental health service user asking for advice on disclosure of his mental illness in the context of a potential marriage, to assess skills in responding to anticipated discrimination. Statistical analysis of the results is currently underway. However, qualitative feedback from each site suggests a positive impact on subsequent practice.

Criminal justice professionals

Criminal justice professionals are another key group for stigma reduction interventions. The deinstitutionalization of mental health services has led to a significant increase in contact between these officers and people with mental illness when they are unwell or are victims of crime.

A recent review[372] focused on training correctional staff (probation, parole and custodial officers). Most interventions were educational, with one including contact-based elements. A meta-analysis of six studies found a small positive effect on stigmatizing attitudes.

General population

While many countries or regions within countries have conducted, or are currently conducting, population-level anti-stigma programmes, only some have evaluated their impact on stigma towards people with severe mental illness.

Initiatives to promote awareness of and reduce stigma and discrimination against people with schizophrenia include the WPA's Open the Doors programme[373]. This was launched in 1998. Local action groups were set up in 20 countries across Africa, Europe, North and South America, and Asia. However, evaluations published in the academic literature are sparse. We found one from Germany[373], where surveys were undertaken in intervention and control cities before and after the interventions, which mainly comprised workshops for media professionals and panel discussions at public events. The evaluation found improvements in intervention cities, in terms of reduced desire for social distance in relation to transient social relationships but not closer relationships, while in control cities there was no change.

In England, the Time to Change stigma reduction programme (2008-2021) comprised social marketing, intergroup contact events, and work with employers and several target groups[374]. It covered both common and severe mental illness, and the evaluation designed for it just asked about mental illness in general[375]. However, vignettes of people with depression and schizophrenia were used in a separate survey carried out in 2007 and 2015 as part of the British Social Attitudes Surveys, conducted by the National Centre for Social Research. In 2023, two years after the end of the programme, the same vignettes were added to a repeat of the evaluation survey[376], so that both measures using general terms (mental illness or mental health problems) and measures using vignettes of people with depression and schizophrenia could be compared.

The stigma measures using questions about mental illness or mental health problems in general showed an increase in stigma between 2019 and 2023, following the improvements seen between 2008 and 2019, such that, although attitudes were still more positive since 2008, stigma-related knowledge and willingness to interact began to decline before the end of the programme and were finally the same as in 2009. In contrast, the questions based on vignettes of men with depression or schizophrenia showed reduced desire for social distance since 2007. This latter finding may reflect a more lasting impact of the programme, which promoted supportive contact with family, friends and colleagues experiencing a mental health problem[377]. Vignettes about an individual create a sense of familiarity and hence may generate more empathy. In contrast, the responses to the questions about social distance from anyone with a mental illness may reflect a greater desire to avoid others who are unknown, which is consistent with the decline in support for community-based care[376].

Internalized stigma

Internalized stigma, or self-stigma, can occur because of awareness and endorsement of stereotypes by labelled people. This phenomenon is common, reflecting implicit attitudes learned before diagnosis[378], public stigma awareness, and discrimination experiences[379]. It hinders social inclusion, due to avoidance of social and economic opportunities, and interferes with treatment engagement[380]. It is associated with lower self-esteem[381], self-efficacy[382], hope[383] and empowerment[384], and poorer functional[385] and clinical[386] recovery.

A 2015 review[387] identified four interventions for which there is evidence of effectiveness with respect to some outcomes of interest. Psychoeducation aims to increase and apply knowledge using critical thinking to reject stereotypes[388]. Narrative methods, such as Photovoice[389] (taking photographs, in this case to help express the impacts of stigma and facilitate group discussion on how these impacts can be overcome) and narrative enhancement and cognitive therapy (NECT)[390], help people to make sense and create meaning from past experiences and to perceive the self as an active agent. Behavioral decision-making[391] uses tools and experiences to increase hope, empowerment and action directed at one's goals and according to one's values. Cognitive techniques are used to challenge and replace self-stigmatizing thoughts and beliefs[392].

Since that review, a study has used intergroup contact among young people with and without experience of a mental health problem to address internalized stigma, with promising results[393]. Intergroup contact has a good evidence base as a means to reduce prejudice between groups with a history of conflict[394].

Complaints to organizations have been effective in leading to changes in stigmatizing behavior. UK examples include complaints against the coverage of a well-known former boxer's psychiatric inpatient admission in 2003, and the marketing of a "mental patient" Halloween costume in 2013[395]. People with severe mental illness may also wish to complain to services about discriminatory decisions[396].

A recent umbrella review found 34 reviews of interventions for self-stigma, all published between 2012 and 2024[320]. In general, the reviews included studies which reported either an improvement in self-stigma, or in a similar outcome such as stigma stress or self-efficacy. Two reviews with meta-analysis found that the improvements in self-stigma became non-significant over time[397,398], with two exceptions: NECT[399] and the Honest, Open, Proud (HOP) intervention[400,401] (a three-session group programme usually run by pairs of trained individuals with lived experience of mental illness, focusing on self-disclosure[402]).

Differentiation of interventions was recommended for groups with different needs, such as people experiencing intersectional stigma related to gender, ethnicity or employment status[397]. Only two reviews focused on LMICs, finding positive effects of psychoeducation on self-stigma, self-prejudice, and coping with stigma.

Most self-stigma interventions are delivered to groups, a barrier for people unwilling to disclose a mental health condition. There are also limitations to individual cognitive and behavioral therapy, which has been criticized for pathologizing an understandable response to awareness of public stigma and experiences of discrimination[403]. Preference may be given to interventions that are widely accessible, such as psychoeducation[404,405]; do not require group attendance, such as peer support[406,407] or digital interventions[408]; and target help-seeking[409]. A clear learning is the need to assess interventions delivered outside health care, such as social marketing campaigns, which aim to reduce stigma from its sources, but may also reduce self-stigma.

RECOMMENDATIONS FOR ACTION

A common reason for structural exclusion of people with severe mental illness, especially at the level of legislation and policy, is the assumption that they lack decision-making capacity at all times or in relation to all decisions. Another repeated finding is that programmes which aim to either reduce mental illness-related social exclusion through stigma reduction, or to increase social inclusion, tend to neglect severe mental illness. Stigma reduction programmes without a focus on diagnoses often imply targeting common mental disorders through communication that "we all have mental health" or through messages about the prevalence of mental health problems, while those that do focus on one or more diagnoses most commonly do so on depression. We suggest that a combination of both is the most problematic, by appearing to include all illnesses but then only covering some. Evidence for this comes from qualitative interviews of people using the "Every Mind Matters" web resource launched in England in 2019. Fewer mental health problems were covered due to diversion of funding during the COVID-19 pandemic, causing disappointment among some users of the site with more severe problems[410].

It seems that, where services exist for people with severe mental illness, this creates the risk that these services are expected to do everything to promote social inclusion for everyone with a severe mental illness. These people are then excluded from services and opportunities in the community from which they may benefit[411]. The goal of social inclusion requires that mainstream services and opportunities are fully accessible to people with severe mental illness, and that mental health professionals make full use of them.

On the other hand, many people with severe mental illness face particular challenges, for example in relation to loneliness and valued social roles such as paid employment and parenting, for which tailored programmes are needed, with input from both mental health professionals and people with lived experience. The recommendations below aim to maximize inclusion by striking a balance between mainstream and tailored programmes.

1. Amend legislation and policies based on assumptions about mental capacity

Extrapolating from the above-mentioned UK and EU examples, it seems possible that there are many pieces of legislation and many policies which exclude people with current or previous severe mental illness from taking up specific roles, carrying out forms of social participation, or making decisions about their own lives. This discriminatory situation arises when legislation and policies are based on assumptions that having lost decision-making capacity at one time, this cannot be recovered; or that, because decision-making capacity has been shown to be impaired in relation to one type of decision (such as health care), it is impaired in relation to other types of decision, such as voting preference or decisions about personal finance.

Our first recommendation is that governments scrutinize all legislation that potentially contains discriminatory clauses such as these, and amend it to eliminate discrimination based on mental illness. As mental health legislation itself may contain discriminatory aspects[412], we recommend review of this legislation using established frameworks[245], with the aim of reform where needed to promote autonomy and choice, supported by advocacy and shared decision-making processes.

2. Decriminalize suicide, attempted suicide, and use and possession of substances for personal use

Legislation that criminalizes suicide in line with religious prohibition is ineffective[98] and harmful. In countries where suicide is still illegal, civil society organizations, such as health professional representatives, charities and patient and carer groups, can draw hope and learn from the recent successful social and mass media campaign “Patients not Criminals” in Pakistan, which involved engagement of policy makers, media and mental health professionals, and speaking out by those with lived experience of the impact of this legislation[413].

Similarly, focusing on harm reduction and treatment for substance use disorders instead of criminalizing possession of drugs for personal use would benefit the significant proportions of people with severe mental illness who have comorbid substance use problems[414].

3. Improve the evidence base for the effectiveness, cost-effectiveness and implementation outcomes of interventions aimed to foster social inclusion

This review has highlighted limited evidence for effectiveness, cost-effectiveness and implementation outcomes of interventions aimed to foster social inclusion for people with severe mental illness in several areas.

In relation to education, in addition to the evidence of Recovery Colleges’ effectiveness in relation to broad aspects of social inclusion such as social network size and vocational outcomes[415], we recommend research on these Colleges’ effectiveness as an adult education model in facilitating access to mainstream education. As an intervention more tailored than Recovery Colleges to help people with severe mental illness to access education, supported education has been the subject of a few trials, but the evidence base is much less than for supported employment[186]. As the success of the latter is for many people limited to gaining low-paid, low-skilled work, we recommend more focus on interventions such as supported education which may open up more career choices. Further, education may help people develop other skills important in facilitating social inclusion, from literacy to social skills.

Regarding tailored interventions to support intimate relationships, the case has been established that these are needed, and a small number of trials of some interventions are now underway. There is likewise a case for the development and evaluation of parenting programmes tailored for people with severe mental illness with children of each age range. It appears that some programmes have been developed, but neither usable trial evidence nor evidence from other controlled study designs is available[220]. Intervention components that may influence feasibility, acceptability, maintenance of fidelity and sustainability should be identified during the adaptation process to maximize future equitable implementation.

4. Enable staff of mental health and other services to work in ways that maximize access to local resources which promote social inclusion

Several factors hinder access to community assets to promote social inclusion by people with severe mental illness. Within mental health services, there is an under-emphasis on the importance of maintaining knowledge of these resources and good working relationships with relevant providers during training. This lack of emphasis may reflect prioritization of treatment provision and risk assessment in those services. Within community assets, barriers limiting openness to working with mental health services include stigma, lack of confidence in dealing with people with severe mental illness, and low capacity. At the structural level, historically poor relationships between the statutory and voluntary sector in some countries and insecure funding for some community resources hinder development of partnership working.

Resource mapping[416] of community assets is one step in the process required to ensure effective access to these assets by people with severe mental illness. The mapping process must be repeated regularly, as new organizations start and others are defunded or change their mission. Mental health professionals must form and maintain good working relationships with community service providers, such that they transfer skills and knowledge and advocate for their clients while avoiding either allowing stigma to go unaddressed or making counterproductive accusations of stigma. They must also work with their clients in ways that increase their self-confidence, for example through shared decision-making.

Community service providers must consider their obligations under equality legislation covering people with disabilities, including those with additional, intersecting characteristics that can lead to even more marginalization, and work to ensure equity. Gaps in services identified through mapping that result in geographical variations in access must be flagged to relevant organizations. Research is needed on services where mental health and other community services work together well, to identify strategies for successful spread and sustainment.

5. Engage with employers to design jobs with more flexibility

The flexibility of the agrarian sector promotes employment for people with severe mental illness, whose symptomatic and functional outcomes are better in rural than in urban areas, despite less access to health care. As urbanization continues across the world, it poses a significant threat to many of those currently benefiting from agrarian employment, and an enormous challenge to all those with an interest in employment for people with severe mental illness.

Although supported employment is now widely provided in many countries and heavily promoted by those involved in its development and evaluation, its implementation is unlikely to make it universally available at all times during the life of someone with severe mental illness. Further, this approach has limitations in terms of who benefits and where[417], and the types of jobs that recipients gain, which in some economies are scarce[178], and in other economies are available but are low paid.

We recommend that people with lived experience, mental health professionals and employer representatives collaborate with the aim of identifying, implementing and monitoring the types of workplace accommodations needed for people with severe mental illness to work in mainstream employment. National policies to mandate and/or incentivize this process are needed, followed if needed by litigation in response to implementation failure. We further recommend that vocational rehabilitation specialists and Recovery Colleges provide training and teaching on self-employment.

6. Include severe mental illness explicitly in stigma reduction programmes and target structural along with interpersonal discrimination

The association in the public perception between psychosis and violence may make stigma reduction harder in relation to this group. There is some evidence for this based on analysis of newspaper coverage of mental illness over the course of England's Time to Change stigma reduction programme. While the probability of articles about other diagnoses being coded as stigmatizing fell over time, this was not the case for articles including the term schizophrenia, for which it was unchanged in 2016 and 2019 compared to 2008 and 2009[418].

Ignoring the greater difficulty in reducing stigma against this group risks exacerbating existing differences in levels of stigma between those with common versus severe mental illness[419], and potentially even increasing the level of stigma towards people with severe mental illness through "othering", since excluding psychosis or other less common conditions from campaign content may imply that stigma reduction is somehow not merited in relation to these groups.

Just as it is all too easy to focus on common mental disorders when delivering stigma reduction programmes, it is also tempting to focus on interpersonal stigma reduction at the expense of structural discrimination. The latter is more politically challenging, especially if government funders proscribe structural discrimination targets, while the evidence base for contact-based education for interpersonal stigma reduction means that it is easy to make the case for focusing on this[190].

Therefore, we recommend that people with severe mental illness be consulted about their experiences of exclusion across all life areas, and that priority targets are chosen accordingly. These priorities will vary by setting. For example, in low-resource communities where formal employment may be the exception, they will more likely include interventions to address the systematic exclusion of people with mental health conditions from community development programmes, livelihood opportunities, micro-finance schemes and other economic opportunities[190], as opposed to discrimination by employers.

7. Support the development of conceptual competencies in the mental health workforce

Explanatory frameworks impact on support for social inclusion. Transitioning to a mental health system which is more diverse in this regard will involve changing the prevailing culture. A stronger emphasis on ontological and epistemological training within professional education would improve the foundational knowledge and attitudes needed for epistemic humility[174].

The development of demonstration sites which use a wider range of explanatory frameworks to support meaning-making would create immersive training opportunities for professionals, inform clinical innovation, and allow the benefits and harms of a decreased emphasis on clinical models to be evaluated[420]. Experience from settings where biomedical and other models (e.g. traditional medicine, faith and spiritual healers) are integrated can inform clinical practice.

CONCLUSIONS

In this review we identify strategies to increase social inclusion at the levels of national legislation, services providing mental health care, and other community assets. Gaps in research and provision in relation to loneliness and some valued social roles such as parenting and intimate relationships are at first glance surprising, and suggest their neglect at the expense of a focus on economic productivity through employment and on inpatient cost containment through consistent use of medication.

Foundational research is needed to develop interventions to support people with severe mental illness in fulfilling social roles that are critically important both for them and for their partners, relatives and carers. There is no research on support for women to make and maintain safe and satisfying intimate relationships, despite their increased vulnerability to domestic abuse and financial exploitation, and hardly any on interventions for men. Research to develop and evaluate such support should be part of suicide prevention strategies, due to the relatively stronger relationship between suicidality and romantic loneliness, as opposed to other types of loneliness. The key actors therefore include not just researchers and research commissioners, but also public health officials. Similarly, policy makers and professionals concerned with child welfare and development have an interest in the tailoring and evaluation of parenting interventions for people with severe mental illness.

A second focus should be on the equitable implementation of interventions with a sufficient evidence base, and de-implementation of interventions which are exclusionary. To be considered in this context are the above-mentioned needed legal changes: rescindment of discriminatory legislation, decriminalization of suicide and possession of drugs for personal use, and reforms of mental health legislation to promote autonomy and choice. The key actors in this area are therefore legislators and those who lobby them. Uptake of QualityRights training is a relatively straightforward step, while greater implementation of family interventions for psychosis continues to be a challenge to be brought to the attention of those experienced in or interested in implementation science[421,422].

A third group of interventions are those which require more tailoring to context and more ambition. IPS has been focused on increasing employment in low-paid, entry-level jobs. Supported education has been relatively neglected, as have other means to support people into self-employment, which in many countries is a more viable option. Similarly, interventions to avoid homelessness and destitution such as Housing First, with a strong but very context-dependent evidence base, require adaptation to different welfare and housing policy contexts, especially in LMICs, where intensive and specialist mental health support is not available.

Finally, there is a pressing need to evaluate services and interventions which have a strong theoretical basis and have become widespread in some countries in the absence of evaluation, in order to identify their key components, effectiveness and cost-effectiveness before encouraging further spread. Above we have discussed Recovery Colleges, which may be vulnerable to funding cuts if a better evidence base is not established. This includes not only studies of their effectiveness for people with severe mental illness, but also of their accessibility to this group following implementation. This requires service providers and researchers to co-produce the evidence base. It will frequently not be ethical to conduct RCTs of services already available, so researchers and funders will need to consider theory-based approaches and natural experiment designs.

The development and use of an evidence base for tailored interventions to be delivered within mental health services may be more straightforward than ensuring that people with severe mental illness gain and maintain equity in relation to use of other community assets, whether for physical health care, leisure or education, as these require inter-agency working and agreement about the responsibilities of each. Our recommendations cover both the more straightforward and the more difficult actions, in the hope that those suited to addressing each will respond.

ACKNOWLEDGEMENTS

M. Slade acknowledges support from the UK National Institute for Health and Care Research (NIHR) Nottingham Biomedical Research Centre. M. Slade, C. Henderson and Y. Kotera acknowledge funding from a NIHR Programme Grant for Applied Research (no. NIHR200605). A. Salla and C. Henderson are funded by an NIHR Policy Research Programme grant (no. NIHR205233). C. Henderson is also funded by a Maudsley Charity Living Well With Psychosis grant (no. 2946). P. Coventry is supported by an NIHR Public Health Research grant (no. NIHR157698), a Programme Development Grant (no. NIHR206939), and Programme Grants for Applied Research (nos. RP-PG-1016-20003 and NIHR200607) and Health and Social Care Delivery Research (no. NIHR151887); and by NIHR Applied Research Collaboration Yorkshire & Humber. The views expressed here are those of the authors and not necessarily those of the funders. The authors would like to thank M. Rashed for providing background information during the drafting of the manuscript.

REFERENCES

1. Badcock JC, Shah S, Mackinnon A et al. Loneliness in psychotic disorders and its association with cognitive function and symptom profile. Schizophr Res 2015; 169:268-73.
2. Liu NH, Daumit GL, Dua T et al. Excess mortality in persons with severe mental disorders: a multilevel intervention framework and priorities for clinical practice, policy and research agendas. World Psychiatry 2017;16:30-40.
3. Chan JKN, Correll CU, Wong CSM et al. Life expectancy and years of potential life lost in people with mental disorders: a systematic review and meta-analysis. EClinicalMedicine 2023;65:102294.
4. Khare C, Mueser KT, Fulford D et al. Employment functioning in people with severe mental illnesses living in urban vs. rural areas in India. Soc Psychiatry Psychiatr Epidemiol 2020;55:1593-606.
5. Yang LH, Phillips MR, Li X et al. Employment outcome for people with schizophrenia in rural v. urban China: population-based study. Br J Psychiatry 2013; 203:272-9.
6. Corker E, Hamilton S, Robinson E et al. Viewpoint survey of mental health service users' experiences of discrimination in England 2008-2014. Acta Psychiatr Scand 2016;134:6-13.
7. Henderson C, Stuart H, Hansson L. Lessons from the results of three national antistigma programmes. Acta Psychiatr Scand 2016;134(Suppl. 446):3-5.
8. Gabbidon J, Brohan E, Clement S et al. Development and initial validation of the Questionnaire on Anticipated Discrimination (QUAD). BMC Psychiatry 2011;13:297.

9. Wright S, Henderson C, Thornicroft G et al. Measuring the economic costs of discrimination experienced by people with mental health problems: development of the Costs of Discrimination Assessment (CODA). Soc Psychiatry Psychiatr Epidemiol 2015;50:787-95.
10. Hamilton S, Corker E, Weeks C et al. Factors associated with experienced discrimination among people using mental health services in England. J Ment Health 2016;25:350-8.
11. Henderson C, Brohan E, Clement S et al. Decision aid on disclosure of mental health status to an employer: feasibility and outcomes of a randomised controlled trial. Br J Psychiatry 2013;203:350-7.
12. Henderson C, Ouali U, Bakolis I et al. Training for mental health professionals in responding to experienced and anticipated mental health-related discrimination (READ-MH): protocol for an international multisite feasibility study. Pilot Feasibility Stud 2022;8:257.
13. World Health Organization. Guidance on mental health policy and strategic action plans. Geneva: World Health Organization, 2025.
14. Halvorsrud K, Nazroo J, Otis M et al. Ethnic inequalities in the incidence of diagnosis of severe mental illness in England: a systematic review and new meta-analyses for non-affective and affective psychoses. Soc Psychiatry Psychiatr Epidemiol 2019;54:1311-23.
15. Selten JP, van der Ven E, Termorshuizen F. Migration and psychosis: a meta-analysis of incidence studies. Psychol Med 2020;50:303-13.
16. Jester DJ, Thomas ML, Sturm ET et al. Review of major social determinants of health in schizophrenia-spectrum psychotic disorders: I. Clinical outcomes. Schizophr Bull 2023;49:837-50.
17. McGinty EE, Alegria M, Beidas RS et al. The Lancet Psychiatry Commission: transforming mental health implementation research. Lancet Psychiatry 2024;11:368-96.
18. Puschner B. Social inclusion: a fundamental PROM for evaluating recovery-oriented global mental health programmes. Eur Psychiatry 2023;66(Suppl. 1):S34.
19. Rosenheck RA. Introduction to the Special Section: Toward social inclusion. Psychiatr Serv 2012;63:425-6.
20. Silver H. The contexts of social inclusion. https://ssrn.com/abstract=2879940.
21. Ballard K. Thinking in another way: ideas for sustainable inclusion. Int J Incl Educ 2013;17:762-75.
22. Kotera Y, Ronaldson A, Hayes D et al. Cross-cultural insights from two global mental health studies: self-enhancement and ingroup biases. Int J Ment Health Addict 2025;23:3572-81.
23. Fisher MH, Athamanah LS, Sung C et al. Applying the self-determination theory to develop a school-to-work peer mentoring programme to promote social inclusion. J Appl Res Intellect Disabil 2020;33:296-309.
24. Filia K, Menssink J, Gao CX et al. Social inclusion, intersectionality, and profiles of vulnerable groups of young people seeking mental health support. Soc Psychiatry Psychiatr Epidemiol 2022;57:245-54.
25. McConkey R, Collins S. Using personal goal setting to promote the social inclusion of people with intellectual disability living in supported accommodation. J Intell Disabil Res 2010;54:135-43.
26. Adamus C, Mötteli S, Jäger M et al. Independent housing and support for non-homeless individuals with severe mental illness: randomised controlled trial vs. observational study – study protocol. BMC Psychiatry 2020;20:319.
27. Martin L, Cobigo V. Definitions matter in understanding social inclusion. J Policy Pract Intellect Disabil 2011;8:276-82.
28. Whaley BA, Martinis JG, Pagano GF et al. The Americans with Disabilities Act and equal access to public spaces. Laws 2024;13:10.3390/laws13010005.
29. Whitley R, Shepherd G, Slade M. Recovery colleges as a mental health innovation. World Psychiatry 2019;18:141-2.
30. Kotera Y, Ronaldson A, Hayes D et al. 28-country global study on associations between cultural characteristics and Recovery College fidelity. NPJ Ment Health Res 2024;3:46.
31. McKay C, Nugent KL, Johnsen M et al. A systematic review of evidence for the Clubhouse Model of psychosocial rehabilitation. Adm Policy Ment Health 2018;45:28-47.
32. Olney S, Dickinson H. Australia's New National Disability Insurance Scheme: implications for policy and practice. Policy Des Pract 2019;2:275-90.
33. Buli-Holmberg J, Sigstad HMH, Morken I et al. From the idea of inclusion into practice in the Nordic countries: a qualitative literature review. Eur J Spec Needs Educ 2023;38:79-94.
34. Askeland GA, Strauss H. The Nordic welfare model, civil society and social work. In: Strauss H, Noble C, Littlechild B (eds). Global social work. Sydney: Sydney University Press, 2014:241-54.
35. Harsløf I, Slomic M, Håvold OKS. Establishing individual care plans for rehabilitation patients: traces of self-targeting in the Norwegian Universal Welfare State. Nord J Soc Res 2019;10:24-47.
36. Skorpen S, Søndenaa E. Norwegian perspectives on health care for people with intellectual and developmental disabilities. J Policy Pract Intellect Disabil 2024;21:e12492.
37. Gustafsson J, Peralta J, Danermark B. Supported employment and social inclusion – experiences of workers with disabilities in wage subsidized employment in Sweden. Scand J Disabil Res 2018;20:26-36.
38. Yu LB, Tsui MC, Zhang GF et al. Impact of integrated supported employment program on people with schizophrenia: perspectives of participants and caregivers. J Rehabil 2016;82:11-7.
39. Wang Y, An S, Yang X et al. Disease information disclosure among patients with mental illness and their family members in China. Front Psychiatry 2022; 13:1036568.
40. Dahl N. Social inclusion of senior citizens in Japan: an investigation into the "Community-based Integrated Care System". Contemp Jpn 2018;30:43-59.
41. Lee J. Supporting the social integration of migrant women in South Korea through language services: roles of marriage migrant interpreters in multicultural family support centre counselling services. Translator 2021;27:57-74.
42. Kato TA, Kanba S, Teo AR. Hikikomori: multidimensional understanding, assessment, and future international perspectives. Psychiatry Clin Neurosci 2019;73:427-40.
43. Watts J. Public health experts concerned about "hikikomori". Lancet 2002;359: 1131.
44. Singapore Ministry of Health. National mental health and well-being strategy. Singapore: Singapore Ministry of Health, 2023.
45. Zhu Y, Li X, Zhao M. Promotion of mental health rehabilitation in China: community-based mental-health services. Consort Psychiatr 2020;1:21-7.
46. Padmakar A, de Wit EE, Mary S et al. Supported housing as a recovery option for long-stay patients with severe mental illness in a psychiatric hospital in South India: learning from an innovative de-hospitalization process. PLoS One 2020;15:e0230074.
47. Mathias K, Singh P, Butcher N et al. Promoting social inclusion for young people affected by psycho-social disability in India – a realist evaluation of a pilot intervention. Glob Public Health 2019;14:1718-32.
48. Nazir H, Rowther AA, Rauf N et al. 'Those whom I have to talk to, I can't talk to': perceived social isolation in the context of anxiety symptoms among pregnant women in Pakistan. Health Soc Care Community 2022;30:e5885-96.
49. Kitayama S, Salvador CE, Nanakdewa K et al. Varieties of interdependence and the emergence of the modern West: toward the globalizing of psychology. Am Psychol 2022;77:991-1006.
50. Sabry WM, Vohra A. Role of Islam in the management of psychiatric disorders. Indian J Psychiatry 2013;55(Suppl. 2):S205-14.
51. Sarsour O. The role of religion in the social inclusion of Arab refugees and immigrants in Europe. Int J Humanit Soc Sci Educ 2021:6.
52. Beitin BK, Aprahamian M. Family values and traditions. In: Nassar-McMillan SC, Ajrouch KJ, Hakim-Larson J (eds). Biopsychosocial perspectives on Arab Americans: culture, development, and health. New York: Springer, 2014:67-88.
53. Aramouny C, Kerbage H, Richa N et al. Knowledge, attitudes, and beliefs of catholic clerics' regarding mental health in Lebanon. J Relig Health 2020;59: 257-76.
54. Thomas J, Al-Qarni N, Furber SW. Conceptualising mental health in the United Arab Emirates: the perspective of traditional healers. Mental Health Relig Cult 2015;18:134-45.
55. Salinas-Perez JA, Ghuloum S, Gutierrez-Colosia MR et al. Analysis of the mental health service provision in Qatar: progressing in community mental health in a Middle East country. Front Psychiatry 2022;13:1095788.
56. Khaled SM, Al-Abdulla M, Tulley I et al. Qatar's National Mental Health Study – The World Mental Health Qatar. Int J Methods Psychiatr Res 2024;33(Suppl. 1):e2008.
57. Alhabeeb AA, Khayat AI, Makkawi AA et al. Religious mosque leaders (Khateebs): awareness, perceptions, practices and attitude towards mental health, Riyadh region, Saudi Arabia. Int Neuropsychiatr Dis J 2020;13:1-12.
58. Al Zaben F, Khalifa DA, Sehlo MG et al. Religious involvement and health in dialysis patients in Saudi Arabia. J Relig Health 2015;54:713-30.
59. Abu-Ras W, Aboul-Enein BH, Almoayad F et al. Mosques and public health promotion: a scoping review of faith-driven health interventions. Health Educ Behav 2024;51:677-90.
60. Al-Shannaq Y, Aldalaykeh M. Suicide literacy, suicide stigma, and psychological help seeking attitudes among Arab youth. Curr Psychol 2023;42:6532-44.
61. Nascimento MS, Batista e Silva MB. Ocultamento do auxílio? Programa de Volta Para Casa em documentos e eventos. Ciênc Saúde Coletiva 2022;27:111-21.
62. da Silva JL, Valentim AF, Lyra J. Loucura em território: experimentando produção de saúde com beneficiários do programa "De volta para casa". Rev Psicol

Polít 2020;20:51-64.

63. Gómez-Restrepo C, Casasbuenas NG, Ortiz-Hernández N et al. Role of the arts in the life and mental health of young people that participate in artistic organizations in Colombia: a qualitative study. BMC Psychiatry 2022;22:757.
64. Gall A, Anderson K, Howard K et al. Wellbeing of Indigenous peoples in Canada, Aotearoa (New Zealand) and the United States: a systematic review. Int J Environ Res Public Health 2021;18:5832.
65. New Zealand's Ministry of Health – Manatū Hauora. Te Whare Tapa Whā model of Māori health. https://www.health.govt.nz.
66. Government of Canada. First Nations Mental Wellness Continuum Framework: summary report. https://www.sac-isc.gc.ca/eng.
67. Holt-Lunstad J. Social connection as a critical factor for mental and physical health: evidence, trends, challenges and future implications. World Psychiatry 2024;23:312-32.
68. Mezey G, White S, Harrison I et al. Modelling social exclusion in a diagnostically-mixed sample of people with severe mental illness. Int J Soc Psychiatry 2022;68:420-8.
69. Taylor HO, Cudjoe TKM, Bu F et al. The state of loneliness and social isolation research: current knowledge and future directions. BMC Public Health 2023;23:1049.
70. Patmisari E, Huang Y, Orr M et al. Interventions supporting meaningful connections for people with serious mental illness: a concept-framed systematic narrative review. Soc Psychiatry Psychiatr Epidemiol 2025;60:1257-82.
71. Cacioppo S, Grippo AJ, London S et al. Loneliness: clinical import and interventions. Perspect Psychol Sci 2015;10:238-49.
72. Morrish N, Choudhury S, Medina-Lara A. What works in interventions targeting loneliness: a systematic review of intervention characteristics. BMC Public Health 2023;23:2214.
73. Grillich L, Titscher V, Klingenstein P et al. The effectiveness of interventions to prevent loneliness and social isolation in the community-dwelling and old population: an overview of systematic reviews and meta-analysis. Eur J Public Health 2023;33:235-41.
74. Ma R, Mann F, Wang J et al. The effectiveness of interventions for reducing subjective and objective social isolation among people with mental health problems: a systematic review. Soc Psychiatry Psychiatr Epidemiol 2020;55:839-76.
75. Lee CY, Ahmed N, Ikthabi S et al. The experience of loneliness among people with psychosis: qualitative meta-synthesis. PLoS One 2024;19:e0315763.
76. Birken M, Chipp B, Shah P et al. Exploring the experiences of loneliness in adults with mental health problems: a participatory qualitative interview study. PLoS One 2023;18:e0280946.
77. Giacco D, Palumbo C, Strappelli N et al. Social contacts and loneliness in people with psychotic and mood disorders. Compr Psychiatry 2016;66:59-66.
78. Renwick L, Owens L, Lyne J et al. Predictors of change in social networks, support and satisfaction following a first episode psychosis: a cohort study. Int J Nurs Stud 2017;76:28-35.
79. Alasmawi K, Mann F, Lewis G et al. To what extent does severity of loneliness vary among different mental health diagnostic groups: a cross-sectional study. Int J Ment Health Nurs 2020;29:921-34.
80. Boysen GA, Morton J, Nieves T. Mental illness as a relationship dealbreaker. Stigma Health 2019;4:421-8.
81. Boysen GA, Isaacs RA. Perceptions of people with mental illness as sexually exploitable. Evol Behav Sci 2022;16:38-52.
82. Brohan E, Slade M, Clement S et al. Development and psychometric validation of the Discrimination and Stigma Scale (DISC). Psychiatry Res 2013;208:33-40.
83. Frerichs J, Billings J, Barber N et al. Influences on participation in a programme addressing loneliness among people with depression and anxiety: findings from the Community Navigator Study. BMC Psychiatry 2020;20:565.
84. Tee H, Chevalier A, Webber M et al. Who wants more social contacts? A cross-sectional study of people with psychotic disorders in England. Schizophr Res 2022;240:46-51.
85. Boucher ME, Groleau D, Whitley R. Recovery and severe mental illness: the role of romantic relationships, intimacy, and sexuality. Psychiatr Rehabil J 2016; 39:180-2.
86. Pinfold V, Sweet D, Porter I et al. Health services and delivery research. Improving community health networks for people with severe mental illness: a case study investigation. Southampton: NIHR Journals Library, 2015.
87. White R, Haddock G, Varese F et al. "Sex isn't everything": views of people with experience of psychosis on intimate relationships and implications for mental health services. BMC Psychiatry 2021;21:307.
88. Eager S, Killaspy H, Joanna C et al. Understanding the social inclusion needs of people living in mental health supported accommodation. BMC Res Notes 2023;16:156.
89. Mann F, Bone JK, Lloyd-Evans B et al. A life less lonely: the state of the art in interventions to reduce loneliness in people with mental health problems. Soc Psychiatry Psychiatr Epidemiol 2017;52:627-38.
90. Giacco D, Chevalier A, Patterson M et al. Effectiveness and cost-effectiveness of a structured social coaching intervention for people with psychosis (SCENE): protocol for a randomised controlled trial. BMJ Open 2021;11:e050627.
91. Stefanidou T, Ambler G, Bartl G et al. Randomised controlled trial of the Community Navigator programme to reduce loneliness and depression for adults with treatment-resistant depression in secondary community mental health services: trial protocol. Trials 2023;24:652.
92. Lockwood G, Henderson C, Thornicroft G. Equality Act 2010 and mental health. Br J Psychiatry 2012;200:182-3.
93. UK Parliament. Mental Health (Discrimination) Act 2013. https://bills.parliament.uk/bills/1027.
94. European Union Agency for Fundamental Rights. The right to political participation of persons with mental health problems and persons with intellectual disabilities. Vienna: European Union Agency for Fundamental Rights, 2010.
95. United Nations. Convention on the Rights of Persons with Disabilities. New York: United Nations, 2006.
96. European Union Agency for Fundamental Rights. Political participation of people with disabilities: new developments. Luxembourg: Publications Office of the European Union, 2024.
97. Lifeline International. Decriminalise suicide worldwide. https://www.suicide-decrim.network.
98. The Lancet. Punishing the tortured: criminalisation of suicide. Lancet 2023;401: 1241.
99. Harm Reduction International. The global state of harm reduction 2022. London: Harm Reduction International, 2022.
100. Chow WS, Priebe S. Understanding psychiatric institutionalization: a conceptual review. BMC Psychiatry 2013;13:169.
101. Duffy RM, Kelly BD. India's Mental Healthcare Act, 2017: content, context, controversy. Int J Law Psychiatry 2019;62:169-78.
102. Swanson J, Swartz M, Ferron J et al. Psychiatric advance directives among public mental health consumers in five U.S. cities: prevalence, demand, and correlates. J Am Acad Psychiatry Law 2006;34:43-57.
103. Srebnik DS, Russo J, Sage J et al. Interest in psychiatric advance directives among high users of crisis services and hospitalization. Psychiatr Serv 2003;54: 981-6.
104. de Jong MH, Kamperman AM, Oorschot M et al. Interventions to reduce compulsory psychiatric admissions: a systematic review and meta-analysis. JAMA Psychiatry 2016;73:657-64.
105. Molyneaux E, Turner A, Candy B et al. Crisis-planning interventions for people with psychotic illness or bipolar disorder: systematic review and meta-analyses. BJPsych Open 2019;5:e53.
106. Bone JK, McCloud T, Scott HR et al. Psychosocial interventions to reduce compulsory psychiatric admissions: a rapid evidence synthesis. EClinicalMedicine 2019;10:58-67.
107. Elbogen EB, Van Dorn R, Swanson JW et al. Effectively implementing psychiatric advance directives to promote self-determination of treatment among people with mental illness. Psychol Public Policy Law 2007;13:10.1037/1076-8971.13.4.273.
108. Swanson JW, Swartz MS, Elbogen EB et al. Facilitated psychiatric advance directives: a randomized trial of an intervention to foster advance treatment planning among persons with severe mental illness. Am J Psychiatry 2006;163:1943-51.
109. Thornicroft G, Farrelly S, Szmukler G et al. Clinical outcomes of Joint Crisis Plans to reduce compulsory treatment for people with psychosis: a randomised controlled trial. Lancet 2013;381:1634-41.
110. Thom K, Lenagh-Glue J, O'Brien AJ et al. Service user, whānau and peer support workers' perceptions of advance directives for mental health. Int J Ment Health Nurs 2019;28:1296-305.
111. Miller RD. Advance directives for psychiatric treatment: a view from the trenches. Psychol Public Policy Law 1998;4:728-45.
112. Valentine L, Grace D, Pryor I et al. "When I'm thinking straight, i can put things in place for when I'm not". Exploring the use of advance statements in first-episode psychosis treatment: young people, clinician, and carer perspectives. Community Ment Health J 2021;57:18-28.
113. Gather J, Henking T, Juckel G et al. Advance refusals of treatment in situations of danger to self or to others – ethical and legal considerations on the implementation of advance directives in psychiatry. In: Gather J, Henking T, Nossek A et al (eds). Beneficial coercion in psychiatry?: foundations and challenges. Münster: Mentis, 2017:245-62.
114. Wilder CM, Swanson JW, Bonnie RJ et al. A survey of stakeholder knowledge, experience, and opinions of advance directives for mental health in Virginia.

Adm Policy Ment Health 2013;40:232-9.

115. Appelbaum PS. Psychiatric advance directives and the treatment of committed patients. Psychiatr Serv 2004;55:751-2.
116. Srebnik DS, Rutherford LT, Peto T et al. The content and clinical utility of psychiatric advance directives. Psychiatr Serv 2005;56:592-8.
117. Srebnik DS, Russo J. Consistency of psychiatric crisis care with advance directive instructions. Psychiatr Serv 2007;58:1157-63.
118. Lasalvia A, Patuzzo S, Braun E et al. Advance statements in mental healthcare: time to close the evidence to practice gap. Epidemiol Psychiatr Sci 2023; 32:e68.
119. Shields LS, Pathare S, van Zelst SD et al. Unpacking the psychiatric advance directive in low-resource settings: an exploratory qualitative study in Tamil Nadu, India. Int J Ment Health Syst 2013;7:29.
120. Babatunde A, Ruck Keene A, Simpson A et al. Advance statements for Black African and Caribbean people (AdStAC): protocol for an implementation study. BMC Psychiatry 2023;23:344.
121. Barrett B, Waheed W, Farrelly S et al. Randomised controlled trial of joint crisis plans to reduce compulsory treatment for people with psychosis: economic outcomes. PLoS One 2013;25:e74210.
122. Eads R, Lee M, Liu C et al. The power of perception: lived experiences with diagnostic labeling in mental health recovery without ongoing medication use. Psychiatr Q 2021;92:889-904.
123. Galderisi S, Appelbaum PS, Gill N et al. Ethical challenges in contemporary psychiatry: an overview and an appraisal of possible strategies and research needs. World Psychiatry 2024;23:364-86.
124. Gooding P. Good practices in the Council of Europe to promote voluntary measures in mental health services. Strasbourg: Council of Europe, 2021.
125. World Health Organization. Mental health, human rights and standards of care. Copenhagen: WHO Regional Office for Europe, 2018.
126. Skinner A, Occhipinti J, Song Y et al. Population mental health improves with increasing access to treatment: evidence from a dynamic modelling analysis. BMC Psychiatry 2022;22:692.
127. Topor A, Boe T, Larsen I. The lost social context of recovery psychiatrization of a social process. Front Sociol 2022;7:832201.
128. World Health Organization. Mental health atlas 2020. Geneva: World Health Organization, 2021.
129. Appelbaum P, Gutheil T. "Rotting with their rights on": constitutional theory and clinical reality in drug refusal by psychiatric patients. Bull Am Acad Psychiatry Law 1979;7:306-15.
130. Richter D, Dixon J. Models of mental health problems: a quasi-systematic review of theoretical approaches. J Ment Health 2023;32:396-406.
131. Slade M. Personal recovery and mental illness. Cambridge: Cambridge University Press, 2009.
132. Bracken P, Thomas P. Postpsychiatry. Mental health in a postmodern world. Oxford: Oxford University Press, 2005.
133. Stein D, Shoptaw S, Vigo D et al. Psychiatric diagnosis and treatment in the 21st century: paradigm shift versus incremental integration. World Psychiatry 2022;21:393-414.
134. Perkins R, Repper J. Social inclusion and recovery. London: Bailliere Tindal, 2003.
135. Benning T. Limitations of the biopsychosocial model in psychiatry. Adv Med Educ Pract 2015;6:347-52.
136. Roberts A. The biopsychosocial model: its use and abuse. Med Health Care Philos 2023;26:367-84.
137. Mohtashemi R, Stevens J, Jackson P et al. Psychiatrists' understanding and use of psychological formulation: a qualitative exploration. BJPsych Bull 2016;40: 212-6.
138. Williamson S. The biopsychosocial model: not dead, but in need of revival. BJPsych Bull 2022;46:232-4.
139. Barone DF, Maddux JE, Snyder CR. Social cognitive psychology: history and current domains. New York: Plenum,1997.
140. Mittelmark M, Bauer G, Vaandrager L et al (eds). The handbook of salutogenesis, 2nd ed. London: Springer, 2022.
141. Johnstone L, Boyle M. The Power Threat Meaning Framework: towards the identification of patterns in emotional distress, unusual experiences and troubled or troubling behaviour, as an alternative to functional psychiatric diagnosis. Leicester: British Psychological Society, 2018.
142. Tew J. Towards a socially situated model of mental distress. In: Spandler H, Anderson J, Sapey B (eds). Madness, distress and the politics of disablement. Bristol: Policy Press, 2015:69-82.
143. Sen A. Development as freedom. New York: Knopf, 1999.
144. Nussbaum M. Frontiers of justice. Disability, nationality, species membership. Cambridge: Harvard University Press, 2006.
145. Mäki-Opas T, Pieper R, Vaarama M. Exploring the capability approach to quality of life in disadvantaged population groups. Sci Rep 2022;12:15248.
146. White R, Imperiale M, Perera E. The Capabilities Approach: fostering contexts for enhancing mental health and wellbeing across the globe. Global Health 2016;12:16.
147. Brunner R. Why do people with mental distress have poor social outcomes? Four lessons from the capabilities approach. Soc Sci Med 2017;191:160-7.
148. Tøssebro J. Scandinavian disability policy: from deinstitutionalisation to non-discrimination and beyond. Alter 2016;10:111-23.
149. Meekosha H. Drifting down the Gulf Stream: navigating the cultures of disability studies. Disabil Soc 2004;19:721-33.
150. Rowe M, Pelletier J. A response to the marginalization of people with mental illnesses. J Forensic Psychol Pract 2012;12:366-81.
151. Berghs M, Atkin K, Graham H et al. Implications for public health research of models and theories of disability: a scoping study and evidence synthesis. Public Health Res 2016;4:8.
152. British Medical Association. "It's broken". Doctors' experiences on the frontline of a failing mental healthcare system. London: British Medical Association, 2024.
153. Slade M, Amering M, Farkas M et al. Uses and abuses of recovery: implementing recovery-oriented practices in mental health systems. World Psychiatry 2014;13:12-20.
154. Rashed M. In defense of madness: the problem of disability. J Med Philos 2019; 16:150-74.
155. Garbe M. Spiritual emergence and spiritual emergency. In: Jaffe M, Nicola W, Floersch J et al (eds). Spirituality in mental health practice. New York: Routledge, 2020:47-62.
156. Rose D. Service user/survivor-led research in mental health: epistemological possibilities. Disabil Soc 2017;32:773-89.
157. Russo J, Sweeney A (eds). Searching for a Rose Garden: challenging psychiatry, fostering mad studies. Monmouth: PCCS Books, 2016.
158. Slade M, Rennick-Egglestone S, Todowede O. The transformative potential of citizen science for mental health. Lancet Psychiatry 2024;11:246-8.
159. Johansson J, Holmes D. "Recovery" in mental health services, now and then: a poststructuralist examination of the despotic State machine's effects. Nurs Inq 2024;31:e12558.
160. Sinclair A, Gillieatt S, Fernandes C et al. Inclusion as assimilation, integration, or co-optation? A post-structural analysis of inclusion as produced through mental health research on peer support. Qual Health Res 2023;33:543-55.
161. Kuzman R, Slade M, Puschner B et al. Clinical decision-making style preferences of European psychiatrists: results from the Ambassadors survey in 38 countries. Eur Psychiatry 2022;65:e75.
162. Puschner B, Becker T, Mayer B et al. Clinical decision making and outcome in the routine care of people with severe mental illness across europe (CEDAR). Epidemiol Psychiatr Sci 2016;25:69-79.
163. Pelletier J-F, Corbière M, Lecomte T et al. Citizenship and recovery: two intertwined concepts for civic-recovery. BMC Psychiatry 2015;15:37.
164. Pathare S, Funk M, Drew Bold N et al. Systematic evaluation of the QualityRights programme in public mental health facilities in Gujarat, India. Br J Psychiatry 2021;218:196-203.
165. Pearson H, Adams B, Eaton J et al. Community mental health good practice guide: peer support. Laudenbach: CBM Global Disability Inclusion, 2021.
166. Dell N, Long C, Mancini M. Models of mental health recovery: an overview of systematic reviews and qualitative meta-syntheses. Psychiatr Res J 2021;44:238-53.
167. Price-Robertson R, Obradovic A, Morgan B. Relational recovery: beyond individualism in the recovery approach. Adv Ment Health 2017;15:108-20.
168. Smith-Merry J, Sturdy S. Recovery in Scotland: the rise and uncertain future of a mental health social movement. Soc Ment Health 2013;3:114-32.
169. Cohen C. Neorecovery: a critical analysis of the relationship between Neoliberalism and the Recovery Movement. Community Ment Health J 2025;61:248-53.
170. Arnaud S, Gagné-Julien A-M. The new self-advocacy activism in psychiatry: toward a scientific turn. Philos Psychol 2024;37:2623-46.
171. Morrow M, Weisser J. Towards a social justice framework of mental health recovery. Stud Soc Justice 2012;6:27-43.
172. Harper D, Speed E. Uncovering recovery: the resistible rise of recovery and resilience. Stud Social Justice 2012;6:9-25.
173. Wegerhoff D, Ward T, Dixon L. Epistemic pluralism and the justification of conceptual strategies in science. Theory Psychol 2022;32:443-66.
174. Stein DJ, Nielsen K, Hartford A et al. Philosophy of psychiatry: theoretical advances and clinical implications. World Psychiatry 2024;23:215-32.
175. Yang LH, Chen FP, Sia KJ et al. "What matters most": a cultural mechanism

moderating structural vulnerability and moral experience of mental illness stigma. Soc Sci Med 2014;103:84-93.

176. Schomerus G, Angermeyer MC. Blind spots in stigma research? Broadening our perspective on mental illness stigma by exploring 'what matters most' in modern Western societies. Epidemiol Psychiatr Sci 2021;30:e26.
177. Hatfield B, Huxley P, Mohamad H. Accommodation and employment: a survey into the circumstances and expressed needs of users of mental health services in a Northern town. Br J Soc Work 1992;22:61-73.
178. Chimara M, Van Niekerk L, van Biljon HM. Scoping review exploring vocational rehabilitation interventions for mental health service users with chronic mental illness in low-income to upper-middle-income countries. BMJ Open 2022;12:e059211.
179. McGurk SR, Mueser KT, Feldman K et al. Cognitive training for supported employment: 2-3 year outcomes of a randomized controlled trial. Am J Psychiatry 2007;164:437-41.
180. Bell M, Zito W, Greig T et al. Neurocognitive enhancement therapy with vocational services: work outcomes at two-year follow-up. Schizophr Res 2008; 105:18-29.
181. McGurk SR, Mueser KT, Xie H et al. Cognitive enhancement treatment for people with mental illness who do not respond to supported employment: a randomized controlled trial. Am J Psychiatry 2015;172:852-61.
182. Twamley EW, Thomas KR, Burton CZ et al. Compensatory cognitive training for people with severe mental illnesses in supported employment: a randomized controlled trial. Schizophr Res 2019;203:41-8.
183. Rodríguez Pulido F, Caballero Estebaranz N, González Dávila E et al. Cognitive remediation to improve the vocational outcomes of people with severe mental illness. Neuropsychol Rehabil 2021;31:293-315.
184. Lysaker PH, Bond G, Davis LW et al. Enhanced cognitive-behavioral therapy for vocational rehabilitation in schizophrenia: effects on hope and work. J Rehabil Res Dev 2005;42:673-82.
185. Glynn SM, Marder SR, Noordsy DL et al. An RCT evaluating the effects of skills training and medication type on work outcomes among patients with schizophrenia. Psychiatr Serv 2017;68:271-7.
186. Barnett P, Steare T, Dedat Z et al. Interventions to improve social circumstances of people with mental health conditions: a rapid evidence synthesis. BMC Psychiatry 2022;22:302.
187. Reed K, Kalaga H. Focusing on employment in primary mental health care: a scoping review. Work 2018;59:3-13.
188. Toffolutti V, Stuckler D, McKee M et al. The employment and mental health impact of integrated Improving Access to Psychological Therapies: evidence on secondary health care utilization from a pragmatic trial in three English counties. J Health Serv Res Policy 2021;26:224-33.
189. Wagner SL, Koehn C, White MI et al. Mental health interventions in the workplace and work outcomes: a best-evidence synthesis of systematic reviews. Int J Occup Environ Med 2016;7:1-14.
190. Thornicroft G, Sunkel C, Alikhon Aliev A et al. The Lancet Commission on ending stigma and discrimination in mental health. Lancet 2022;400:1438-80.
191. Burns T, Catty J, Becker T et al. The effectiveness of supported employment for people with severe mental illness: a randomised controlled trial. Lancet 2007;370:1146-52.
192. Trani JF, Bakhshi P, Kuhlberg J et al. Mental illness, poverty and stigma in India: a case-control study. BMJ Open 2015;5:e006355.
193. Yu YH, Peng MM. Development and poverty dynamics in severe mental illness: a modified capability approach in the Chinese context. Int J Environ Res Public Health 2022;19:2351.
194. Shefer G, Henderson C, Frost-Gaskin M et al. Only making things worse: a qualitative study of the impact of wrongly removing disability benefits from people with mental illness. Community Ment Health J 2016;52:834-41.
195. Hamilton S, Lewis-Holmes E, Pinfold V et al. Discrimination against people with a mental health diagnosis: qualitative analysis of reported experiences. J Ment Health 2014;23:88-93.
196. Frost-Gaskin M, O'Kelly R, Henderson C et al. A welfare benefits outreach project to users of community mental health services. Int J Soc Psychiatry 2003;49: 251-63.
197. Sullivan G, Burnam A, Koegel P. Pathways to homelessness among the mentally ill. Soc Psychiatry Psychiatr Epidemiol 2000;35:444-50.
198. Loubière S, Lemoine C, Boucekine M et al. Housing First for homeless people with severe mental illness: extended 4-year follow-up and analysis of recovery and housing stability from the randomized Un Chez Soi d'Abord trial. Epidemiol Psychiatr Sci 2022;31:e14.
199. Gutman SA, Kerner R, Zombek I et al. Supported education for adults with psychiatric disabilities: effectiveness of an occupational therapy program. Am J Occup Ther 2009;63:245-54.
200. Killackey E, Allott K, Jackson HJ et al. Individual placement and support for vocational recovery in first-episode psychosis: randomised controlled trial. Br J Psychiatry 2019;214:76-82.
201. Nuechterlein KH, Subotnik KL, Ventura J et al. Enhancing return to work or school after a first episode of schizophrenia: the UCLA RCT of Individual Placement and Support and Workplace Fundamentals Module training. Psychol Med 2020;50:20-8.
202. Fowler D, Hodgekins J, French P. Social recovery therapy in improving activity and social outcomes in early psychosis: current evidence and longer term outcomes. Schizophr Res 2019;203:99-104.
203. Rogers ES, Anthony WA, Lyass A et al. A randomized clinical trial of vocational rehabilitation for people with psychiatric disabilities. Rehab Couns Bull 2006;49:143-56.
204. Australian Healthcare Associates. Literature review to inform the development of Recovery Colleges in Western Australia. Melbourne: Australian Healthcare Associates, 2018.
205. Bester K, McGlade A, Darragh E. Is co-production working well in recovery colleges? Emergent themes from a systematic narrative review. J Ment Health Train Ed Pract 2022;17:48-60.
206. Thériault J, Lord M, Briand C et al. Recovery colleges after a decade of research: a literature review. Psychiatr Serv 2020;71:928-40.
207. Hayes D, Camacho E, Ronaldson A et al. Evidence-based Recovery Colleges: developing a typology based on organisational characteristics, fidelity, and funding. Soc Psychiatry Psychiatr Epidemiol 2024;59:759-68.
208. Hayes D, Hunter-Brown H, Camacho E et al. Recovery College characteristics, fidelity, commissioning models and unit costs: a cross-sectional global survey of 28 countries. Lancet Psychiatry 2023;10:768-79.
209. Toney R, Knight J, Hamill K et al. Development and evaluation of a Recovery College fidelity measure. Can J Psychiatry 2019;64:405-14.
210. Kotera Y, Miyamoto Y, Vilar-Lluch S et al. Cross-cultural comparison of Recovery College implementation between Japan and England: corpus-based discourse analysis. Int J Ment Health Addict 2025;23:4362-86.
211. Toney R, Elton D, Munday E et al. Mechanisms of action and outcomes for students in Recovery Colleges. Psychiatr Serv 2018;69:1222-9.
212. Claisse C, Durrant A, Branley-Bell D et al. 'Chugging along, plugging in and out of it': understanding a place-based approach for community-based support of mental health recovery. Soc Sci Med 2024;348:116823.
213. Hall T, Jordan H, Reifels L et al. A process and intermediate outcomes evaluation of an Australian Recovery College. J Recovery Ment Health 2018;1:7-20.
214. Szmukler GI, Burgess P, Herrman H et al. Caring for relatives with serious mental illness: the development of the Experience of Caregiving Inventory. Soc Psychiatry Psychiatr Epidemiol 1996;31:137-48.
215. Campbell L, Hanlon MC, Poon AW et al. The experiences of Australian parents with psychosis: the second Australian National Survey of Psychosis. Aust N Z J Psychiatry 2012;46:890-900.
216. Howard LM, Kumar C, Leese M et al. The general fertility rate in women with psychotic disorders. Am J Psychiatry 2002;159:991-7.
217. Harries CI, Smith DM, Gregg L et al. Parenting and serious mental illness (SMI): a systematic review and metasynthesis. Clin Child Fam Psychol Rev 2023;26:303-42.
218. Jeffery D, Clement S, Corker E et al. Discrimination in relation to parenthood reported by community psychiatric service users in the UK: a framework analysis. BMC Psychiatry 2013;13:120.
219. Tuck M, Wittkowski A, Gregg L. A balancing act: a systematic review and metasynthesis of family-focused practice in adult mental health services. Clin Child Fam Psychol Rev 2023;26:190-211.
220. Radley J, Grant C, Barlow J et al. Parenting interventions for people with schizophrenia or related serious mental illness. Cochrane Database Syst Rev 2021;10: CD013536.
221. World Health Organization. Defining sexual health: report of a technical consultation on sexual health, 28-31 January 2002. Geneva: World Health Organization, 2006.
222. Thornicroft G, Tansella M, Becker T et al. The personal impact of schizophrenia in Europe. Schizophr Res 2004;69:125-32.
223. Hughes E, Mitchell N, Gascoyne S et al. The RESPECT study: a feasibility randomised controlled trial of a sexual health promotion intervention for people with serious mental illness in community mental health services in the UK. BMC Public Health 2020;20:1736.
224. Forrester-Jones R, Dixon J, Jaynes B. Exploring romantic need as part of mental health social care practice. Disabil Soc 2023;39:2611-33.
225. Laxhman N, Greenberg L, Priebe S. Satisfaction with sex life among patients with schizophrenia. Schizophr Res 2017;190:63-7.
226. White R, Haddock G, Haarmans M et al. Being more satisfied with romantic

relationship status is associated with increased mental wellbeing in people with experience of psychosis. Front Psychiatry 2023;14:1232973.
227. McClelland H, Evans JJ, O'Connor RC. The association of family, social and romantic loneliness in relation to suicidal ideation and self-injurious behaviours. J Psychiatr Res 2023;158:330-40.
228. Urry K, Chur-Hansen A, Khaw C. 'It's not really a part of standard practice': institutional silencing of sexuality within Australian mental health settings. Qual Health Res 2022;32:543-55.
229. White R, Haddock G, Varese F. Supporting the intimate relationship needs of service users with psychosis: what are the barriers and facilitators? J Ment Health 2020;29:314-20.
230. Hughes E, Edmondson AJ, Onyekwe I et al. Identifying and addressing sexual health in serious mental illness: views of mental health staff working in two National Health Service organizations in England. Int J Ment Health Nurs 2018;27:966-74.
231. Emery-Rhowbotham A, Killaspy H, Eager S et al. 'Finding a relationship' conversations between mental health and social care staff, and service users. medRxiv 2024;2024.05.09.24307104.
232. Caiada M, Felix S, Guionnet S et al. Promoting intimate relationships in mental illness: a systematic review of interventions. Community Ment Health J 2024;60:536-51.
233. Hache-Labelle C, Abdel-Baki A, Lepage M et al. Romantic relationship group intervention for men with early psychosis: a feasibility, acceptability and potential impact pilot study. Early Interv Psychiatry 2021;15:753-61.
234. Cloutier B, Lecomte T, Diotte F et al. Improving romantic relationship functioning among young men with first-episode psychosis: impact of a novel group intervention. Behav Modif 2023;47:1170-92.
235. Proudlock S, Hallé L. Tapestry: a social relationship agency. A Life in the Day 2006;10:15-7.
236. Clayton A, O'Connell MJ, Bellamy C et al. The Citizenship Project Part II: impact of a citizenship intervention on clinical and community outcomes for persons with mental illness and criminal justice involvement. Am J Community Psychol 2013;51:114-22.
237. Viola E, Martorana M, Ceriotti D et al. The effects of cultural engagement on health and well-being: a systematic review. Front Public Health 2024;12:1369066.
238. Crone DM, O'Connell EE, Tyson PJ et al. 'Art Lift' intervention to improve mental well-being: an observational study from UK general practice. Int J Mental Health Nurs 2013;22:279-86.
239. Coventry PA, Brown JE, Pervin J et al. Nature-based outdoor activities for mental and physical health: systematic review and meta-analysis. SSM Popul Health 2021;16:100934.
240. United Nations General Assembly. Report of the Special Rapporteur on the right of everyone to the enjoyment of the highest attainable standard of physical and mental health. New York: Human Rights Council, 2017.
241. United Nations General Assembly. Report of the Special Rapporteur on the right of everyone to the enjoyment of the highest attainable standard of physical and mental health. New York: Human Rights Council, 2019.
242. United Nations General Assembly. Report of the Special Rapporteur on the right of everyone to the enjoyment of the highest attainable standard of physical and mental health. New York: Human Rights Council, 2020.
243. Mion A, Ventura C. The WHO QualityRights Initiative and its use worldwide: a literature review. Int J Soc Psychiatry 2024;70:424-36.
244. Cruz K, Guerrero A, Scafuto J et al. Atenção à crise em saúde mental: um desafio para a reforma psiquiátrica brasileira. Revista Do NUFEN 2019;11:117-32.
245. Funk M, Drew N. WHO's QualityRights Initiative: transforming services and promoting rights in mental health. Health Hum Rights 2020;22:69-75.
246. World Health Organization. WHO QualityRights e-training on mental health. Geneva: World Health Organization, 2022.
247. Parwiz K, de Almeida J. QualityRights in Kabul mental health hospital. WAPR Bull 2022;48:43-8.
248. Braga C, Delgado P. Respect of peoples' human rights: QualityRights Initiative and Brazilian mental health policy & services. WAPR Bull 2022;48:37-42.
249. Rican P, Prochazka M. Experiences with QualityRights audits and effort to reduce restraints. WAPR Bull 2022;48:26-30.
250. Juodkaite D. Monitoring of human rights of persons in health and social care institutions in Lithuania using the WHO Quality Rights toolkit. WAPR Bull 2022;48:31-7.
251. Poynton-Smith E, Orrell M, Osei A et al. A quantitative analysis of human rights-related attitude changes towards people with mental health conditions and psychosocial, intellectual, or cognitive disabilities following completion of the WHO QualityRights e-training in Ghana. Int J Ment Health Syst 2023;17:46.
252. Morrisey F. An evaluation of attitudinal change towards CRPD rights following delivery of the WHO QualityRights training programme. Ethics Med Public Health 2020;13:100410.
253. Gill N, Drew N, Rodrigues M et al. Bringing together the World Health Organization's QualityRights initiative and the World Psychiatric Association's programme on implementing alternatives to coercion in mental healthcare: a common goal for action. BJPsych Open 2023;10:e23.
254. Anthony WA. Recovery from mental illness: the guiding vision of the mental health system in the 1990s. Psychosoc Rehabil J 1993;16:11-23.
255. Productivity Commission. Mental health, Report no. 95. Canberra: Productivity Commission, 2020.
256. Mental Health Commission of Canada. Putting recovery into practice. An introduction to the Guidelines for Recovery-Oriented Practice. Ottawa: Mental Health Commission of Canada, 2020.
257. Hospital Authority and Social Welfare Department. Service framework of personalised care for adults with severe mental illness in Hong Kong. Hong Kong: Hospital Authority and Social Welfare Department, 2016.
258. Government of India, Ministry of Health and Family Welfare. New pathways, new hope. National Mental Health Policy of India. New Delhi: Ministry of Health and Family Welfare, 2014.
259. Department of Health and Social Care. Mental health and wellbeing plan: discussion paper. London: UK Government, 2023.
260. World Health Organization. Mental health, human rights and legislation. Geneva: World Health Organization, 2023.
261. World Health Organization. Guidance on community mental health services: promoting person-centred and rights-based approaches. Geneva: World Health Organization, 2021.
262. World Health Organization. Comprehensive mental health action plan 2013-2030. Geneva: World Health Organization, 2021.
263. Orsi J, Marmirolli F, de Aquino P et al. Recovery processes reported by people with severe mental illness in Brazil: systematic review and thematic synthesis. Transcult Psychiatry (in press).
264. Kanehara A, Koike H, Fujieda Y et al. Culture-dependent and universal constructs and promoting factors for the process of personal recovery in users of mental health services: qualitative findings from Japan. BMC Psychiatry 2022;22:105.
265. Nowak I, Waszkiewicz J, Świtaj P et al. A qualitative study of the subjective appraisal of recovery among people with lived experience of schizophrenia in Poland. Psychiatr Q 2017;88:435-46.
266. Saavedra J, Arias-Sánchez S, Matías-García S et al. "I don't believe I'm going to recover from anything". Understanding recovery amongst people with severe mental illness attending community health services in Spain. Disabil Rehabil 2022;44:5974-82.
267. de Wet A, Pretorius C. Perceptions and understanding of mental health recovery for service users, carers, and service providers: a South African perspective. Psychiatr Rehabil J 2021;44:157-65.
268. Chao P, Hsieh W, Yeh S et al. Factors associated with personal recovery among psychiatric nursing home residents. J Psychiatr Ment Health Nurs 2022;29:852-60.
269. Roberts G, Boardman J. Understanding 'recovery'. Adv Psychiatr Treat 2013;19:400-9.
270. Amering M, Schmolke M. Recovery in mental health. Reshaping scientific and clinical responsibilities. Chichester: Wiley, 2009.
271. Royal Australia and New Zealand College of Psychiatrists. Recovery and the psychiatrist. Melbourne: Royal Australia and New Zealand College of Psychiatrists, 2016.
272. South London and Maudsley NHS Foundation Trust and South West London and St. George's Mental Health NHS Trust. Recovery is for all. Hope, agency and opportunity in psychiatry. A position statement by consultant psychiatrists. London: South London and Maudsley NHS Foundation Trust and South West London and St. George's Mental Health NHS Trust, 2010.
273. Gambino M, Pavlo A, Ross D. Recovery in mind: perspectives from postgraduate psychiatric trainees. Acad Psychiatry 2016;40:481-8.
274. Soundy A, Stubbs B, Roskell C et al. Identifying the facilitators and processes which influence recovery in individuals with schizophrenia: a systematic review and thematic synthesis. J Ment Health 2015;24:103-10.
275. Isaacs A, Brooks H, Lawn S et al. Effectiveness of personal recovery facilitators in adults with schizophrenia and other psychoses: a systematic review of reviews and narrative synthesis. Schizophr Res 2022;246:132-47.
276. Piat M, Wainwright M, Sofouli E et al. Factors influencing the implementation of mental health recovery into services: a systematic mixed studies review. Syst Rev 2021;10:134.
277. Le Boutillier C, Chevalier A, Lawrence V et al. Staff understanding of recovery-orientated mental health practice: a systematic review and narrative synthesis.

Implement Sci 2015;10:87.
278. Sainsbury Centre for Mental Health. Implementing Recovery. A new framework for organisational change. London: Sainsbury Centre for Mental Health, 2010.
279. Stickley T, Wright N, Slade M. The art of recovery: outcomes from participatory arts activities for people using mental health services. J Ment Health 2018; 27:367-73.
280. Iwasaki Y, Coyle C, Shank J et al. Role of leisure in recovery from mental illness. Am J Psychiatr Rehabil 2014;17:147-65.
281. Linde J, Schmid M, Ruud T et al. Social factors and recovery: a longitudinal study of patients with psychosis in mental health services. Community Ment Health J 2023;59:294-305.
282. Kirkbride JB, Anglin DM, Colman I et al. The social determinants of mental health and disorder: evidence, prevention and recommendations. World Psychiatry 2024;23:58-90.
283. Chmielowska M, Zisman-Ilani Y, Saunders R et al. Trends, challenges, and priorities for shared decision making in mental health: the first umbrella review. Int J Soc Psychiatry 2023;69:823-40.
284. Thomas E, Simmons M, Mathai C et al. Peer-facilitated decision making in mental health: promises, pitfalls, and recommendations for research and practice. Psychiatr Serv 2023;74:401-6.
285. Sandhu B. Lived experience leadership. London and New Haven: Clore Social Leadership and Tsai CITY, 2019.
286. Killackey E. Lived, loved, laboured, and learned: experience in youth mental health research. Lancet Psychiatry 2023;10:916-8.
287. Karbouniaris S, Abma T, Wilken J et al. Use of experiential knowledge by mental health professionals and its contribution to recovery: literature review. J Recovery Ment Health 2020;4:4-19.
288. Leamy M, Clarke E, Le Boutillier C et al. A national survey of recovery practice in community mental health teams. Br J Psychiatry 2016;209:340-6.
289. King A, Brophy L, Fortune T et al. Factors affecting mental health professionals' sharing of their lived experience in the workplace: a scoping review. Psychiatr Serv 2020;71:1047-64.
290. Zamir A, Tickle A, Sabin-Farrell R. A systematic review of the evidence relating to disclosure of psychological distress by mental health professionals within the workplace. J Clin Psychol 2022;78:1712-38.
291. Karbouniaris S, Wilken P, Weerman A et al. Experiential knowledge of mental health professionals: service users' perceptions. Eur J Ment Health 2022;17:23-37.
292. Riches S, Schrank B, Brownell T et al. Therapist self-disclosure in positive psychotherapy for psychosis. Clin Psychol Forum 2020;327:14-21.
293. Dunlop B, Woods B, Lovell J et al. Sharing Lived Experiences Framework (SLEF): a framework for mental health practitioners when making disclosure decisions. J Soc Work Pract 2022;36:25-39.
294. Yim C, Chieng J, Tang X et al. Umbrella review on peer support in mental disorders. Int J Ment Health 2023;52:379-400.
295. Davidson L, Bellamy C, Guy K et al. Peer support among persons with severe mental illnesses: a review of evidence and experience. World Psychiatry 2012;11:123-8.
296. White S, Foster R, Marks J et al. The effectiveness of one-to-one peer support in mental health services: a systematic review and meta-analysis. BMC Psychiatry 2020;20:534.
297. Dark F, Patton M, Newton R. A substantial peer workforce in a psychiatric service will improve patient outcomes: the case for. Australas Psychiatry 2021;25: 441-4.
298. Cooper R, Saunders K, Greenburgh A et al. The effectiveness, implementation, and experiences of peer support approaches for mental health: a systematic umbrella review. BMC Med 2024;22:72.
299. Pathare S, Kalha J, Krishnamoorthy S. Peer support for mental illness in India: an underutilised resource. Epidemiol Psychiatr Sci 2018;27:415-9.
300. Shields-Zeeman L, Pathare S, Walters BH et al. Promoting wellbeing and improving access to mental health care through community champions in rural India: the Atmiyata intervention approach. Int J Ment Health Syst 2017;11:6.
301. World Health Organization. Advocacy for mental health. Mental health policy and service guidance package. Geneva: World Health Organization, 2003.
302. Abbasinia M, Ahmadi F, Kazemnejad A. Patient advocacy in nursing: a concept analysis. Nurs Ethics 2020;27:141-51.
303. Ridley J, Newbigging K, Street C. Mental health advocacy outcomes from service user perspectives. Ment Health Rev 2018;23:280-92.
304. Ungar T, Knaak S, Szeto A. Theoretical and practical considerations for combating mental illness stigma in health care. Community Ment Health J 2016;52: 262-71.
305. Zaske H, Freimuller L, Wolwer W et al. Anti-stigma competence for mental health professionals: results of a pilot study of a further education programme for people working in psychiatric and psychosocial settings. Fortschr Neurol Psychiatr 2014;82:586-92.
306. Accreditation Council for Graduate Medical Education. Common program requirements. https://www.acgme.org.
307. Frank J, Snell L, Sherbino J (eds). CanMEDS 2015 physician competency framework. Ottawa: Royal College of Physicians and Surgeons of Canada, 2015.
308. Alem A, Pain C, Araya M et al. Co-creating a psychiatric resident program with Ethiopians, for Ethiopians, in Ethiopia: the Toronto Addis Ababa Psychiatry Project (TAAPP). Acad Psychiatry 2010;34:424-32.
309. Browne M. Independent advocacy in Ireland: current context and future challenge. Dublin: Safeguarding Ireland, 2018.
310. Cheung IW, Silva DS, Miller KJ et al. A qualitative study of clinicians' perspectives on independent rights advice for involuntary psychiatric patients in British Columbia, Canada. PLoS One 2021;16:e0247268.
311. Pulman A, Sloan H, Fenge L-A. Advocacy in practice: who advocates for the advocates? Practice 2025;37:41-57.
312. Ridley J, Newbigging K, McKeown M et al. Independent mental health advocacy: the right to be heard. London: Kingsley, 2015.
313. Ionescu A, Mannell J, Vaughan M et al. Misunderstood and underappreciated: a critical review of mental health advocacy and activism in low- and middle-income countries. Health Policy Plan 2024;39:528-39.
314. Wahl O. Mass media images of mental illness: a review of the literature. J Community Psychol 1992;20:343-52.
315. Angermeyer MC, Schulze B. Reinforcing stereotypes: how the focus on forensic cases in news reporting may influence public attitudes towards the mentally ill. Int J Law Psychiatry 2001;24:469-86.
316. Pirkis J, Blood RW, Francis C et al. On-screen portrayals of mental illness: extent, nature, and impacts. J Health Commun 2006;11:523-41.
317. Corrigan PW, Watson AC, Gracia G et al. Newspaper stories as measures of structural stigma. Psychiatr Serv 2005;56:551-6.
318. Maiorano A, Lasalvia A, Sampogna G et al. Reducing stigma in media professionals: is there room for improvement? Results from a systematic review. Can J Psychiatry 2017;62:702-15.
319. Flego A, Reifels L, Mihalopoulos C et al. Cost-effectiveness of media reporting guidelines for the prevention of suicide. Suicide Life Threat Behav 2022;52: 1048-57.
320. World Bank. Reduction of mental health related stigma and discrimination: global overview. Washington: World Bank Group, 2024.
321. Crespo-Gonzalez C, Rae J, Hill R et al. Mental health training programmes for community pharmacists, pharmacy staff and students: a systematic review. Pharm Educ 2023;23:62-3.
322. Hooblaul M, Nadasan T, Oladapo OM. Mental health education for physiotherapists: a scoping review. S Afr J Psychiatry 2023;29:21-7.
323. Ferguson MS, Reis JA, Rabbetts L et al. The effectiveness of suicide prevention education programs for nurses: a systematic review. Crisis 2018;39:96-109.
324. Maynard K. Reducing student nurse stigmatization of the patient who misuses opioids: a scoping review. J Addict Nurs 2020;31:47-59.
325. Kolodziej ME, Johnson BT. Interpersonal contact and acceptance of persons with psychiatric disorders: a research synthesis. J Consult Clin Psychol 1996;64:1387-96.
326. Lien Y-Y, Lin H-S, Lien Y-J et al. Challenging mental illness stigma in healthcare professionals and students: a systematic review and network meta-analysis. Psychol Health 2021;36:669-84.
327. Petkari E, Masedo Gutierrez AI, Xavier M et al. The influence of clerkship on students' stigma towards mental illness: a meta-analysis. Med Educ 2018;52: 694-704.
328. Piot M-A, Dechartres A, Attoe C et al. Simulation in psychiatry for medical doctors: a systematic review and meta-analysis. Med Educ 2020;54:696-708.
329. Piot M-A, Dechartres A, Attoe C et al. Effectiveness of simulation in psychiatry for nursing students, nurses and nurse practitioners: a systematic review and meta-analysis. J Adv Nurs 2022;78:322-47.
330. Wong JCM, Chua JYX, Chan PY et al. Effectiveness of educational interventions in reducing the stigma of healthcare professionals and healthcare students towards mental illness: a systematic review and meta-analysis. J Adv Nurs 2024;25:4074-88.
331. Cheung J, Chan CY, Cheng HY. The effectiveness of interventions on improving the mental health literacy of health care professionals in general hospitals: a systematic review of randomized controlled trials. J Am Psychiatr Nurses Assoc 2023;30:465-79.
332. Heim E, Henderson C, Kohrt BA et al. Reducing mental health-related stigma among medical and nursing students in low- and middle-income countries: a systematic review. Epidemiol Psychiatr Sci 2019;29:e28.

333. Bte Abd Malik NN, Kannusamy P, Klanin-Yobas P. The effectiveness of mental health-related theoretical education and clinical placement in mental health settings in changing the attitudes of health care students towards mental illness: a systematic review. JBI Libr Syst Rev 2012;10:4019-76.
334. Brunero S, Jeon Y-H, Foster K. Mental health education programmes for generalist health professionals: an integrative review. Int J Ment Health Nurs 2012; 21:428-44.
335. Classen B, Tudor K, Johnson F et al. Embedding lived experience expertise across the mental health tertiary education sector: an integrative review in the context of Aotearoa New Zealand. J Psychiatr Ment Health Nurs 2021;28:1140-52.
336. Knaak S, Modgill G, Patten SB. Key ingredients of anti-stigma programs for health care providers: a data synthesis of evaluative studies. Can J Psychiatry 2014;59(Suppl. 1):S19-26.
337. Muirhead K, Macaden L, Smyth K et al. Establishing the effectiveness of technology-enabled dementia education for health and social care practitioners: a systematic review. Syst Rev 2021;10:252.
338. Zubala A, Lyszkiewicz K, Lee E et al. Large-scale online education programmes and their potential to effect change in behaviour and practice of health and social care professionals: a rapid systematic review. Interact Learn Environ 2019;27:797-812.
339. Carrara BS, Fernandes RHH, Bobbili SJ et al. Health care providers and people with mental illness: an integrative review on anti-stigma interventions. Int J Soc Psychiatry 2021;67:840-53.
340. Goh Y-S, Ow Yong QYJ, Tam WW. Effects of online stigma-reduction programme for people experiencing mental health conditions: a systematic review and meta-analysis. Int J Ment Health Nurs 2021;30:1040-56.
341. Adewuyi M, Morales K, Lindsey A. Impact of experiential dementia care learning on knowledge, skills and attitudes of nursing students: a systematic literature review. Nurs Educ Pract 2022;62:103351.
342. Jensen RAA, Musaeus P, Pedersen K. Virtual patients in undergraduate psychiatry education: a systematic review and synthesis. Adv Health Sci Educ Theory Pract 2024;29:329-47.
343. Smyth D, Wilson C, Searby A. Undergraduate nursing student knowledge and attitudes of healthcare consumers with problematic alcohol and other drug use: a scoping review. Int J Ment Health Nurs 2021;30(Suppl. 1):1293-309.
344. Szekely R, Mason O, Frohlich D et al. The use of virtual reality to reduce mental health stigma among healthcare and non-healthcare students: a systematic review. Behav Inf Technol 2023;44:2116-33.
345. Liu G, Jack H, Piette A et al. Mental health training for health workers in Africa: a systematic review. Lancet Psychiatry 2016;3:65-76.
346. Caulfield A, Vatansever D, Lambert G et al. WHO guidance on mental health training: a systematic review of the progress for non-specialist health workers. BMJ Open 2019;9:e024059.
347. Keynejad R, Spagnolo J, Thornicroft G. WHO Mental Health Gap Action Programme (mhGAP) intervention guide: updated systematic review on evidence and impact. Evid Based Ment Health 2021;24:124-30.
348. Bielenberg J, Swisher G, Lembke A et al. A systematic review of stigma interventions for providers who treat patients with substance use disorders. J Subst Abuse Treat 2021;131:108486.
349. Raj CT. The effectiveness of mental health disorder stigma-reducing interventions in the healthcare setting: an integrative review. Arch Psychiatr Nurs 2022;39:73-83.
350. Heim E, Kohrt BA, Koschorke M et al. Reducing mental health-related stigma in primary health care settings in low- and middle-income countries: a systematic review. Epidemiol Psychiatr Sci 2018;29:e3.
351. Brohan E, Slade M, Clement S et al. Experiences of mental illness stigma, prejudice and discrimination: a review of measures. BMC Health Serv Res 2010; 10:80.
352. Thornicroft G, Bakolis I, Evans-Lacko S et al. Key lessons learned from the INDIGO global network on mental health related stigma and discrimination. World Psychiatry 2019;18:229-30.
353. Magnan E, Weyrich M, Miller M et al. Stigma against patients with substance use disorders among health care professionals and trainees and stigma-reducing interventions: a systematic review. Acad Med 2024;99:221-31.
354. Gkioka M, Schneider J, Kruse A et al. Evaluation and effectiveness of dementia staff training programs in general hospital settings: a narrative synthesis with Holton's three-level model applied. J Alzheimers Dis 2020;78:1089-108.
355. Hwong A, Wang K, Bent S et al. Breast cancer screening in women with schizophrenia: a systematic review and meta-analysis. Psychiatr Serv 2020;71:263-8.
356. Mitchell AJ, Pereira IE, Yadegarfar M et al. Breast cancer screening in women with mental illness: comparative meta-analysis of mammography uptake. Br J Psychiatry 2014;205:428-35.
357. Kisely S, Crowe E, Lawrence D. Cancer-related mortality in people with mental illness. JAMA Psychiatry 2013;70:209-17.
358. Flores EJ, Neil JM, Tiersma KM et al. Feasibility and acceptability of a collaborative lung cancer screening educational intervention tailored for individuals with serious mental illness. J Am Coll Radiol 2021;18:1624-34.
359. Weinstein LC, Stefancic A, Cunningham AT et al. Cancer screening, prevention, and treatment in people with mental illness. CA Cancer J Clin 2016;66:134-51.
360. van Nieuwenhuizen A, Henderson C, Kassam A et al. Emergency department staff views and experiences on diagnostic overshadowing related to people with mental illness. Epidemiol Psychiatr Sci 2013;22:255-62.
361. Lamontagne-Godwin FR, Henderson C, Lafarge C et al. The effectiveness and design of informed choice tools for people with severe mental illness: a systematic review. J Ment Health 2023;32:260-75.
362. Fujiwara M, Yamada Y, Etoh T et al. A feasibility study of provider-level implementation strategies to improve access to colorectal cancer screening for patients with schizophrenia: ACCESS2 (N-EQUITY 2104) trial. Implement Sci Commun 2024;5:2.
363. Corrigan PW, Mittal D, Reaves CM et al. Mental health stigma and primary health care decisions. Psychiatry Res 2014;218:35-8.
364. Lasalvia A, Zoppei S, Van BT et al. Global pattern of experienced and anticipated discrimination reported by people with major depressive disorder: a cross-sectional survey. Lancet 2012;381:55-62.
365. Thornicroft G, Brohan E, Rose D et al. Global pattern of experienced and anticipated discrimination against people with schizophrenia: a cross-sectional survey. Lancet 2009;373:408-15.
366. Deb T, Lempp H, Bakolis I et al. Responding to experienced and anticipated discrimination (READ): anti-stigma training for medical students towards patients with mental illness – study protocol for an international multisite non-randomised controlled study. BMC Med Educ 2019;19:41.
367. Lassman F, Henderson RC, Dockery L et al. How does a decision aid help people decide whether to disclose a mental health problem to employers? Qualitative interview study. J Occup Rehabil 2015;25:403-11.
368. Guerrero Z, Iruretagoyena B, Parry S et al. Anti-stigma advocacy for health professionals: a systematic review. J Ment Health 2024;33:394-414.
369. Li J, Fan Y, Zhong HQ et al. Effectiveness of an anti-stigma training on improving attitudes and decreasing discrimination towards people with mental disorders among care assistant workers in Guangzhou, China. Int J Ment Health Syst 2019;13:1.
370. Griffith JL, Kohrt BA. Managing stigma effectively: what social psychology and social neuroscience can teach us. Acad Psychiatry 2016;40:339-47.
371. Sheely-Moore AI, Kooyman L. Infusing multicultural and social justice competencies within counseling practice: a guide for trainers. Adultspan J 2011;10: 102-9.
372. Oostermeijer S, Morgan AJ, Ross AM et al. Stigmatising attitudes of probation, parole and custodial officers towards people with mental health issues: a systematic literature review and meta-analysis. Legal Criminol Psychol 2023; 28:165-99.
373. Gaebel W, Zäske H, Baumann AE et al. Evaluation of the German WPA "Program against stigma and discrimination because of schizophrenia – Open the Doors": results from representative telephone surveys before and after three years of antistigma interventions. Schizophr Res 2008;98:184-93.
374. Henderson C, Thornicroft G. Stigma and discrimination in mental illness: Time to Change. Lancet 2009;373:1928-30.
375. Robinson EJ, Henderson C. Public knowledge, attitudes, social distance and reporting contact with people with mental illness 2009-2017. Psychol Med 2019;49:2717-26.
376. Ronaldson A, Henderson C. Investigating changes in mental illness stigma and discrimination after the Time to Change programme in England. BJPsych Open 2024;10:e199.
377. González-Sanguino C, Potts LC, Milenova M et al. Time to Change's social marketing campaign for a new target population: results from 2017 to 2019. BMC Psychiatry 2019;19:417.
378. Freiere P. Pedagogy of the oppressed. New York: Seabury, 1970.
379. Roberts SJ, Demarco R, Griffin M. The effect of oppressed group behaviours on the culture of the nursing workplace: a review of the evidence and interventions for change. J Nurs Manag 2009;17:288-93.
380. Kamaradova D, Latalova K, Prasko J et al. Connection between self-stigma, adherence to treatment, and discontinuation of medication. Patient Prefer Adherence 2016;10:1289-98.
381. Corrigan PW, Watson AC. Understanding the impact of stigma on people with mental illness. World Psychiatry 2002;1:16-20.
382. Ritsher JB, Otilingam PG, Grajales M. Internalized stigma of mental illness:

psychometric properties of a new measure. Psychiatry Res 2003;121:31-49.
383. Lien YJ, Chang HA, Kao YC et al. Self-stigma mediates the impact of insight on current suicide ideation in suicide attempters with schizophrenia: results of a moderated mediation approach. Suicide Life Threat Behav 2018;48:661-76.
384. Brohan E, Elgie R, Sartorius N et al. Self-stigma, empowerment and perceived discrimination among people with schizophrenia in 14 European countries: the GAMIAN-Europe study. Schizophr Res 2010;122:232-8.
385. Yanos PT, West ML, Gonzales L et al. Change in internalized stigma and social functioning among persons diagnosed with severe mental illness. Psychiatry Res 2012;200:1032-4.
386. Holubova M, Prasko J, Latalova K et al. Are self-stigma, quality of life, and clinical data interrelated in schizophrenia spectrum patients? A cross-sectional outpatient study. Patient Prefer Adherence 2016;10:265-74.
387. Yanos PT, Lucksted A, Drapalski AL et al. Interventions targeting mental health self-stigma: a review and comparison. Psychiatr Rehabil J 2015;38:171-8.
388. Lucksted A, Drapalski AL, Brown CH et al. Outcomes of a psychoeducational intervention to reduce internalized stigma among psychosocial rehabilitation clients. Psychiatr Serv 2017;68:360-7.
389. Russinova Z, Rogers ES, Gagne C et al. A randomized controlled trial of a peer-run antistigma photovoice intervention. Psychiatr Serv 2014;65:242-6.
390. Hansson L, Lexen A, Holmen J. The effectiveness of narrative enhancement and cognitive therapy: a randomized controlled study of a self-stigma intervention. Soc Psychiatry Psychiatr Epidemiol 2017;52:1415-23.
391. Rusch N, Abbruzzese E, Hagedorn E et al. The efficacy of Coming Out Proud to reduce stigma's impact among people with mental illness: pilot randomised controlled trial. Br J Psychiatry 2014;204:249-51.
392. Wood L, Byrne R, Enache G et al. A brief cognitive therapy intervention for internalised stigma in acute inpatients who experience psychosis: a feasibility randomised controlled trial. Psychiatry Res 2018;262:303-10.
393. Martinez-Hidalgo MN, Lorenzo-Sanchez E, Lopez Garcia J et al. Social contact as a strategy for self-stigma reduction in young adults and adolescents with mental health problems. Psychiatry Res 2017;260:443-50.
394. Al Ramiah A, Hewstone M. Intergroup contact as a tool for reducing, resolving, and preventing intergroup conflict: evidence, limitations, and potential. Am Psychol 2013;68:527-42.
395. Betton V, Borschmann R, Docherty M et al. The role of social media in reducing stigma and discrimination. Br J Psychiatry 2015;206:443-4.
396. Hamilton S, Pinfold V, Cotney J et al. Qualitative analysis of mental health service users' reported experiences of discrimination. Acta Psychiatr Scand 2016;134(Suppl. 446):14-22.
397. Buchter RB, Messer M. Interventions for reducing self-stigma in people with mental illnesses: a systematic review of randomized controlled trials. Ger Med Sci 2017;15:Doc07.
398. Wood L, Byrne R, Varese F et al. Psychosocial interventions for internalised stigma in people with a schizophrenia-spectrum diagnosis: a systematic narrative synthesis and meta-analysis. Schizophr Res 2016;176:291-303.
399. Jagan S, Mohd Daud TI, Chia LC et al. Evidence for the effectiveness of psychological interventions for internalized stigma among adults with schizophrenia spectrum disorders: a systematic review and meta-analyses. Int J Environ Res Public Health 2023;20:5570.
400. Rüsch N, Kösters M. Honest, Open, Proud to support disclosure decisions and to decrease stigma's impact among people with mental illness: conceptual review and meta-analysis of program efficacy. Soc Psychiatry Psychiatr Epidemiol 2021;56:1513-26.
401. Klein T, Kosters M, Corrigan PW et al. Does the peer-led Honest, Open, Proud program reduce stigma's impact for everyone? An individual participant data meta-regression analysis. Soc Psychiatry Psychiatr Epidemiol 2023;58:1675-85.
402. HOP. Why honest, open, proud (hop)? www.hopprogram.org.
403. Pyle M, Pilling S, Machin K et al. Peer support for internalised stigma experienced by people with psychosis: rationale and recommendations. Psychosis 2018;10:146-52.
404. Demissie M, Hanlon C, Birhane R et al. Psychological interventions for bipolar disorder in low- and middle-income countries: systematic review. BJPsych Open 2018;4:375-84.
405. Luo H, Li Y, Yang BX et al. Psychological interventions for personal stigma of patients with schizophrenia: a systematic review and network meta-analysis. J Psychiatr Res 2022;148:348-56.
406. Evans M, Barker H, Peddireddy S et al. Peer-delivered services and peer support reaching people with schizophrenia: a scoping review. Int J Ment Health 2023;52:338-60.
407. Orock AN, Nicette G. A review of literature of peer-based recovery support in substance abuse and the implications for effective implementation in Seychelles. J Subst Use 2022;27:115-21.
408. Abtahi Z, Potocky M, Eizadyar Z et al. Digital interventions for the mental health and well-being of international migrants: a systematic review. Res Soc Work Pract 2023;33:518-29.
409. Mills H, Mulfinger N, Raeder S et al. Self-help interventions to reduce self-stigma in people with mental health problems: a systematic literature review. Psychiatry Res 2020;284:112702.
410. Stuart R, Shah P, Olive RR et al. Experiences of Every Mind Matters, Public Health England's adult mental health literacy campaign: a qualitative interview study. BMC Public Health 2023;23:398.
411. O'Brien C, Gardner-Sood P, Corlett SK et al. Provision of health promotion programmes to people with serious mental illness: a mapping exercise of four South London boroughs. J Psychiatr Ment Health Nurs 2014;21:121-7.
412. Gurung D, Subedi B, Kohrt BA et al. Development of a mental health-related structural stigma measurement framework in the healthcare system setting: a modified Delphi study. PLoS One 2025;20:e0316999.
413. British Asian Trust. Working together to achieve decriminalisation of suicide in Pakistan. www.britishasiantrust.org.
414. The Lancet. Drug decriminalisation: grounding policy in evidence. Lancet 2023;402:1941.
415. Hayes D, Henderson C, Bakolis I et al. Recovery Colleges Characterisation and Testing in England (RECOLLECT): rationale and protocol. BMC Psychiatry 2022;22:627.
416. Selamu M, Asher L, Hanlon C et al. Beyond the biomedical: community resources for mental health care in rural Ethiopia. PLoS One 2015;10:e0126666.
417. Mueser KT, McGurk SR. Supported employment for persons with serious mental illness: current status and future directions. Encephale 2014;40(Suppl. 2):S45-56.
418. Hildersley R, Potts L, Anderson C et al. Improvement for most, but not all: changes in newspaper coverage of mental illness from 2008 to 2019 in England. Epidemiol Psychiatr Sci 2020;29:e177.
419. Institute of Mental Health. Mind Matters: a study of mental health literacy 2022-2023. www.imh.com.sg.
420. Ingall B-R, McPhilbin M, Lewandowski F et al. Personal explanations for psychosis: a systematic review and thematic synthesis. Schizophr Bull Open 2025;6:sgaf006.
421. Bucci S, Berry K, Barrowclough C et al. Family interventions in psychosis: a review of the evidence and barriers to implementation. Aust Psychol 2016;51:62-8.
422. Norheim I, Pedersen R, Selle ML et al. Implementation of guidelines on family involvement for persons with psychotic disorders: a pragmatic cluster randomized trial. Effect on relatives' outcomes and family interventions received. Front Psychiatry 2024;15:1381007.

DOI:10.1002/wps.70031

Harnessing civil society to promote social inclusion of people with severe mental illness

The engaging and comprehensive review by Henderson et al[1] outlines current barriers to social inclusion among people with severe mental illness. As with any insightful paper, this review raises several important questions. One concerns the relative roles and responsibilities of different sectors of society in promoting social inclusion in people with severe mental illness.

I contend that six actors and sectors are directly implicated in this process. First are individuals with severe mental illness, who can use their agency to engage in actions that enhance social inclusion, for example joining recovery colleges or other community organizations. Second is the family, who can encourage social engagement by providing moral, practical and social support. Third are official health services, which can provide offerings such as supported employment and peer support, while empowering patients' agency through therapeutic interventions. Fourth is the government, which can introduce or amend legislation to reduce discrimination against people with severe mental illness, while also funding anti-stigma campaigns. Fifth is business and the private sector, which can adopt socially inclusive workplace policies that provide opportunities for people with severe mental illness. The final sector is civil society, which remains under-harnessed and under-appreciated, despite much promise and innovation in this sector[2].

But what is civil society? A broad definition refers to "non-state not-for-profit voluntary organizations formed by people in that social sphere", and includes faith-based organizations, civic groups, sports clubs, social clubs, outdoor groups, recreational groups, and other voluntary associations[3]. These are typically bottom-up, grassroots and community-led organizations, firmly rooted in local neighborhoods, which may focus on a single activity with a specific mission, or deliver a variety of programs with a broad mission. For example, faith-based organizations such as neighborhood churches may deliver multiple groups and programs, such as youth groups. Other organizations, such as sports clubs or gardening clubs, will focus on a single regular activity based on a shared interest, typically including weekly activities.

Evidence presented by Henderson et al[1] converges with the wider literature to indicate that involvement in these groups can be instrumental in reducing loneliness and isolation, while promoting social inclusion and sense of belonging. For example, a seminal randomized study[4] involved clinical staff working with patients to identify personalized areas of interest, with staff then helping patients engage in social activities "outside the services' resources and with members of the community at large". Results indicated a significant increase in social networks compared to a control group, and at one- and two-year follow-up.

Similarly, a review paper found that initiatives which encourage community engagement are the most effective in facilitating social network improvements, when compared to options such as social skills training[5]. This can include participation in groups centred on a wide variety of activities such as walking, conservation, arts and crafts. Some of these activities often have the added benefit of improving physical health, which is vitally important given the elevated risk of cardiovascular problems and obesity in this population.

What is it about civil society participation that contributes to such gains? To start, participants may make diverse connections with new people beyond mental health services, which can open doors to local friendships, increased social capital, and even job opportunities. Indeed, such "weak ties" (sometimes known as bridging social capital) are known to catalyze important elements of social inclusion. However, they are frequently absent in people with severe mental illness[6]. This absence may be particularly severe in patients who have spent considerable time in clinic-based groups and hospital-based activities limited to interactions with staff and other patients.

Moreover, such civil society groups typically revolve around a shared activity which is enjoyable and involves the acquisition of new skills, imparting a sense of accomplishment and mastery to people with severe mental illness. This means that there is intrinsic motivation to engage and return. Participation in such meaningful activities outside the mental health system, where the individual is not identified as a patient, has been recognized as instrumental in the recovery process[7], and is consistent with an "all of society approach" to mental illness[2]. Such informal organizations can be particularly important in resource poor settings, where professional clinical coverage may be thin. Indeed, the finding that people with schizophrenia in low-income countries have better recovery than those in Western countries has been explained as partly due to wider social networks and greater community involvement among patients in the former[6].

Unfortunately, civil society organizations remain under-harnessed by mental health systems in Western countries. Some evidence suggests that service providers will sometimes signpost and encourage patients with depression and anxiety to use such organizations, but that this remains uncommon for people with severe mental illness[8]. The lingering notion that people with severe mental illness are incapable of participating meaningfully in such organizations may be involved. But such stigmatizing notions surrounding social competence have recently been disproven. For example, robust evidence indicates that people with severe mental illness can successfully work in the competitive market, belying archaic yet common beliefs that they could not work[7].

All this raises another question: what can service providers do to better promote the utilization of civil society organizations by people with severe mental illness? Some mental health service providers have attempted to launch similar groups within the wider mental health system, only open to patients and located within mental health facilities. These programs may be helpful in some respects, but will not contribute to social inclusion nor community integration in the same manner as participation in a civil society organization.

Instead, service providers can consider three courses of action that may be helpful. First, as suggested by Henderson et al[1], service providers can engage in resource mapping, liaison and collaboration with civil society organizations, with appropriate information shared with patients. The literature on religion and mental health offers useful examples of liaison and collaboration between faith-based organizations such as churches and the mental health sector, especially for minority and immigrant patients[9]. Some of these partnerships have included mental health education for the clergy and the congregation to ensure that the receiving environment is well-equipped to help. This could provide a useful model for similar liaison and collaboration.

Second, social prescribing has much potential to help people with severe mental illness connect with civil society organizations and participate in meaningful activities therein. Such prescribing is highly person-centred, as patients express preferences that are personally meaningful, which are realized through clinical (and sometimes financial) support. However, the literature suggests that research and practice in social prescribing and mental health tends to focus on anxiety and depression[8]. Moreover, social prescribing is not equally available across countries. Greater efforts should be made to implement and expand social prescribing for severe mental illness.

Finally, other actors are also instrumental in fostering connections with civil society. Families can play a vital role in supporting such connections, and should be encouraged and empowered to help as part of psychoeducation interventions. Moreover, the private sector may be able to offer charitable grants to initiatives and programs that attempt to connect patients with civil society organizations.

All this is consistent with recent calls for an "all of society" approach, that aims to shift an excessive reliance on biomedically oriented mental health services towards a multi-pronged strategy that includes an instrumental role for civil society[2]. Such action is long overdue.

Rob Whitley
Department of Psychiatry, Douglas Research Centre, McGill University, Montreal, QC, Canada

1. Henderson C, Kotera Y, Lloyd-Evans B et al. World Psychiatry 2026;25:56-82.
2. Patel V, Saxena S, Lund C et al. Lancet 2003;402:656-66.
3. Greer SL, Wismar M, Pastorino G et al. Civil society and health: contributions and potential. Copenhagen: European Observatory on Health Systems and Policies, 2017.
4. Terzian E, Tognoni G, Bracco R et al. Can J Psychiatry 2013:58:622-31.
5. Webber M, Fendt-Newlin M. Soc Psychiatry Psychiatr Epidemiol 2017;52:369-80.
6. Whitley R, McKenzie K. Harv Rev Psychiatry 2005;13:71-84.
7. Drake RE, Whitley R. Can J Psychiatry 2014;59:236-42.
8. Cooper M, Avery L, Scott J et al. BMJ Open 2022;12:e060214.
9. Perez LG, Cardenas C, Blagg T et al. Psychiatr Serv 2025;76:61-81.

DOI:10.1002/wps.70004

What can complex systems theory reveal about social inclusion

Historically, mental health care was managed within asylums, where all aspects of life – daily routines, work and social interactions – were encompassed within the institutional setting. With the introduction of psychotropic medications, it became possible to manage many psychiatric conditions outside those settings, facilitating the process of deinstitutionalization. With the rise of evidence-based medicine and the momentum of the Decade of the Brain, mental illness increasingly came to be conceptualized like any other medical disorder – a condition to be fixed primarily at the biological level, with an expectation that people could re-enter society without the need for special accommodations. In practice, many individuals with severe mental illness remain now as socially and economically segregated as they were before in the asylum era – in single-room occupancies, homeless shelters or carceral institutions, often concentrated in impoverished urban neighborhoods. To put it bluntly, the asylum has not disappeared; but simply been decentralized and dispersed.

This has led to a renewed emphasis on interventions aimed at enhancing quality of life through social inclusion. With this, we have circled back: many of the social challenges once managed within institutions now re-emerge as critical responsibilities of psychiatry, as described in the paper by Henderson et al[1]. This paper outlines seven key recommendations to improve social inclusion for people with severe mental illness: amending legislation, decriminalizing suicide and substance possession, improving the evidence base for social inclusion, increasing mental health staff's knowledge of community resources, developing more flexible employment opportunities, reducing stigma, and enhancing conceptual competencies among professionals. Although each addresses important challenges, they are treated to some extent as isolated actions. I will argue here that they are better understood as interconnected parts of a complex system, and advocate for a paradigm shift going from isolated interventions to be tested in clinical trials to a dynamic, complex system characterized by multilevel interactions[2].

This shift can also be described as moving from a complicated to a complex system. Complicated systems – like assembling a jigsaw – are difficult but ultimately solvable through understanding each component part. With enough time and knowledge, one can predict and control the system's behavior. In contrast, complex systems involve interconnected components whose interactions give rise to emergent, unexpected phenomena that cannot be understood in isolation. In the worst case, well-intentioned interventions focusing on one component of a system can lead to unforeseen consequences elsewhere. On the other hand, system thinking can help us identify leverage points where small changes may generate equally unexpected but positive outcomes, also termed the "ripple effect".

The Health Complexity Framework[3] is a model designed to support systematic thinking about complex problems by connecting insights across biological, psychological, social and structural domains. It provides a structured approach to understanding complex health-related issues through three core dimensions: patterns, mechanisms and dynamics. These dimensions encompass seven defining features of complex systems: emergence, interactions, nonlinearity, interference, feedback loops, adaptation and evolution.

Patterns refer to the observable outcomes – such as unemployment, homelessness, social isolation, and inequitable access to health care – that manifest among people with severe mental illness. Key questions to address at this stage include: How does social exclusion of people with mental illness vary across time, place and populations? Which subgroups, based on age, occupation, migration status, socioeconomic background or geography, are most affected?

Mechanisms represent the underlying processes driving these patterns. The mechanisms involve intricate multilevel interactions, nonlinearity (where small changes can produce disproportionate effects) and interference, as factors amplify or dampen each other's impact. For example, biological vulnerabilities, behavioral tendencies, social networks, and structural inequalities may interact to worsen exclusion. Critical questions include: How do these diverse forces combine and spread? Does exclusion propagate through social networks or within specific employment sectors? Are there critical thresholds in the way excluding mechanisms such as stigma evolve?

Dynamics capture the system's development over time, shaped by adaptation, feedback loops and evolution. Individuals, communities and institutions respond continuously to shifting conditions, sometimes reinforcing exclusion, other times fostering inclusion. Feedback loops may perpetuate cycles of marginalization or promote recovery, emphasizing that social exclusion is not a static condition but a dynamic process. Important questions include: How do political and social systems respond to historical change, and how do these responses affect experiences of exclusion? Is there a reinforcing loop between mental illness, social exclusion, and declining health?

Feedback loops may be of special interest to identify effective targets of interventions and to avoid destabilizing the system in a harmful way. I will briefly discuss four potential feedback loops, where well-intended interventions may have unintended harmful consequences.

First, incidents of violent behavior committed by individuals diagnosed with mental disorders are very rare. When such events do occur, they are often amplified by the media and, paradoxically, sometimes used by professional organizations to justify the need for additional resources. However, this focus on risk can unintentionally reinforce fear and stigma among the general public[4]. As a result, people with mental illness may become further marginalized and isolated, which ironically can increase the likelihood of violent incidents. Social marginalization itself is a significant risk factor for violence, and has been described in the US literature as part of the "deaths of despair" phenomenon affecting individuals living on the fringes of society.

Second, as mental health care broadens to include activities such as creative writing, nature, music, spirituality, and social connection, there is an increasing pressure to validate them within a medical evidence paradigm. Questioning whether such ordinary human activities "work" can be subtly stigmatizing, implying that people with mental illness require special justification to engage in everyday life. Rather than continually testing their effectiveness, the focus should shift toward ensuring equal opportunities for meaningful participation, recognizing these activities as valuable ends in themselves, not merely as instruments for improving health[5]. Although often well-intentioned, the medicalization of everyday activities can reinforce stigma and hinder the development of inclusive societies that ensure broad access to meaningful engagement for all – and thus ultimately serve the opposite purpose.

As a third example, the Danish anti-stigma campaign One of Us has been widely recognized for its efforts to reduce stigma surrounding mental illness through personal storytelling and public engagement. However, some scholars have raised concerns that, despite its good intentions, the campaign may inadvertently reinforce stigma[6]. They argued that these campaigns, while aiming to promote inclusion, might unintentionally create a narrative where individuals with mental health conditions are expected to overcome challenges through personal effort alone. This perspective could inadvertently place the burden of recovery on individuals, neglecting the importance of societal intervention. Further, by including primarily people with less severe disabilities, those with more severe conditions risk further stigmatization.

Finally, efforts to destigmatize mental illness by framing it as "a disorder like any other" – often rooted in the idea of a "broken brain" – have, perhaps counterintuitively, been shown to increase stigma rather than reduce it[7]. This biomedical narrative was intended to legitimize mental illness by aligning it with physical health conditions such as diabetes or heart disease, emphasizing that it is not a personal failing but a biological dysfunction. However, research has found that, while such explanations may reduce blame, they also tend to increase perceptions of chronicity, unpredictability and dangerousness[7].

These examples of unintended consequences from interventions within complex systems help illustrate the value of understanding social inclusion as a complex, dynamic process. With this, I support the current movement to embrace this complexity[2] by drawing on a diverse range of epistemic perspectives and integrating multiple levels of the system. This calls for a pluralistic methodological approach[8] – one that combines nomothetic (generalizable) and idiographic (individualized) research, blends quantitative and qualitative methods, and actively incorporates knowledge from various disciplines and lived experiences. This approach moves beyond reductionist causality and acknowledges uncertainty, emergence, and context-dependence as intrinsic to mental health and social inclusion.

Combining methodological pluralism with the Health Complexity Framework offers a promising next step in advancing the biopsychosocial model. This model has sometimes been criticized for lack of operational clarity[9], as it fails to specify how the interplay of biological, psychological and social factors can be studied. If successful, a conceptually sound biopsychosocial model may be the next step to qualify research on social inclusion of people with severe mental illness.

Helene Speyer
Copenhagen Research Center for Mental Health, Copenhagen, Denmark

1. Henderson C, Kotera Y, Lloyd-Evans B et al. World Psychiatry 2026;25:56-82.
2. Öngür D, Paulus MP. Lancet Psychiatry 2025;12:220-7.
3. Rod NH, Broadbent A, Rod MH et al. Epidemiology 2023;34:505-14.
4. Metzl JM, MacLeish KT. Am J Public Health 2015;105:240-9.
5. Speyer H, van Os J. Lancet Psychiatry 2024;11:398-9.
6. Oute J, Huniche L, Nielsen CT et al. Adv Appl Sociol 2015;5:273-85.
7. Loughman A, Haslam N. Cogn Res Princ Implic 2018;3:43.
8. Stein DJ, Nielsen K, Hartford A et al. World Psychiatry 2024;23:215-32.
9. Williamson S. BJPsych Bull 2022;46:232-4.

DOI:10.1002/wps.70005

Rethinking stigma reduction programs for people with severe mental illness

As Henderson et al[1] outline in their comprehensive and thoughtful review, people with severe mental illness experience high rates of social exclusion. The authors make several recommendations for addressing this issue, one of which is to include severe mental illness explicitly in stigma reduction programmes. To assist with setting priority targets for social inclusion and stigma reduction, they also recommend consulting people with severe mental illness about their experiences of exclusion across all life areas.

In Australia, in 2019-2020, we conducted a large-scale community consultation project, including interviews and focus groups with almost 250 people[2]. The project had the explicit aim of asking “people with mental illness, that is poorly understood in the community” what they thought should be central elements of a national stigma and discrimination reduction strategy. The above terminology is used in Australia’s Fifth National Mental Health and Suicide Prevention Plan, and arguably highlights a view that use of terms such as severe mental illness or specific diagnoses should be avoided. Nonetheless, in this project, we defined our scope as including psychosis, schizophrenia, bipolar disorder and borderline personality disorder, to ensure that the focus was on severe mental illness rather than on depression or anxiety.

There was strong support for a national strategy to tackle stigma and discrimination towards people with mental illness, with many noting the need for a long-term approach and ongoing evaluation. The most common theme was ensuring that people with lived experience are central to any strategy, including in leadership, co-design, delivery and evaluation roles. Success will require that sufficient flexibility, financial support and mentoring accompany all lived experience roles. This is even more important for people from Indigenous or culturally and linguistically diverse backgrounds, who may face additional challenges. Participants also emphasized the importance of addressing both structural and interpersonal discrimination. Health services, workplaces and media were identified as key priority settings for targeted action.

Support for anti-stigma initiatives that explicitly focus on severe mental illness comes from evidence that stigma is not a unidimensional construct, and that attitudes and experiences of discrimination vary according to diagnosis. We have made progress in addressing some aspects of stigma, but have been less successful in others. In high-income countries, we have reduced beliefs that depression and anxiety are due to personal weakness, that they do not need treatment, and that an experience of depression is not relatable[3]. We have been far less successful in shifting beliefs about people with psychosis or schizophrenia. Arguably, we have widened the stigma gap between people with mild to moderate anxiety and depression and those with severe mental illness[3]. Moreover, evidence from two Australian nationally representative surveys shows that, between 2011 and 2024, while beliefs about personal weakness and dangerousness for depression, psychosis and long-term schizophrenia have decreased, desire for social distance from a person with these conditions remains unchanged or has even increased[4]. These findings point to the need for novel approaches to reducing stigma against people with severe mental illness.

Including severe mental illness explicitly in stigma reduction programs also requires us to productively resolve the tension between critiques of the biomedical paradigm in mental illness and the need to tailor anti-stigma programs for the specific diagnoses in which people with severe mental illness report the most discrimination. Those who reject the biomedical paradigm argue that diagnostic labels reinforce power imbalances between clinicians and patients, fail to account for cultural and contextual factors in mental illness, and contribute to social exclusion and coercive treatment practices[2]. While it is obviously possible in person-to-person interactions to respect individual choices about the use of diagnostic terms, this is less likely to be possible in programs or campaigns targeted to groups.

Notable examples of stigma towards people with specific diagnoses include attitudes towards people with borderline personality disorder among health professionals[5], or “diagnostic overshadowing” of physical health problems in people with long-term schizophrenia[6]. Tackling these issues in health services will require structural changes that involve collaboration between senior leaders and people with lived experience of severe mental illness, as well as ongoing training, including as part of continuing professional development. This may be particularly critical for early-career health professionals, who may receive training as students, but often struggle to maintain positive attitudes once they are employed in workplaces where negative attitudes toward people with mental illness are pervasive[2].

Structural reforms to facilitate collaboration between health services, employment services, employers and social services are also likely to be essential to extending inclusion in competitive employment[7]. In the broader community, we also need to build the evidence base for interventions to tackle fears about unpredictability, burdensomeness and lowered productivity. Campaigns and educational interventions with key messages that focus on the contribution that people with mental illness can make, as well as specific and practical suggestions for employers to provide support, should be adequately resourced and supported, including with ongoing training. Supporting small-to-medium businesses is likely to be particularly important as, while they are employers of large numbers of people, they do not typically have the support of Human Resources departments.

Given that many recent mental health awareness and anti-stigma campaigns have tended to move away from diagnostic terms in favour of non-specific ones, such as mental health challenges or mental health issues, innovative programs should have their messaging and content carefully developed and rigorously evaluated. A particular challenge is likely to relate to striking a balance between being realistic and adopting a strengths-based focus. This is likely to require a nuanced approach that does not lend itself well to brief messaging. We need to explicitly test programs and campaign messages that are realistic and do not shy away from the challenges of having severe mental illness, but that build empathy and understanding. They should also explore how to specifically acknowledge the benefits and strengths that lived experience of mental illness can bring, including greater empathy, interpersonal skills, assertiveness, creativity, adaptability and resilience. A focus on positive, supportive behaviors – what people can do rather than what they should not – is also likely to be important, as evidenced by the anti-stigma effects of Mental Health First Aid training[8].

People with lived experience of severe mental illness should be empowered and supported to have central and active roles in all aspects of stigma reduction. Inclusive stakeholder engagement, involving employers, health professionals and other end-users, is also critical. Programs and campaigns developed with input only from a limited group of people may not capture the diversity of perspectives necessary for broad applicability. Ultimately, the effectiveness of stigma reduction programs should be measured by their ability to bring about tangible behavior change in their target audiences.

With some exceptions, rigorous evaluation has generally not been a strength of anti-stigma programs. A 2018 meta-analysis[9] of trials of interventions aiming to reduce stigma towards severe mental illness showed that educational and "contact" interventions had small-to-medium effects on attitudes. However, many trials lacked methodological rigor, with common problems including lack of credible control groups, use of convenience samples, and failure to measure longer-term impacts, assess mechanisms of change, or include behavioral (rather than attitudinal) measures.

Future efforts should build on successful initiatives that have shifted public attitudes towards anxiety and depression, and now urgently expand to addressing attitudes and behaviors towards people with severe mental illness.

Nicola Reavley
Centre for Mental Health and Community Wellbeing, Melbourne School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia

1. Henderson C, Kotera Y, Lloyd-Evans B et al. World Psychiatry 2026;25:56-82.
2. Centre for Mental Health, Melbourne School of Population and Global Health. Reducing stigma and discrimination towards people with mental illness. Melbourne: Centre for Mental Health, University of Melbourne. www.mentalhealthcommission.gov.au.
3. Schomerus G, Schindler S, Sander C et al. Eur Psychiatry 2022;65:e78.
4. Reavley NJ, Ross AN, Green R et al. Submitted for publication.
5. Baker J, Beazley PI. J Psychiatr Pract 2022;28:275-93.
6. Thornicroft G, Brohan E, Rose D et al. Lancet 2009;373:408-15.
7. Patmisari E, Huang Y, Orr M et al. PLoS One 2024;19:e0304527.
8. Morgan AJ, Ross A, Reavley NJ. PLoS One 2018;13:e0197102.
9. Morgan AJ, Reavley NJ, Ross A et al. J Psychiatr Res 2018;103:120-33.

DOI:10.1002/wps.70007

Social inclusion in global mental health contexts: how can we do more for what matters most?

Global mental health seeks to address inequities in mental health, particularly in low- and middle-income countries (LMICs). Its goals have evolved over time from an initial focus on expanding access to mental health care to improving the mental health of populations, and re-imagined in terms of the who, what and how of achieving better mental health. Alongside this, there has been a vital focus on addressing mental health-related human rights abuses, stigma and discrimination. However, these efforts have not adequately addressed what commonly matters most to people with mental health conditions and their families, i.e. social inclusion. In responding to Henderson et al's timely and important paper[1], I draw on learning about social inclusion in an Ethiopian context, where I have lived and worked for many years, and consider the evidence and actions needed to re-orient ourselves to the priority of social inclusion in diverse LMICs.

Social inclusion, described in Henderson et al's paper as "being able to participate in activities valued within one's community or wider society as one would wish", is at the heart of what members of a rural Ethiopian community described as "*restoring the person's life*"[2]. In that setting, social inclusion encompasses being enabled and allowed to carry out valued social roles, such as participation in the rich network of community groupings (e.g., burial societies, savings groups) and major events of life (e.g., visiting postnatal women, the sick, the bereaved); contributing labour and care to the community and family, and being trusted in collaborative farming or work activities. The consequences of not being socially included can be economically dire, as subsistence farming activities and informal trading rest on mutual reciprocity. Among households of a person with a severe mental health condition, 33% experienced severe food insecurity, compared to 16% of households in the general population[3].

Recovery journeys are heavily constrained by lack of economic and social inclusion. Women with severe mental health conditions face intersecting disadvantages that work against social inclusion. Gender norms combine with stigmatizing attitudes about people with severe mental illness to constrain women's control over their sexual and reproductive health, and label women as unmarriageable and unsuitable for motherhood. The disadvantages for both men and women emanating from lack of social inclusion are propagated within families of the person and across generations, resulting in lost opportunities for relationships, education and economic betterment, poorer health and premature mortality[4].

This illustration from Ethiopia demonstrates the contextually embedded nature of social inclusion and its profound ramifications for the dignity of people with severe mental health conditions and their families. Further work is needed to understand how social inclusion to support recovery is conceptualized across non-Western settings. The current lack of conceptual clarity presents an immediate challenge for the measurement of social inclusion. None of the existing measures are fit for purpose[5]. Without agreed core concepts allowing for the development of contextualized measures of social inclusion, we have little sense of whether interventions are achieving what matters most for people with mental health conditions and their families.

In a recent systematic review of interventions for people with psychosis in LMICs, which had social inclusion as the primary outcome of interest, only six out of 316 evaluations (4%) reported social inclusion as an outcome, operationalized as participation in social life, economic life (including employment) or political life[6].

Families play a pivotal role in supporting recovery of people with severe mental health conditions in many LMICs where welfare support is minimal. Therefore, measurement of valued aspects of inclusion in family life is likely to be important. Measurement of social inclusion in terms of organizations and services may be possible. For example, people with severe mental health conditions have been identified as a vulnerable group to be prioritized for community development efforts, and yet frequently are "left behind". The extent to which aid and development programmes include people with these conditions would be a valuable indicator of inclusion that could be readily operationalized in many contexts. Indicators of parity of access to quality physical and mental health services also reflect a key aspect of social inclusion that is essential for addressing inequities in health and survival.

What, then, are the implications for how we conceptualize and prioritize interventions for people with severe mental health conditions in diverse LMIC contexts? Interventions to achieve social inclusion necessarily go beyond individual-focused mental health treatments and should consider what aspects of inclusion are valued by the persons themselves, while delicately balancing the inclusion needs of families. Henderson et al highlight the apparent lack of relationship between availability of mental health services and employment inclusion for people with severe mental health conditions in China and India[1]. However, for most people with these conditions, access to biomedical treatment brings benefits that go beyond symptom control.

Models of locally accessible mental health care integrated within primary care in Ethiopia[7] led to reduced food insecurity and reduced instances of restraint, and catalyzed community responses that increased inclusion – for example, of people with severe mental health conditions who were homeless. Nonetheless, this model did not enable "restoration of the person's life" for many, due to inadequacies in mental health care options (e.g., high burden of side effects from first-generation antipsychotics, lack of family level interventions), an inability to address economic and attitudinal barriers to accessing care, and the absence of targeted interventions to support economic and community inclusion.

Interventions that directly target poverty in households of a person with a severe mental health condition have potential to promote social inclusion through multiple pathways, including improved ability to access mental health care and enhanced opportunities to participate in the reciprocal social obligations that underpin full participation in society and economic life. At present, evidence on the impacts of cash transfers or other forms of economic interventions for people with severe mental illness is lacking. While many middle-income countries have national social protection programmes for people with disabilities, individuals with severe mental illness are often systematically excluded, while such programmes are often lacking in low-income countries, demanding focused advocacy.

Rights-based approaches grounded in social justice, such as community-based rehabilitation or inclusive development, assume that enabling factors for inclusion require changes in communities. A trial of community-based rehabilitation in a rural Ethiopian setting sought to engage community leaders and advocate for opportunities for people with severe mental health conditions to be involved in work and community activities alongside engagement in mental health care, demonstrating improvements in functioning, although not employment[8].

Empowerment and involvement of people with lived experience in advocating for the support and inclusion that they value and prioritize is a key approach. In Ethiopia, empowerment activities and participatory action research with people with severe mental health conditions led both to subjective reports of feeling socially valued as well as successful mobilization of community support that facilitated inclusion[9].

Advocacy efforts for social inclusion may be enhanced by social contact interventions involving people with severe mental illness. When these people present their life experiences and recovery journeys to leaders, planners and policy makers, those who hold power may be motivated to change structures and influence attitudes to enable inclusion.

Efforts to achieve social inclusion for people with severe mental health conditions in diverse LMICs require a reorientation to what matters most to these people in their family and community, the services they interact with, and the wider societal and political context. Ensuring that lived experience voices drive this process is essential.

Charlotte Hanlon
Division of Psychiatry, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK; Department of Psychiatry, School of Medicine, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia

The author is supported by funding from the UK National Institute for Health and Care Research (NIHR) through the NIHR Global Health Research Group on Homelessness and Mental Health in Africa (grant no. NIHR134325), and from the Wellcome Trust (grants no. 222154/Z20/Z and 223615/Z/21/Z). The views expressed here are those of the author and not necessarily those of the funding bodies.

1. Henderson C, Kotera Y, Lloyd-Evans B et al. World Psychiatry 2026;25:56-82.
2. Mall S, Hailemariam M, Selamu M et al. Epidemiol Psychiatr Sci 2017;26:43-52.
3. Tirfessa K, Lund C, Medhin G et al. Trop Med Int Health 2020;25:414-23.
4. Fekadu W, Craig TKJ, Kebede D et al. EClinicalMedicine 2021;41:101151.
5. Baumgartner JN, Burns JK. Int J Epidemiol 2014;43:354-64.
6. Barber S, McPhail L, Xue S et al. medRxiv 2025;2025.10.20.25338375.
7. Fekadu A, Hanlon C, Medhin G et al. Br J Psychiatry 2016;208:s4-12.
8. Asher L, Birhane R, Weiss HA et al. Lancet Glob Health 2022;10:e530-42.
9. Abayneh S, Lempp H, Kohrt BA et al. Int J Ment Health Syst 2022;16:33.

DOI:10.1002/wps.70006

Use of artificial intelligence to enhance social inclusion in mental health care: promises and pitfalls

Social inclusion plays a pivotal role in mental health recovery, serving as both a dynamic process (e.g., active pursual of educational and employment opportunities) and a desired outcome (e.g., tangible achievements such as vocational training completion and job attainment). This experience is relevant for both personal and functional recovery, encompassing subjective feelings of hope and sense of belonging alongside objective, measurable results[1].

Globally, the rapid evolution of artificial intelligence (AI) is changing the landscape of social inclusion, bringing forth promises and perils for individuals with severe mental illness (SMI). The central question is not whether AI will have an impact, but how its various applications will shape the social inclusion of this population. Digital inclusion, i.e. the ability to access technology and digital content, is itself a critical aspect of the broader inclusion-exclusion debate within society. By enabling access to communication and information, digital inclusion facilitates improvements across important life domains, including health care and social welfare services, social connections, education and employment. In this sense, AI holds significant potential to enhance social inclusion.

Emerging evidence highlights the positive impact of AI technologies on social inclusion for individuals with various disabilities[2]. For example, in employment, AI-driven platforms can facilitate more flexible work arrangements, remote work options, and a wider range of job opportunities. Similarly, studies have shown that robotic AI companions can provide support and facilitate self-monitoring of health status for older adults. These achievements in crucial functional domains demonstrate the potential of AI to address specific needs.

AI algorithms can effectively analyze large, intricate datasets, enabling the creation of more precise predictive models to identify key determinants of social inclusion outcomes. Given the complex variables and dynamic interactions involved in social inclusion, these models can guide targeted interventions by professionals, and empower individuals with SMI to enhance their ability to achieve desired social inclusion outcomes.

AI applications in mental health care can enhance diagnostic processes and support continuous monitoring of individual recovery. Various machine learning models and deep learning methods, implemented through mobile applications, have shown varying degrees of success in managing symptoms and improving outcomes related to recovery and social inclusion[3,4]. Moreover, AI-assisted language capabilities enable individuals with SMI to access recovery narratives, connect with peers globally, and engage in supportive online communities, fostering deeper friendships and a stronger sense of community across linguistic and cultural boundaries.

While AI presents opportunities for enhancing social inclusion, significant challenges exist regarding its potential to truly facilitate this process for individuals with SMI. A primary concern stems from the current state of AI technology. While human-inspired AI can recognize social cues and emotions and generate expressive responses, it lacks true empathy. We are still developing "humanized AI", where cognitive, emotional and social intelligence converge, allowing machines to simulate human experiences of pain, hope, suffering and healing[5].

Healing, in its essence, often transcends mere text or verbal communication. Meaningful connections, deep acceptance, and empathy between individuals arise from a shared understanding of lived experiences, sometimes conveyed through simply being present with one another – something that an AI agent can never replicate. Recent research suggests that AI technologies are best utilized as supplementary tools within human-human interactions, rather than as standalone solutions in human services[4]. Moreover, some applications may be designed to foster addictive tendencies, targeting vulnerable groups to maximize product benefits, which raises ethical concerns and highlights the need for robust personal data protection[6].

AI algorithms trained on biased data may further entrench social divisions and deepen isolation. For instance, a recent study revealed significant differences in SMI outcomes suggested by four large language models (LLMs): ChatGPT-3.5, ChatGPT-4, Claude, and Bard[7]. The ChatGPT-3.5 model suggested a notably pessimistic prognosis for individuals with schizophrenia under professional treatment compared to other LLMs. Such narratives often foster a culture of limited hope, and stigmatized perceptions linking SMI with violence and poor outcomes. This issue is particularly relevant as people with SMI, caregivers and health care professionals increasingly utilize LLMs for consultations. The messages that these models provide can significantly impact patient care, and are crucial for social inclusion, guidance and interventions. Therefore, they need to be aligned with current research evidence.

While recognizing the potential of AI to promote social inclusion, it is crucial to consider that the digital gap will actually widen. Marginalized communities, including those with SMI, often lack the essential resources such as high-speed Internet, quality devices, and digital literacy training needed to fully leverage AI. This disparity means that average users access less sophisticated tools, while the privileged few reap the benefits of superior resources. Moreover, a significant challenge in AI lies in the misalignment of algorithms, which prioritize prominent data patterns and may overlook essential human values and experiences such as resilience, citizenship, and the importance of human virtues. This unintended oversight could have far-reaching implications for AI's impact on social inclusion in mental health.

To ensure that AI advances social inclusion, the active involvement of individuals with lived experience is crucial now more than ever. However, the window of opportunity may be missed unnoticeably. The principle of "nothing about us without us" should guide AI development. A Canadian study highlights the need for diverse participants representing various recovery experiences and perspectives from developed and developing countries[8]. Professionals must advocate for the rights of individuals with SMI and their caregivers, while vendors and innovators should prioritize the voices of those with lived experience and critically examine training data.

The mention of AI also brings to mind the concept of appreciative inquiry (AI+), a strengths-based approach that can significantly enhance social inclusion[9]. By focusing on what works well within organizations and communities, AI+ fosters a collaborative dialogue among stakeholders. This approach encourages a positive culture and collective vision for social good. Following a 5-D cycle (Definition, Discovery, Dream, Design and Destiny), it invites participants to envision possibilities and co-create actionable strategies. Ultimately, AI+ not only enhances engagement and innovation, but also promotes sustainable change by building on existing strengths. However, social inclusion, as both a recovery process and an outcome, is a non-linear journey where each individual has his/her own pace and readiness. Poorly implemented or forced social inclusion can be more harmful than social isolation.

In conclusion, while AI offers transformative opportunities to enhance social inclusion in mental health care, addressing ethical concerns and engaging individuals with lived experience in technology development is imperative. By prioritizing inclusivity and incorporating the voices of those with SMI, we can create AI systems that genuinely support social inclusion, fostering a culture of hope and belonging for individuals with SMI on a global scale.

Samson Tse
Department of Social Work and Social Administration, University of Hong Kong, Hong Kong, SAR, China

1. Henderson C, Kotera Y, Lloyd-Evans B et al. World Psychiatry 2026;25:56-82.
2. Voultsiou E, Moussiades L. Educ Inf Technol 2025;30:19141-81.
3. Muetunda F, Sabry S, Jamil ML et al. ACM Trans Comput Healthc 2025;5:1-24.
4. Torous J, Linardon J, Goldberg SB et al. World Psychiatry 2025;24:156-74.
5. Singh A, Mourya P, Singh V et al. Int Sci J Eng Manag 2025;4:1-7.
6. van Kolfschooten HB, van Oirschot J. When people become data points: the potential impact of AI in mental healthcare. Amsterdam: Health Action International, 2025.
7. Elyoseph Z, Levkovich I. JMIR Mental Health 2024;11:e53043.
8. Morgan P, Cogan NA. J Public Ment Health 2025;24:150-65.
9. Barrett FJ. Appreciative inquiry: a positive approach to building cooperative capacity. Chagrin Falls: Taos Institute Publishing, 2005.

DOI:10.1002/wps.70008

Advancing social inclusion for people with co-occurring mental health and substance use disorders

People with co-occurring mental health and substance use disorders tend to experience more social exclusion than those with a mental health or substance use disorder alone. The intersection of psychiatric distress and substance use often complicates clinical care and intensifies barriers to addressing social determinants of health such as housing and employment. Co-occurring mental health and substance use also strains relationships with family members and friends, and often reduces community engagement. These challenges are exacerbated by the stigma associated with this comorbidity[1], and can be further compounded by unemployment, homelessness or criminal justice involvement. Integrated, evidence-based treatment that addresses both mental illness and substance use[2], while promoting recovery and community connection, is essential for advancing the social inclusion of these individuals.

Over the past 30 years, the field has shifted from traditional approaches to treatment, which operated in silos by separating mental health and addiction services[3]. In the past, clients were entering treatment either through the mental health or substance use service system, depending on which problem area was more severe or based on availability of treatment slots. This siloed approach often unnecessarily fragmented care and contributed to treatment dropout, poor long-term engagement and, ultimately, increased social isolation. While people still occasionally talk about receiving silo-based care, the field has advanced, and integrated treatment models are now offered in many contexts worldwide. These integrated approaches reduce barriers to care access, improve continuity of care, and create space for whole health recovery that includes the pursuit of meaningful life roles and social inclusion.

In people with co-occurring mental health and substance use problems, stable housing is often a critical need that can reduce social isolation and support social and community engagement. Without stable housing, engagement in treatment, social services, and other aspects of community life remains limited. The Housing First model, which offers immediate access to housing without preconditions such as sobriety or treatment compliance, exemplifies a low-barrier approach that supports both stability and dignity[4].

In Housing First, wraparound supports are embedded, and people can benefit from psychiatric and substance use services, community outreach, and linkages to social service agencies. An overriding philosophy of this approach is that people are not punished for engaging in risky behaviors, as it is understood that these behaviors, such as substance use relapses, often occur during the recovery process. Individuals who receive Housing First have been found to maintain their housing and pursue other personal life goals, which in turn reduces social isolation.

Employment is another critical component of recovery for individuals with co-occurring mental health and substance use disorders. It does not only provide financial stability, but also offers a pathway to social identity, community belonging, and self-efficacy. Individual Placement and Support (IPS) has been found to increase competitive employment outcomes and reduce reliance on emergency services among those with co-occurring disorders[5]. Offering clients with this comorbidity a multidisciplinary team-based care in addition to employment support has been found to be critical[5].

When implementing IPS for clients with co-occurring disorders, several factors should be considered. These include such things as avoiding the prescription of addictive medications, or preparing clients to address any possible prior legal involvement during the application process. An IPS staff member might assess job suitability in relation to the person's time in recovery and level of comfort for such things as working in an environment that may expose to alcoholic beverages. Despite these challenges, ongoing employment can help individuals build social networks, develop a sense of purpose, and pursue regular peer interactions.

Peer support is gaining recognition globally, with growing evidence suggesting that it offers a particularly effective means of fostering social inclusion[6]. For individuals with mental health and substance use disorders, a peer support specialist is defined as someone who has lived experience of both challenges and is in stable recovery. Peer support specialists bring authenticity and hope to recovery-oriented systems and the clients they support. Moreover, they serve as role models and offer suggestions based on their lived mental health and substance use recovery journeys. They can also play a proactive role in connecting clients to recovery resources by bringing them to 12-step meetings or introducing them to recovery events in the community to promote substance-free social engagement. Peer roles themselves offer valued social identities and meaningful employment opportunities. Programs such as *Atmiyata* in India have shown that community-based peer interventions are both feasible and culturally relevant also in low-resource settings[7].

Finally, the field has continued to evolve to better serve the disparate needs of individuals with co-occurring mental health and substance use problems via multi-component interventions with a goal of promoting recovery, social inclusion and community integration. These multi-component interventions often integrate many of the aforementioned approaches into one service delivery model. One such evidence-based intervention, developed specifically for people with co-occurring mental health and substance use disorders, is Maintaining Independence and Sobriety Through Systems Integration, Outreach, and Networking (MISSION)[9]. This intervention has been adapted for people who are also homeless, in the criminal justice system, or veterans, as these individuals tend to have high rates of social isolation.

Delivered by a case manager and peer specialist team, MISSION embodies the promise of comprehensive, integrated, team-based whole health care that incorporates mental health and addiction treatment, assertive community outreach, and housing and employment support to address situational barriers to care and promote community inclusion[9]. The flexibility of MISSION, along with ongoing recovery planning, enhances treatment engagement, improves mental health and substance use outcomes, and promotes social inclusion, especially among individuals disengaged from traditional services.

Ultimately, social inclusion is not a secondary outcome. It must be a central goal of any treatment for co-occurring mental health and substance use disorders. Evidence-based interventions must extend beyond clinical stabilization to support individuals in reclaiming roles, rights, and relationships with family and others in their communities. Systems of care that integrate services and foreground inclusion can help individuals move from surviving on the margins to thriving within communities. This is the standard of care that we must embrace if we are to fulfill the promise of dignity, equity, social inclusivity and recovery for this often marginalized population.

David Smelson
Department of Medicine, Division of Health Systems Sciences, University of Massachusetts Chan Medical School, Worcester, MA, USA

1. Corrigan PW, Schomerus G, Shuman V et al. Am J Addict 2017;26:67-74.
2. Drake RE, Bond GR. Psychiatr Clin N Am 2020;43:67-78.
3. Mueser KT, Noordsy DL, Drake RE et al. Integrated treatment for dual disorders: a guide to effective practice. New York: Guilford, 2003.
4. Tsemberis S, Gulcur L, Nakae M. Am J Public Health 2004;94:651-6.
5. Bond GR, Drake RE, Becker DR. World Psychiatry 2012;11:32-9.
6. Chinman M, George P, Dougherty RH et al. Psychiatr Serv 2014;65:429-41.
7. Shields-Zeeman L, Pathare S, Walters BH et al. Int J Ment Health Syst 2017;11:6.
8. Smelson D, Kalman D, Losonczy M et al. Community Ment Health J 2012;48: 127-32.
9. Sawh L, Smelson D. In: O'Donohue W, James L, Snipes C (eds). Practical strategies and tools to promote treatment engagement. Cham: Springer, 2017:133-50.

DOI:10.1002/wps.70010

Dismantling structural violence to enable structural transformation and consequently social inclusion

As Henderson et al[1] compellingly argue, traditional approaches to social inclusion in mental health overwhelmingly emphasize individual-level, clinically-focused interventions. These are often aimed at reducing societal burden and increasing economic productivity[2]. Here I propose a fundamentally different vision – one that aims to address the structural violence sustaining disability-linked poverty and exclusion, rather than continuing to rework the individualized solutions that have become the staple of contemporary mental health policy.

This alternative approach draws on the abolitionist-leaning principles of non-reformist reforms, that "aim to undermine the prevailing political, economic, [and] social order, construct an essentially different one, and build democratic power toward emancipatory horizons"[3]. Central to such reforms is a commitment to centering those directly impacted, and a deep skepticism toward solutions that ultimately reproduce exclusionary systems.

At this historical juncture – the mid 2020s – prevailing paradigms for addressing "severe mental illness" remain rooted in biomedical (or at best biopsychological) models of disability, and individual-level interventions that are in turn delivered within ever more marketized health care delivery systems. Meanwhile, in the US and elsewhere, the increasingly visible failures of deinstitutionalization have inspired new regimes of surveillance, coercion, and behavioral control. These include the expansion of compulsory treatment, the proliferation of residential facilities that, while smaller in size, otherwise replicate the logics of the asylums they replaced, and even the development of new technologies of surveillance such as ingestible event marker sensors intended to track drug ingestion and thereby facilitate "compliance".

In societies where social worth is primarily equated with economic productivity, disability is not only feared, but persistently devalued. In virtually all high-income countries, those who cannot work can access disability benefits – however, benefits policies are routinely structured to ensure a standard of living well below that of even lower-middle-class workers. Indeed, in the US, disability-based welfare policies essentially function as a mechanism of enforced impoverishment: save or earn just slightly above the disability benefit threshold and you risk losing not only monetary entitlements, but also access to life-sustaining health care and housing.

Capitalism does not merely devalue disability – it fundamentally shapes the mental health system. In the US, public sector providers, particularly in high-cost coastal cities, rarely earn a living wage. Peer support and community health workers – disproportionately people of color and, by definition, disabled or systems-involved – are generally paid even less. The system exploits the emotional labor of individuals occupying these roles while relegating "lived experience" to the bottom of the professional hierarchy, extracting relational investments without material reciprocity.

Extractivism and managerialism also find a friend in the evidence-based practice movement. A still ascendent "knowledge regime"[4], this movement has given rise to a suite of linear, manualized interventions – ranging from third-wave cognitive therapies to motivational strategies. Aligning with narrow clinical trial methodologies and the constraints they impose, evidence-based practices are most often time-limited, centering reproducible technologies of intervention while decentering intuition, the unique and unpredictable but essential dynamics of any relationship between two or more people, the adaptation of people and systems. Such interventions may produce modest short-term effects, but rarely move the needle on deeper social integration. And they contribute all too perfectly to the cost-cutting, access-limiting, standardizing goals of managed care.

The above examples all arguably function as forms or manifestations of structural violence[5] – violence enacted through unequal structures rather than overt physical assault or injury. Such violence is rendered invisible precisely because it is so deeply embedded in institutions and practices that has come to seem "normal" and inevitable. Whether we look to the mental health system's reliance on coercion, the entrenchedness of disability poverty, or workings of extractive capitalism, we see illustrated the normalization of structures of oppression. Within academia, deep epistemic inequalities also powerfully contribute through the exclusion of those directly impacted within the very processes through which knowledge about psychiatric conditions and structures is produced.

The fundamental problem with reformist approaches is that they center incremental "fixes" to what are more fundamentally unjust systems. Reformist logic in turn "insulates" policies such as psychiatric institutionalization, workfare and disability-related coercion from deeper scrutiny, casting them as "problems for regulation, rather than products of status quo power relations"[3]. The same logic pervades the evidence-based practice and implementation science movements, as noted above. And reformism tends to enable the same people, the same in-groups, to remain in power, promising this or that incremental change as a means of rationalizing disinvestment in deep change.

Non-reformist reform, by contrast, seeks to dismantle these foundations. It insists that systems producing mass disability-linked poverty, coercion, and epistemic exclusion are neither natural nor inevitable. It also insists that real transformation cannot come from above – from elite institutions or expert clinicians – but be led from below, from those whose lives are directly impacted by these systems. A non-reformist stance recognizes that it is not inevitable for people with psychiatric disabilities to die 15-20 years earlier than their peers in the world's wealthiest countries; that poverty and premature death should never be expected. That it is not *de rigueur* that cognitive decline from iatrogenic causes erodes decades of potential, or that shame accompanies madness and mental difference. These are not inevitable outcomes of "illness", but of the structural violence that surrounds the experiences we have decided to label as such.

As abolitionists say over and over again, a different world is possible – but only if we start from different premises. If schizophrenia is framed as a "curable" neurobiological illness, the resulting interventional logics will center pharmaceuticals and underlying pathology – in fact driving exclusion. If, instead, we recognize madness, distress and disability as phenomena irreducible to biology – as polyvalent, culturally generative and politically meaningful – entirely different possibilities of intervention and social belongingness (re)emerge. And if we begin to reframe the "problem" of psychiatric disability not as an issue of faulty biology, but of underlying structures of exclusion, the same is true: fundamentally different strategies, policies and practices start to make sense and take form.

Research can help with this transformation – illuminating current conditions, exposing logics of oppression through careful scholarly analysis – but the status quo will only truly change when structures change. For those currently in positions of power, their biggest contribution may be a combination of humility (about the limits of individual but also collective academic or empirical knowledge, acknowledging where, in the contemporary health sciences, the status quo has generally taken policy and practice concerning severe mental illness) and a willingness to join others, most especially those directly impacted, in non-reformist, democratic movements working to name sources of injustice and build a new world.

Nev Jones
School of Social Work, University of Pittsburgh, Pittsburgh, PA, USA

1. Henderson C, Kotera Y, Lloyd-Evans B et al. World Psychiatry 2026;25:56-82.
2. Fey J. Neoliberalism and mental health. London: Routledge, 2024.
3. Akbar AA. Yale Law Journal 2022;132:2497-609.
4. Tanenbaum SJ. Health Aff 2005;24:163-73.
5. Farmer PE, Nizeye B, Stulac S et al. PLoS Med 2006;10:e449-63.

DOI:10.1002/wps.70009

Social inclusion in mental health: a Latin American perspective

Despite substantial efforts, many widely adopted frameworks on social inclusion of people with severe mental illness continue to operate within a narrow scope, insufficiently questioning and engaging with the structural forces that shape exclusion[1]. Here I argue that the advancement of social inclusion requires examining history, cultural contexts and other macro-social forces, especially in the Global South, and that Latin American frameworks, notably the Social Determination of Health Framework[2], have been developed in response to these challenges.

Latin America has a rich yet under-recognized tradition of linking health with social context. For many decades, movements in social medicine, collective health, and critical epidemiology across the region have highlighted gaps in conventional health paradigms, and proposed approaches to address the social drivers of illness and inclusion[2]. These traditions emerged from a recognition that health inequities cannot be fully addressed without confronting root causes[2]. Pioneering researchers such as J. Breilh and N. de Almeida-Filho have argued that health and disease are not merely influenced by social factors, but are fundamentally produced by them[3]. Accordingly, this perspective calls for a research agenda inseparable from social action and transformation. While these traditions originated in Latin America, key concepts and practices have been adopted by some scholars in the Global North, particularly in social and psychiatric epidemiology[3].

The Social Determination of Health Framework offers several unique contributions to the field of social inclusion in mental health [4]. First, it foregrounds history, recognizing that phenomena such as stigma, social isolation and exclusion are inseparable from the broader trajectories of political violence, neoliberal reforms and cultural domination. This approach challenges the tendency to decontextualize exclusion, exploring how historical processes have constructed the conditions for marginalization. Second, it compels us to ask not just what factors or determinants are associated with exclusion or inclusion, but why such factors are so prevalent among certain vulnerable groups, including people with severe mental illness. It shifts the focus from identifying and describing inequities to investigating their origins. Third, it invites researchers and policy makers to move from description to transformation – aligning scientific inquiry with emancipatory, community-led action. This involves not only producing high-quality evidence, but also co-producing solutions with affected groups and recognizing the legitimacy of experiential and collective knowledge[4].

A potential critique is that these Latin American approaches lack sufficient empirical validation. However, this imbalance itself is part of the problem – a reflection of what has been called the "centrality" of knowledge production in the Global North[5]. Hierarchies of evidence have been constructed to privilege randomized controlled trials and other standard methodologies, sometimes discounting the value of real-world innovations emerging from the Global South. There is an implicit assumption that the most reliable evidence and theories flow from wealthy countries outward, whereas ideas emerging from the Global South are less valid or remain untested[5]. Just as important is the notion of "linearity" in how we think about evidence and implementation. Mainstream health research often envisions a linear pipeline: discovery leads to trials, which lead to scaled implementation and policy[5]. Especially in the Global South, progress in mental health services and systems has often been anything but linear. Historical disruptions – i.e., revolutions, dictatorships, economic crises, and civil conflicts – have required creative, context-driven solutions that did not wait for formal evidence[6].

Mental health reforms are compelling examples of complex sociopolitical phenomena that provide context-sensitive and historically informed frameworks for understanding trends in social inclusion and exclusion. For instance, Brazil's psychiatric reform was catalyzed in the late 20th century by a grassroots human rights movement in the wake of military rule. Brazilian reformers pushed to close asylums and build a network of community-based services[7]. The result was a nationwide shift toward community mental health care, with the establishment of hundreds of psychosocial care centers, and programs such as *De Volta Para Casa* ("Return Home") to reintegrate long-stay patients into society. This reform, enacted via national policy and based on principles of justice and citizenship, moved forward through social mobilization, preceding formal validation by research. Over time, positive outcomes have been documented: improved access to care, reduced psychiatric hospitalizations, and an affirmation of consumers' citizenship and rights in the community[7].

Similarly, Chile's mental health reform was initiated in the 1950s, with very promising developments in community-based mental health services. This movement was then brutally dismantled under dictatorship after 1973 – community mental health was banned as "communist" and many progressive clinicians were persecuted[8]. Yet, these ideas survived underground. With the return to democracy in 1990, Chile began rebuilding mental health services oriented toward primary care and community support. By the 2010s, Chile had a national mental health plan emphasizing outpatient care, psychosocial rehabilitation, and increased inclusion of family and consumers in service design. The historical experience of repression and political transition directly informed Chile's emphasis on rights, community solidarity, and participatory governance in mental health care[8].

The Latin American experiences thus suggest the need for a broader, more pluralistic view of what constitutes evidence and progress in the field. Adopting a social determination lens would push the social inclusion field to revisit some of its core assumptions. It would encourage new research questions, such as: How do colonial histories and ongoing extractive relationships continue to shape mental health outcomes? In what ways do policies designed to promote inclusion inadvertently reinforce structural exclusion? How can we build alliances with social movements and marginalized communities to co-produce more just and effective mental health services and systems? Such an approach would expand the boundaries of the field, foregrounding structural, historical and cultural forces that have too often been neglected.

While social medicine, collective health and critical epidemiology have emerged from the specific contexts of Latin America, their insights are highly relevant beyond this region. Structural racism, economic inequality, and histories of dispossession are not confined to the Global South. By incorporating the Social Determination of Health Framework, the social inclusion field can develop more nuanced, historically informed, and politically engaged responses to exclusion also in Europe, North America, and elsewhere in the Global North. Learning from the Global South is not only a matter of justice or representation; it is also about expanding the analytical and practical toolkit available to those seeking to advance inclusion everywhere. This perspective invites the field to broaden its conceptual and practical horizons and to approach social inclusion and mental health with greater humility and openness[9].

In summary, promoting social inclusion in mental health requires more than technical refinement or evaluation of existing interventions or frameworks. It calls for a paradigm shift: a willingness to ground research, policy and practice in the analysis of power, history and collective action, as exemplified by Latin America's rich academic and community-rooted traditions. Embracing these traditions offers a path forward – one that is more just, more democratic, and ultimately more capable of realizing the full promise of social inclusion for people with severe mental illness. To meet the needs of diverse communities and overcome persistent exclusion, the field must move beyond valuable but narrow approaches and engage with the complexity, creativity, and transformative spirit of social determination in mental health.

Franco Mascayano
Department of Mental Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA; Global Mental Health Program, Institute of Public Health, Universidad Andres Bello, Santiago, Chile

1. Henderson C, Kotera Y, Lloyd-Evans B et al. World Psychiatry 2026;25:56-82.
2. Breilh J. Critical epidemiology and the people's health. Oxford: Oxford University Press, 2021.
3. de Almeida-Filho N. In: Lovell AM, Oppenheimer G (eds). Reimagining psychiatric epidemiology in a global frame: toward a social and conceptual history. New York: University of Rochester Press, 2022:104-38.
4. Montenegro C, Szabzon F. In: Bryant T (ed). Handbook on the social determinants of health. Northampton: Elgar, 2025:248-59.
5. de Almeida-Filho N. Salud Colect 2020;16:e2786.
6. Mascayano F, Cuadra-Malinarich G, de Almeida-Filho N et al. Int J Epidemiol 2024;53:dyae026.
7. de Jesus Mari J, Kieling C, Ferri CP et al. Braz J Psychiatry 2024;46:e20243706.
8. Alvarado R, Valdivia L. In: Markova IS, Chen E (eds). Rethinking psychopathology. Creative convergences. Cham: Springer, 2020:153-62.
9. Abimbola S. The foreign gaze: essays on global health. Marseille: IRD Éditions, 2025.

DOI:10.1002/wps.70011

Do early intervention services for psychosis maintain their effects after transition to usual/modular care? A systematic review and meta-analysis

Gonzalo Salazar de Pablo[1-3], Joao Almeida[1], Jesus Camacho[1,4], José Suárez Campayo[3], Ana Catalan[5-7], Mihai Pop[8], Claudia Aymerich[1,5], Maria Rogdaki[1,7,9], Delbert G. Robinson[10-12], Nina Schooler[13], Philip McGuire[14], Wing-Chung Chang[15,16], Eric Yu-Hai Chen[15,17,18], Merete Nordentoft[19,20], Carsten Hjorthøj[19-21], Nikolai Albert[19,20,22], Marie Starzer[19,20], Vinod Srihari[23], Marcelo Valencia[24], Celso Arango[3], John Kane[10-12], Paolo Fusar-Poli[7,25-27], Christoph U. Correll[10-12,28-31]

[1]Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; [2]Child and Adolescent Mental Health Services, South London and Maudsley NHS Foundation Trust, London, UK; [3]Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario "G. Marañón" School of Medicine, Universidad Complutense, Madrid, Spain; [4]Hospital Clinico San Carlos, Universidad Complutense, Madrid, Spain; [5]Biobizkaia Health Research Institute, Basque Country University, Barakaldo, Bizkaia, Spain; [6]Basurto University Hospital, OSI Bilbao-Basurto, Instituto de Salud Carlos III, Barakaldo, Bizkaia, Spain; [7]Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; [8]East London NHS Foundation Trust, London, UK; [9]Francis Crick Institute, London, UK; [10]Center for Psychiatric Neuroscience, Feinstein Institutes for Medical Research, Manhasset, NY, USA; [11]Division of Psychiatry Research, Zucker Hillside Hospital, Northwell Health, Glen Oaks, NY, USA; [12]Department of Psychiatry, Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA; [13]Department of Psychiatry, SUNY Downstate Medical School, Brooklyn, NY, USA; [14]Department of Psychiatry, University of Oxford, Oxford, UK; [15]Department of Psychiatry, School of Clinical Medicine, LKS Faculty of Medicine, University of Hong Kong, Hong Kong RSA, China; [16]State Key Laboratory of Brain and Cognitive Sciences, University of Hong Kong, Hong Kong RSA, China; [17]Institute of Mental Health, Singapore; [18]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore; [19]Copenhagen Research Centre for Mental Health, Mental Health Services in the Capital Region, Copenhagen, Denmark; [20]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; [21]Department of Public Health, Section of Epidemiology, University of Copenhagen, Copenhagen, Denmark; [22]Mental Health Centre Copenhagen, Copenhagen University Hospital, Copenhagen, Denmark; [23]Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA; [24]Division of Epidemiological and Psychosocial Research, National Institute of Psychiatry, Mexico City, Mexico; [25]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy; [26]Outreach and Support in South-London Service, South London and Maudlsey NHS Foundation Trust, London, UK; [27]Department of Psychiatry and Psychotherapy, Ludwig-Maximilian-University of Munich, Munich, Germany; [28]Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin, Berlin, Germany; [29]German Center for Mental Health (DZPG), partner site Berlin, Berlin, Germany; [30]German Center for Child and Adolescent Health (DZKJ), partner site Berlin, Berlin, Germany; [31]Einstein Center for Population Diversity, Berlin, Germany

Early intervention services (EIS) for psychosis have demonstrated superiority to usual care/modular care (UC/MC) until the end of their delivery. However, the maintenance effects of EIS care after transition to UC/MC are less clear. We aimed to compare these effects vs. UC/MC at least one year after the end of EIS care. This PRISMA and MOOSE-compliant systematic review searched PubMed, EMBASE, PsycINFO and Web of Science databases and Cochrane Central Register of Reviews, without time or language restrictions. We included studies initially designed as randomized controlled trials (RCTs) comparing EIS vs. UC/MC in patients with early-phase psychosis, in which both the intervention and control groups were followed for at least 12 months after cessation of EIS care in the intervention group. Co-primary outcomes were psychiatric hospitalization, duration of hospitalization, and drop-out at the end of follow-up (preferably 5 years post-EIS initiation). Secondary outcomes were severity of total, positive and negative symptoms; quality of life, work involvement, remission, legal offences, antipsychotic use, and suicide attempts. We meta-analyzed six RCTs with data from 13 papers, including 1,416 individuals (mean age: 23.9 years, females: 36.7%). After 2-3 years of receiving UC/MC, subsequent to 2-3 years of EIS care or UC/MC, individuals who originally received EIS care spent less days hospitalized than those continuing UC/MC (n=5, standardized mean difference, SMD=0.128, 95% CI: 0.019-0.237, p=0.021). However, although we confirmed the superiority of EIS care to UC/MC at the end of the intervention period (except for work involvement and legal offences), the two groups did not differ significantly at 2-3 years post-EIS care regarding hospitalization, all-cause drop-out, quality of life; severity of total, positive and negative symptoms; work involvement, remission, legal offences, antipsychotic use, and suicide attempts. In summary, EIS care did not maintain its superiority over UC/MC 2-3 years after its cessation across meta-analyzable outcomes, except for duration of hospitalizations. These results support the need to further develop and potentially extend full or individualized EIS delivery.

Key words: Early intervention services, early-phase psychosis, transition to usual care, hospitalization, quality of life, positive symptoms, negative symptoms, work involvement, suicide attempts

(World Psychiatry 2026;25:95–104)

Schizophrenia is one of the most severe and functionally limiting medical disorders, leading to substantial individual, societal and health care burdens[1,2]. Outcomes in this disorder, including remission and recovery rates, often remain suboptimal[3]. All-cause mortality is increased in people with schizophrenia compared to the general population, with the greatest risk in first-episode (relative risk, RR=7.4) and incident (i.e., earlier-phase) schizophrenia (RR=3.5)[4]. Furthermore, the mean duration of untreated psychosis (DUP) has been estimated as 42.4 weeks worldwide[5], and longer DUP after illness onset has been related to poorer illness outcomes[6-8].

Early intervention strategies/services (EIS) aim to timely detect psychosis symptoms, reduce DUP, and improve early access to effective treatment during what has been called the "critical period" for intervention effectiveness, which is believed to be the first 2-5 years following psychosis onset[9-12].

In a meta-analysis of randomized trials lasting an average of 16.2±7.4 months and including 2,176 patients with first-episode or early-phase schizophrenia (mean illness duration: 159.8±125.4 weeks, mean DUP: 79.9±71.1 weeks), EIS care has been associated, at the end of its delivery, with significantly better outcomes than usual care/modular care (UC/MC)[10]. The improved outcomes included lower treatment discontinuation, less psychiatric hospitalizations, less relapses; more remission, recovery and involvement with school or work; lower severity of total, positive, negative and depressive symptoms as well as general psychopathology; and greater global functioning and quality of life, each evaluated after 6-24 months of active EIS treatment[10].

A limitation of the above meta-analysis was that insufficient studies and outcome data were available to assess the longer-term effects of EIS care vs. UC/MC after the former care ended and patients were followed in usual care environments. However, a robust understanding of whether and which benefits of EIS care are sustained beyond the initial active treatment window is essential to inform clinical decision-making, resource allocation, and long-term service planning. Such information is further relevant to support or challenge the hypothesis of a "critical period" of 2-5 years during which the short-term effects of EIS care would translate into lasting long-term effects on the above-mentioned outcomes.

Clarifying the durability of EIS benefits has far-reaching implications, not only for individual patient trajectories, but also for the sustainability and cost-effectiveness of mental health systems. This information is, therefore, highly relevant for program developers and policy makers, as current strategies may need to be improved or optimized. This could include the potential need for paradigms of selective extension of EIS care for subgroups of patients or for selected outcomes that may be less durable than others.

Based on the above, we aimed to compare meta-analytically – across key clinical, functional, and service use outcomes – the impact of EIS care vs. UC/MC both acutely, at the end of the intervention period, and long-term, i.e. at least one year after its cessation. We hypothesized that EIS care would be superior to UC/MC after transition to the latter for some but not all outcomes.

METHODS

This study was conducted in accordance with the PRISMA 2020 item checklist[13] and MOOSE checklist[14] (see supplementary information). The study protocol was registered on PROSPERO (CRD42023488103).

Literature search

PubMed, EMBASE, PsycINFO and Web of Science databases and Cochrane Central Register of Reviews were searched by two independent researchers. The following search terms were applied from inception until February 18, 2025: (schizophrenia OR schizoaffective OR schizophreniform OR psychosis OR psychotic) AND (recent-onset OR "recent onset" OR "first episode" OR first-episode OR early-phase OR "early psychosis") AND (intervention OR treatment OR management OR integrat* OR multimodal OR assertive OR specialized OR "COAST" OR "JCEP" OR "LEO" OR "OPUS" OR "OTP" OR "PIANO" OR "STEP" OR "RAISE" OR "RAISE-ETP" OR "Valencia") AND ("follow up" OR "follow-up" OR "longitudinal" OR "long term" OR "long-term" OR "maintenance" OR "prospective").

Papers identified were screened as abstracts and, after the exclusion of those not meeting our inclusion criteria, full texts were assessed for eligibility. Searches were completed with manual backward and forward reference searching (looking at previously published papers and those citing the included studies). Any discrepancies were resolved through discussion with the first author.

Any missing data that helped assess eligibility were obtained by contacting the corresponding and/or first and last authors of the studies. Furthermore, at least one author from the included trials was contacted to gather additional information on evaluated outcomes in their studies. Authors from all included studies except one responded to our request and are included as co-authors in this paper.

Inclusion/exclusion criteria

We included: a) randomized controlled trials (RCTs) comparing EIS/coordinated specialized care using an integrated/multimodal program, irrespective of previous service provision, with non-specialized UC/MC; b) for adolescents aged ≥12 years and/or adults; c) diagnosed with first-episode or early-phase (study-defined) psychosis or schizophrenia-spectrum disorders (schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, psychotic disorder not otherwise specified, or affective psychosis); d) in which both the intervention and the control groups were followed for at least 12 months after cessation of EIS care in the intervention group.

We excluded: a) trials initially randomizing patients to EIS care versus a step-down/less intense maintenance treatment, and b) cross-over trials in which EIS care was not stopped, or its intensity was not reduced. For overlapping studies and samples, the largest sample for each outcome was included (allowing ≤50% overlap), but included studies were independent regarding the outcomes.

Outcomes

We used the following co-primary outcomes at follow-up after transition to UC/MC: a) psychiatric hospitalization, measured by proportion of people hospitalized, and duration (days) of hospitalization; b) drop-out, defined by being lost to follow-up (previously referred to as all-cause treatment discontinuation).

Secondary outcomes included: a) quality of life (study-defined); b) severity of total, positive and negative symptoms (study-defined); c) work involvement (% of patients with study-defined work); d) remission (% of patients who met the study-defined definition); e) relapse (% of patients who met the study-defined definition); f) legal offences (% of patients with at least one study-defined offence event); g) antipsychotic use; and h) suicide attempts.

We selected the closest time-point to five years after treatment was started (e.g., after two years of EIS care or UC/MC and three years of follow-up, or after three years of EIS care or UC/MC and two years of follow-up).

The same primary and secondary outcomes were assessed at the end of the initial period of EIS care compared with UC/MC.

Data extraction

Three researchers independently extracted data from the included studies into a database (a Microsoft Excel spreadsheet). The following variables were extracted: first author, publication year, country, program, patient age (mean±SD, range), sex (% females), sample size (baseline, follow-up; total, EIS, UC/MC), race/ethnicity, trial duration (active EIS and post-EIS follow-up, in years), psychiatric diagnoses, outcome results, variables evaluated in sub-analyses and meta-regression analyses, and quality assessment.

Data synthesis

For the meta-analyses of continuous outcomes, we calculated standardized mean differences (SMDs) with their 95% confidence intervals (CIs). For categorical outcomes, we calculated risk ratios (RRs) with their 95% CIs. Intent-to-treat (ITT) data were used whenever possible.

Expecting high heterogeneity, random-effects meta-analyses were conducted whenever at least three studies provided meta-analyzable results[15]. Publication bias was assessed by Egger's test[16], complemented by the "trim and fill" method to correct for the presence of missing studies when risk of publication bias (i.e., small sample bias) was detected. Any correction was based on the assumption that the effect sizes of all the studies were normally distributed around the centre of a funnel plot; in the event of asymmetries, the "trim and fill" method adjusted for the potential effect of unpublished studies.

Heterogeneity among study point estimates was assessed using Q statistics. The proportion of the total variability in the effect size estimates was evaluated by the I^2 index[17] and considered statistically significant when $p<0.05$. $I^2>50\%$ is typically considered an indication of high variability in effect size estimates.

We conducted sub-analyses for the three co-primary outcomes to estimate the association between the outcomes and a) region (Europe vs. the US vs. rest of the world), b) blinding of outcome assessments, c) analyzed data type (ITT vs. observed cases), d) EIS care including vocational/educational rehabilitation, e) EIS care including family therapy, f) EIS care including crisis response teams, g) EIS care including social skills training, h) EIS care including fidelity monitoring, and i) quality assessment results (studies with low risk of bias vs. studies with some concerns).

We conducted meta-regression analyses for the three co-primary outcomes whenever at least four studies provided relevant data, estimating the association between the outcomes and a) sample size, b) number of sites, c) trial duration (total from baseline, EIS treatment, and post-EIS follow-up), d) number of EIS components, e) number of visits, f) proportion of patients with DSM/ICD-defined schizophrenia, g) baseline functioning (measured by the Global Assessment of Functioning, GAF[18]), h) severity of positive symptoms at baseline (subscores from the Positive and Negative Syndrome Scale, PANSS[19]), i) severity of negative symptoms at baseline (subscores from the PANSS), j) presence of at least one prior hospitalization, k) mean patient age, l) % of females, m) % of White people, n) median DUP duration, o) % of patients not followed from on-EIS treatment into the off-EIS treatment study (magnitude of attrition or potential non-random attrition), and p) % of patients with all-cause discontinuation in the post-EIS study.

An additional sensitivity analysis was conducted excluding the Early Assessment Service for Young People with Psychosis (EASY) trial[20,21], as participants were recruited from a low-resource setting and exposed to EIS care before the RCT. We also compared the raw values of continuous and categorical outcomes in the EIS and UC/MC groups (in the on-EIS and off-EIS phases). For continuous outcomes, we considered the most frequently used instrument to evaluate each outcome and required at least two studies to meta-analyze the results.

All analyses were two-sided, with alpha=0.05, using Comprehensive Meta-analysis (CMA) V3[22].

Risk of bias assessment

Cochrane Risk of Bias tool (RoB2)[23] was used to assess whether each study had a high, low or unclear risk of bias in each of the following six domains: random sequence generation, allocation concealment, blinding of participants and study personnel, blinding of outcome assessments, incomplete outcome data, and selective outcome reporting.

The overall risk of bias was classified as low if none of the domains was rated as high risk and at least three domains were rated as unclear risk; as unclear if no or one domain was rated as high risk, but at least four were rated as unclear risk; and as high if more domains were rated as high or unclear risk.

RESULTS

The literature search yielded 3,802 non-duplicate citations, which were screened for eligibility. Ultimately, 13 papers from six studies were included: the OPUS trial[24-30]; Lambeth Early Onset (LEO)[31]; Optimal Treatment Project (OTP)[32]; Recovery After an Initial Schizophrenia Episode - Early Treatment Program (RAISE-ETP)/NAVIGATE[33]; Specialized Treatment Early in Psychosis (STEP)[34]; and EASY[20,21] (see Figure 1 for PRISMA flow chart and Table 1 for characteristics of the included studies).

Altogether, 1,416 individuals were included: 741 in the original EIS intervention group and 675 in the control group. The sample size of each study (including both intervention and control groups) ranged from 50 to 547 individuals. The mean age of the total sample was 23.9 years (range: 20.8-26.6), and 36.7% (range: 18.8-60.0%) were female. The duration of the studies ranged from 5 to 20 years, with all of them providing data after 5 years from the start of the

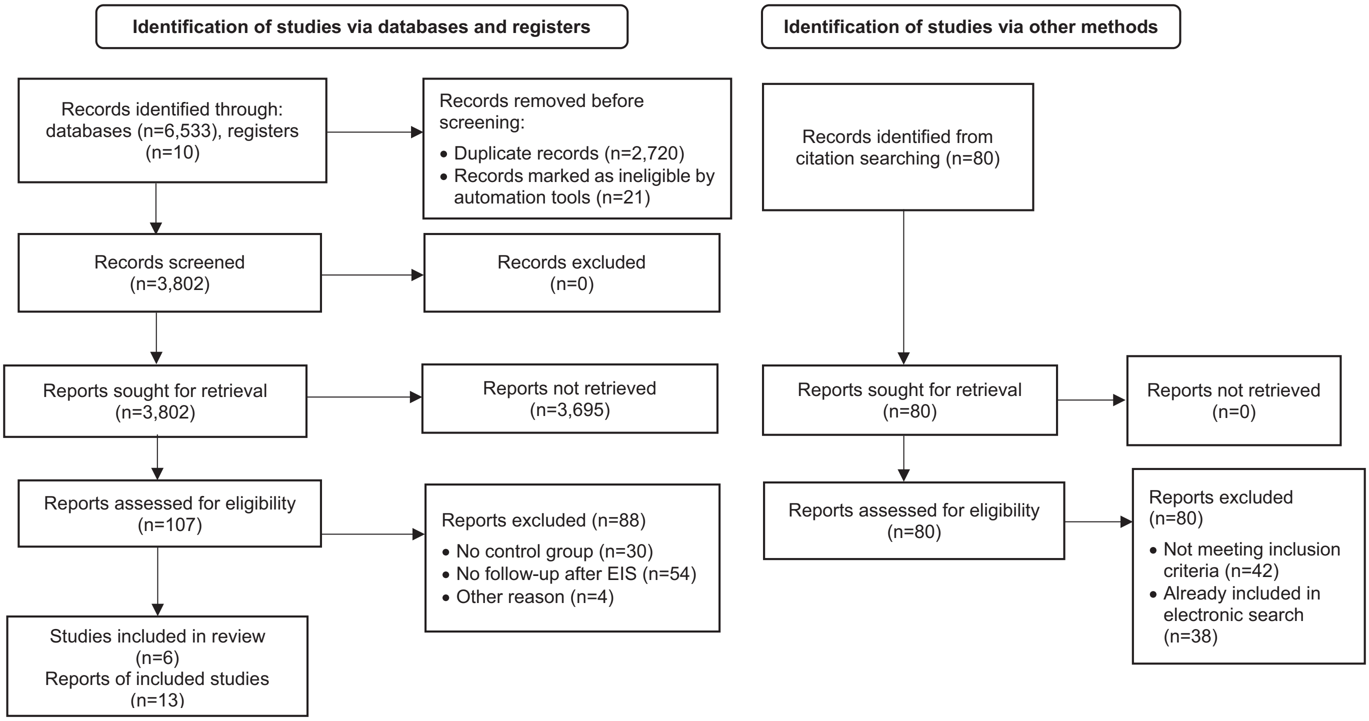


Figure 1 PRISMA flow chart. EIS – early intervention services

RCT, except for one trial[32] that provided data after 10 years (total mean study duration: 5.8 years). All studies had two years of EIS care vs. UC/MC and three years of follow-up, except for one with three years of EIS care vs. UC/MC and two years of follow-up[20,21] (mean EIS intervention: 2.17 years; mean post-EIS intervention: 4.0 years).

Table 1 Main characteristics of included studies

Study	Program (country)	Age, mean±SD (range)	% females	Sample size, baseline (EIS; UC/MC)	Sample size, follow-up (post-EIS; UC/MC)	Duration in years, total (EIS or UC/MC; all UC/MC)	Diagnosis (% schizophrenia)	Risk of bias
Bertelsen et al[30]	OPUS (Denmark)	26.6±6.4 (18-45)	41	547 (275; 272)	301 (151; 150)	5 (2; 3)	67	Low
Chang et al[20]	EASY (Hong Kong)	20.8±3.3 (15-25)	60	154 (82; 72)	143 (76; 67)	5 (3; 2)	84.2	Some concerns
Chang et al[21]	EASY (Hong Kong)	20.8±3.3 (15-25)	60	154 (82; 72)	143 (76; 67)	5 (3; 2)	84.2	Some concerns
Gafoor et al[31]	LEO (UK)	Median: 25	35.4	144 (71; 73)	99 (45; 54)	5.5 (2; 3.5)	72	Some concerns
Hansen et al[29]	OPUS (Denmark)	26.6±6.4 (18-45)	41	547 (275; 272)	164 (84; 80)	20 (2; 18)	67	Some concerns
Hastrup et al[24]	OPUS (Denmark)	26.6±6.4 (18-45)	41	547 (275; 272)	301 (151; 150)	5 (2; 3)	67	Low
Nordentoft et al[27]	OPUS (Denmark)	24.0±4.4 (18-35)	34	63 (34; 29)	63 (34; 29)	5 (2; 3)	89.9	Some concerns
Pollard et al[34]	STEP (US)	22.7±5.1 (16-45)	18.8	117 (60; 57)	99 (54; 45)	7 (2;5)	29	Some concerns
Posselt et al[25]	OPUS (Denmark)	27.1±6.3 (18-45)	41	547 (275; 272)	301 (151; 150)	5 (2; 3)	67.2	Low
Robinson et al[33]	RAISE-ETP (US)	23.0±5.1 (15-40)	27.5	404 (223; 181)	120 (63; 57)	5 (2; 3)	56	Some concerns
Secher et al[28]	OPUS (Denmark)	26.6±6.4 (18-45)	41	547 (275; 272)	347 (181; 166)	10 (2; 8)	67	Low
Sigrúnarson et al[32]	OTP (Norway)	25.4±4.6 (18-35)	38	50 (30; 20)	45 (28; 17)	12 (2; 10)	76	Some concerns
Stevens et al[26]	OPUS (Denmark)	26.6±6.4 (18-45)	41	547 (275; 272)	547 (275; 272)	5 (2; 3)	67	Low

EIS – early intervention services, UC – usual care, MC – modular care

Table 2 Short-term outcomes of early intervention services

			Point estimate					Test for heterogeneity		
Outcome	N (EIS)	N (UC/MC)	SMD/RR	95% CI		z score	p	Q	I^2	p
% hospitalization	599	546	0.908	0.828	0.997	–2.030	0.042	2.091	0.000	0.554
N. days hospitalized	376	365	0.153	0.007	0.299	2.056	0.040	1.917	0.000	0.383
Drop-out	659	603	0.644	0.552	0.751	–5.600	0.000	0.599	0.000	0.963
Positive symptoms	407	365	–0.197	–0.389	–0.006	2.015	0.044	0.000	0.900	0.983
Negative symptoms	407	365	–0.310	–0.517	–0.103	2.937	0.003	0.505	0.000	0.473
Work involvement	407	365	1.053	0.894	1.240	0.617	0.537	0.004	0.000	0.950
Legal offences	291	282	0.847	0.454	1.579	–0.524	0.600	1.149	0.000	0.563
Antipsychotic use	407	365	1.147	1.006	1.307	2.044	0.041	0.176	0.000	0.675
Suicide attempts	407	365	0.560	0.318	0.984	–2.017	0.044	2.392	58.201	0.122

EIS – early intervention services, UC – usual care, MC – modular care, SMD – standardized mean difference, RR – risk ratio

Meta-analytic results

Outcomes at the end of EIS care

Compared to UC/MC, at the end of the EIS period, EIS care was associated with a lower proportion of patients psychiatrically hospitalized (RR=0.908, 95% CI: 0.828-0.997), fewer days hospitalized (SMD=0.153, 95% CI: 0.007-0.299), and decreased drop-out (RR=0.644, 95% CI: 0.552-0.751) (see Table 2 and Figure 2). EIS care was also associated with significantly lower severity of positive symptoms (SMD=–0.197, 95% CI: –0.389 to –0.006) and negative symptoms (SMD=–0.310, 95% CI: –0.517 to –0.103) (see Table 2 and Figure 3).

Use of antipsychotics was more common in individuals on EIS care at the end of the EIS period (RR=1.147, 95% CI: 1.006-1.307). The number of suicide attempts was lower in the EIS vs. UC/MC group (RR=0.560, 95% CI: 0.318-0.984). However, EIS and UC/MC groups did not differ in work involvement (p=0.537) or legal offences (p=0.600) (see Table 2 and supplementary information).

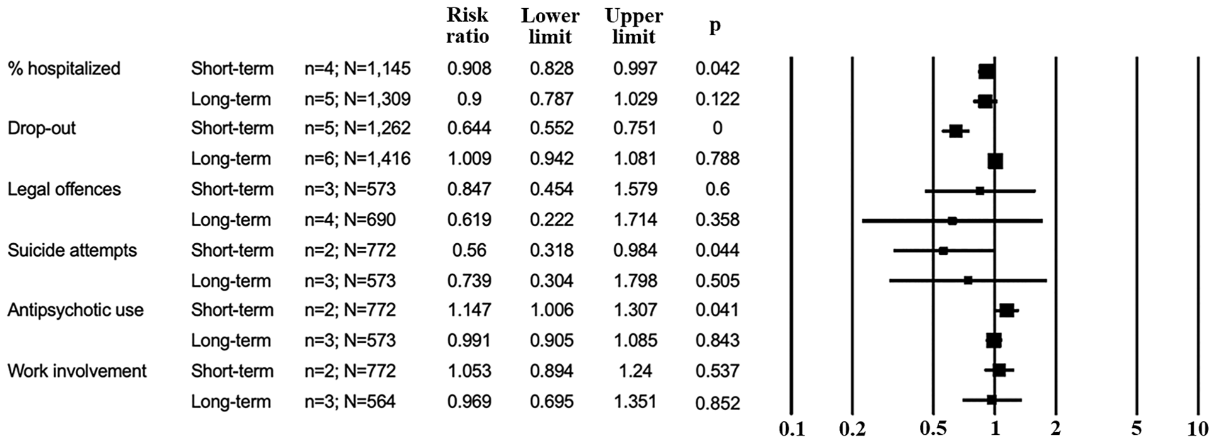
Heterogeneity across studies was not statistically significant (all p>0.05).

Outcomes ≥1 year after cessation of EIS care

Individuals who had originally received EIS care spent less days psychiatrically hospitalized after 5 years (including 2-3 years of UC/MC in both groups) than those receiving UC/MC from the beginning (n=5; EIS: N=691, UC/MC: N=618; SMD=0.128, 95% CI: 0.019-0.237, p=0.021) (see Table 3).

EIS and UC/MC groups did not differ in the proportion of patients hospitalized (n=5; EIS: N=691, UC/MC: N=618; RR=0.90, 95% CI: 0.787-1.029, p=0.122) or drop-out (n=6; EIS: N=741, UC/MC: N=675; RR=1.009, 95% CI: 0.942-1.081, p=0.788) after EIS care cessation (see Table 3 and Figure 2).

EIS and UC/MC groups did also not differ in severity of total,



			Risk ratio	Lower limit	Upper limit	p
% hospitalized	Short-term	n=4; N=1,145	0.908	0.828	0.997	0.042
	Long-term	n=5; N=1,309	0.9	0.787	1.029	0.122
Drop-out	Short-term	n=5; N=1,262	0.644	0.552	0.751	0
	Long-term	n=6; N=1,416	1.009	0.942	1.081	0.788
Legal offences	Short-term	n=3; N=573	0.847	0.454	1.579	0.6
	Long-term	n=4; N=690	0.619	0.222	1.714	0.358
Suicide attempts	Short-term	n=2; N=772	0.56	0.318	0.984	0.044
	Long-term	n=3; N=573	0.739	0.304	1.798	0.505
Antipsychotic use	Short-term	n=2; N=772	1.147	1.006	1.307	0.041
	Long-term	n=3; N=573	0.991	0.905	1.085	0.843
Work involvement	Short-term	n=2; N=772	1.053	0.894	1.24	0.537
	Long-term	n=3; N=564	0.969	0.695	1.351	0.852

Figure 2 Short-term and long-term categorical outcomes of early intervention services (EIS). For % hospitalized, drop-out, legal offences and suicide attempts, risk ratio (RR) <1 indicates benefits of EIS vs. usual care/modular care (UC/MC); for antipsychotic use and work involvement, RR>1 indicates benefits of EIS vs. UC/MC.

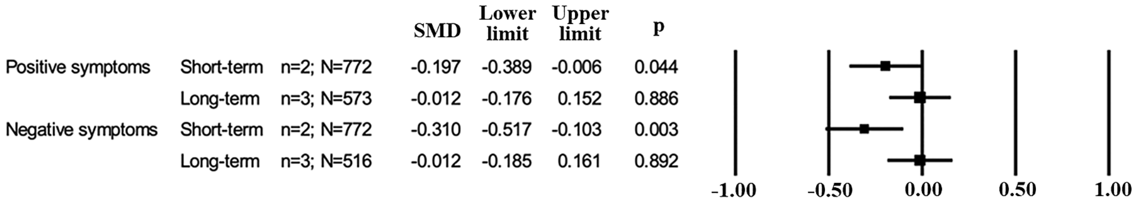


Figure 3 Short-term and long-term continuous outcomes of early intervention services (EIS). Negative values of standardized mean difference (SMD) indicate benefits of EIS vs. usual care/modular care (UC/MC).

positive and negative symptoms; quality of life, work involvement, remission, legal offences, antipsychotic use, or suicide attempts (all p>0.05) (see Table 3 and Figures 2-3).

Heterogeneity across studies was statistically significant for quality of life (Q=7.435, I^2=73.099, p=0.024), indicating high variability in the effect size estimates, but not for the other outcomes.

Sensitivity analyses and publication bias

The proportion of patients with psychiatric hospitalization, duration of hospitalization, and drop-out were not significantly influenced by region of study conduct, blinding of outcome assessment, analyzed data type; EIS care including vocational/educational rehabilitation, or family therapy, or crisis response teams, or social skills training, or fidelity monitoring; or by study quality (all p>0.05) (see also supplementary information).

The proportion of patients with psychiatric hospitalization, duration of hospitalization, and drop-out were not significantly influenced by sample size, number of sites, trial duration, number of treatment components, number of visits, proportion of patients with DSM/ICD-defined schizophrenia, baseline functioning, baseline severity of positive or negative symptoms, prior hospitalizations, mean patient age, sex, ethnicity/race, median DUP, % of patients not followed into the off-EIS treatment study, or % of patients with all-cause discontinuation in the post-EIS study (all p>0.05) (see also supplementary information).

Potential publication bias was found in three of the evaluated outcomes: positive symptoms (t=71.729, p=0.009), negative symptoms (t=19.945, p=0.032), and work involvement (t=48.441, p=0.013). However, adjusted results via trim-and-fill method did not affect the significance of the results (see supplementary information). Excluding the EASY trial did not change the significance of any of the results (see supplementary information).

Of the findings in the short term showing significant superiority of EIS care vs. UC/MC, only the significantly lower number of days hospitalized (47.2 ± 34.5 days vs. 58.4 ± 29.5 days, mean difference: 11.2 ± 3.0 days, p = 0.0002) remained significant after long-term follow-up off-EIS (68.6 ± 20.3 days vs. 75.5 ± 20.1 days, mean difference: 7.0 ± 3.4 days, p = 0.017). All other significant findings on EIS treatment vs. UC/MC lost significance during the follow-up off-EIS period.

This loss of significant group difference favoring EIS care included the previously lower proportion of patients hospital-

Table 3 Long-term outcomes of early intervention services

Outcome	N (post-EIS)	N (UC/MC)	Point estimate					Test for heterogeneity		
			SMD/RR	95% CI		z score	p	Q	I^2	p
% hospitalization	691	618	0.9	0.787	1.029	–1.548	0.122	1.83	0.000	0.767
N. days hospitalized	691	618	0.128	0.019	0.237	2.302	0.021	1.022	0.000	0.906
Drop-out	741	675	1.009	0.942	1.081	0.269	0.788	5.687	12.083	0.338
Quality of life	226	218	0.306	–0.059	0.670	1.645	0.100	7.435	73.099	0.024
Total symptoms	220	207	–0.168	–0.358	0.023	1.726	0.084	1.293	0.000	0.524
Positive symptoms	291	282	–0.012	–0.176	0.152	0.149	0.886	0.900	0.000	0.638
Negative symptoms	250	266	–0.012	–0.185	0.161	0.136	0.892	0.914	0.000	0.633
Work involvement	287	277	0.969	0.695	1.351	–0.186	0.852	0.101	0.000	0.951
Remission	298	292	1.071	0.901	1.274	0.780	0.436	0.086	0.000	0.958
Legal offences	351	339	0.619	0.222	1.714	–0.919	0.358	5.216	42.486	0.157
Antipsychotic use	291	282	0.991	0.905	1.085	–0.198	0.843	0.816	0.000	0.665
Suicide attempts	291	282	0.739	0.304	1.798	–0.666	0.505	5.022	60.175	0.081

post-EIS – individuals receiving UC/MC after an initial EIS care, UC/MC – individuals receiving usual or modular care from the beginning of the trial, SMD – standardized mean difference, RR – risk ratio ized (on-EIS: 50.4% vs. 58.1%, p=0.008; off-EIS: 31.9% vs. 34.5%, p=0.342), lower number of drop-outs (on-EIS: 26.6% vs. 35.1%, p=0.001; off-EIS: 58.3% vs. 59.0%, p=0.813), higher antipsychotic use (on-EIS: 68.5% vs. 59.5%, p=0.015; off-EIS: 61.4% vs. 66.9%, p=0.181), and lower proportion of patients with suicide attempts (on-EIS: 8.3% vs. 28.0%, p=0.002; off-EIS: 7.6% vs. 6.0%, p=0.6314) (see also supplementary information).

Finally, excluding trials that only contributed to long-term but not short-term data did not change the non-significant differences between the prior EIS and prior control groups in any of the outcomes (see supplementary information).

Quality assessment

Altogether, five studies (38.5%) were at low risk of bias and 8 studies (61.5%) were scored as having some concerns (see Table 1 and supplementary information).

DISCUSSION

To our knowledge, this is the first meta-analysis to compare the acute effects of EIS care to the maintenance effects of this care after transition from EIS to UC/MC in people with early-phase psychosis.

We confirmed the superiority of EIS care vs. UC/MC from the prior meta-analysis of the acute effects of EIS[10] in all but two outcomes, despite having only six programs with maintenance data, instead of 10 in that prior meta-analysis[10]. However, after cessation of EIS care, individuals who had received 2-3 years of EIS only spent less days hospitalized than individuals receiving UC/MC from the start, while none of the other meta-analyzed outcomes differed anymore at 2-3 years after EIS cessation. Specifically, after cessation of EIS care, its effects were not superior anymore to those of UC/MC regarding risk of psychiatric hospitalization, drop-out; total, positive or negative symptom severity; quality of life, work involvement, symptomatic remission, legal offences, antipsychotic use, or suicide attempts.

Importantly, there was a mixed picture of why the previously significant differences in favour of the patients randomized to EIS care were lost compared to the control group during off-EIS follow-up. There was some long-term improvement in both the prior EIS and control groups with regard to the proportion of patients hospitalized, with a somewhat greater reduction in the prior control group. Regarding being on antipsychotic treatment, the prior EIS group had an about 10% reduction and the prior control group had an about 10% increase, levelling off the difference in the post-EIS period. As to the proportion of patients with suicide attempts, the numbers remained roughly similarly low in the prior EIS group, but decreased by about 75% in the prior control group. Finally, drop-outs increased in both groups during follow-up, but much more in the prior-EIS group (by about half, compared to the about one-third increase in the control group).

Thus, while EIS care seems beneficial in the short term for reducing hospitalization and improving symptomatic and functional outcomes[10], advantages are lost during ongoing usual care. Although we focused on results after five years to favour consistency, the OPUS trial, using register-based data of the entire study population after 20 years of follow-up, similarly did not find differences between EIS care and UC/MC in symptomatic, functioning, use of services, or mortality outcomes[29].

How can this loss of sustained benefits across almost all meta-analyzable outcomes be explained? Several methodological, illness-related and treatment-related reasons may apply, informed also by the mixed trends in the frequency of good vs. bad outcomes. First, since less studies provided long-term follow-up data, the non-significant findings might simply be due to underpowered analyses. However, we analyzed data from the same studies at the end of EIS care, finding that, even in this smaller dataset of six studies, benefits were replicated in the on-EIS study phase versus the full data set of 10 studies[10].

Second, in observational follow-up studies, lower functioning patients are more likely retained in clinical services, causing a potential floor effect in the post-EIS phase. This possibility is hinted at by the greater drop-out rate in the post-EIS than in the UC/MC group, with a possibility of better responding and functioning patients being lost from the post-EIS group during follow-up. Indeed, in the RAISE-ETP study, only after statistical methods were used that accounted for data not missing at random did the prior EIS group show maintenance of significant benefits over the initial UC group at approximately 3-5 years post-EIS cessation[33].

Third, it may be that antipsychotic non-adherence, which is common in people with early-phase psychosis[35], leads to psychotic relapses, and that the effects of relapses uniformly attenuate treatment benefits[36,37], independent of earlier treatment gains due to EIS care[33]. Fourth, relatedly, it is generally acknowledged that currently available antipsychotics are symptom-based interventions that do not alter the underlying disease process or mechanisms, so that, over time and with treatment gaps and symptomatic worsening, initial benefits of EIS care are washed out.

Fifth, there may be illness phase-specific risks, such as suicide risk, that are highest in the early phases of psychosis[38,39], whereby the overall lower risk later on can level off detectable differences between EIS care and UC/MC. In fact, we observed this pattern regarding the proportion of people with suicide attempts, in that the protective effect of active EIS care was apparent in the short term, and remained at that relatively lower level in the post-intervention EIS group, while the risk in UC/MC decreased, arriving at a similarly lower level during follow-up.

Sixth, the care generally accessed and provided as part of UC/MC may be suboptimal, lacking in consistent antipsychotic coverage (e.g., use of long-acting injectables, LAIs[40,41]), or lacking consistent psychosocial interventions, and this suboptimal care over years could also wash out initial gains made by EIS care.

Taken together, based on the above, it seems that the "all or nothing" approach to EIS, related to the hope for a "critical period" during which EIS "seals the deal", is insufficient. Rather, individualized step-down or step-up treatment approaches may be needed. This strategy is supported by gains that were maintained when EIS care was extended at full or even partial intensity[42-44]. As part of these approaches, subgroups will need to be identified that require more or less interventions, also regarding specific components of the EIS approach.

Some previous studies randomized patients after two years of EIS care to either three more years of EIS or UC/MC, and found some benefits on work alliance and patient satisfaction (but not hospitalization or functional outcomes)[42], and symptom remission[43]. Conversely, in the only RCT comparing EIS care with step-down treatment (although similarly intense as UC/MC and focused on medical management), patients receiving an additional year of EIS care had better outcomes in negative symptoms, depressive symptoms, general psychopathology, global functioning, independent living skills, work productivity, relationships and compliance, than those managed by step-down psychiatric care[44-46]. Furthermore, in an uncontrolled trial, gains made after two years were sustained or increased with EIS care at a lower level after 3 years[47].

While some guidelines recommend continued treatment only for the first two years after a first episode of schizophrenia[48-50], results from our meta-analysis indicate that not only antipsychotic treatment, but also EIS care should be extended beyond two years to maintain their effects, although the intensity of specific psychosocial interventions could possibly be reduced or individualized.

Although we could not confirm sustained impact after cessation of EIS care, individuals who had received that care spent less days hospitalized than those receiving UC/MC throughout, although effect sizes were small. Our results are consistent with a naturalistic, 10-year follow-up using a matched historical control, in which EIS care significantly reduced the duration of psychiatric hospitalizations in the long term (odds ratio, OR=1.29)[51]. Notably, costs were lower with EIS than UC/MC[52], particularly due to reduced inpatient stays[53] and emergency department visits[54]. So, reducing hospitalization duration is important. According to this finding, EIS care may still be beneficial in the long term, and limited statistical power may have prevented us from observing a sustained effect in other outcomes, suggesting that longer-term post-EIS studies are required, and that evaluating long-term results from other RCTs conducted to date and with short-term results available (e.g., Valencia[55] or PIANO[56]) could be beneficial.

None of the numerous tested meta-regressor factors and subanalyses helped deconstruct heterogeneity. It is still possible for some interventions to improve particular outcomes or maintain effects in patient subgroups. However, study-level meta-analyses of bundled interventions are insufficient to answer these questions, calling for individual patient data meta-analyses. Precision psychiatry highlights individual variability, and the need to stratify interventions according to individual characteristics may improve targeted outcomes[57-59]. This may help detect subgroups of individuals requiring an adaptation in the duration of the interventions, specific intervention contents, or higher-intensity interventions[5]. Further research should focus on better understanding the sources of heterogeneity in the acute and long-term response to EIS care.

This study has some limitations. First, with six RCTs and 1,416 subjects, the number of studies and subjects was relatively small, affecting the statistical power of our analyses. Second, we did not have sufficient data to evaluate other outcomes, including depressive symptoms, living independently, recovery, relapse; concurrent obesity, diabetes mellitus, metabolic syndrome, or cardiovascular disease; clozapine use, or treatment resistance. Third, patient and treatment characteristics were heterogeneous; we tried to explore the relevance of this heterogeneity in meta-regression analyses, but without finding any relevant effects, yet statistical power was again a limiting factor.

Fourth, UC/MC in the included RCTs may have consisted of care that is better and more comprehensive than real-world UC/MC, as indicated by the number of treatment elements and intensity. On the other hand, UC/MC may also have been insufficient, causing a floor effect for all outcomes. Fifth, only one study from a low-mental health resource location was included[20], in which a recruitment bias toward those with lower functioning was found. Finally, capable and willing to consent individuals may not be representative of the real-life psychosis population.

In conclusion, benefits of EIS care do not seem to be sustained in the years following initial treatment, except for days hospitalized. These results support the need to further develop and potentially extend, or to differentiate and improve EIS care and its delivery. Since specific components of EIS care may have sustained effects beyond the intervention period, a more comprehensive model of EIS may be necessary to test the full extent of the "critical period" hypothesis.

Future trials evaluating integrated models are warranted to assess whether long-term outcome improvements can be achieved through sustained or stepped interventions, or coordinated interventions that dynamically respond to patient trajectories and needs.

ACKNOWLEDGEMENTS

A. Catalan is supported by the Instituto de Salud Carlos III, and Spanish Ministry of Economy and Competitiveness; C. Arango by the Spanish Ministry of Science and Innovation, the Instituto de Salud Carlos III, and the European Commission. Supplementary information on this study is available at https://osf.io/g98ep/.

REFERENCES

1. Vos T, Flaxman AD, Naghavi M et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2163-96.
2. Tandon R, Nasrallah HA, Keshavan MS. Schizophrenia, "just the facts" 4. Clinical features and conceptualization. Schizophr Res 2009;110:1-23.
3. Catalan A, Richter A, Salazar de Pablo G et al. Proportion and predictors of remission and recovery in first-episode psychosis: systematic review and meta-analysis. Eur Psychiatry 2021;64:e69.
4. Cassidy RM, Yang F, Kapczinski F et al. Risk factors for suicidality in patients with schizophrenia: a systematic review, meta-analysis, and meta-regression of 96 studies. Schizophr Bull 2018;44:787-97.
5. Salazar de Pablo G, Aymerich C, Guinart D et al. What is the duration of untreated psychosis worldwide? – A meta-analysis of pooled mean and median time and regional trends and other correlates across 369 studies. Psychol Med 2024;54:652-62.
6. Morgan C, Thara R, Gureje O et al. Duration of untreated psychosis: a global perspective. World Psychiatry 2025;24:49-50.
7. Catalan A, Salazar de Pablo G, Aymerich C et al. "Short" versus "long" duration of untreated psychosis in people with first-episode psychosis: a systematic re-

view and meta-analysis of baseline status and follow-up outcomes. Schizophr Bull Open 2024;5:sbae201.
8. Salazar de Pablo G, Guinart D, Armendariz A et al. Duration of untreated psychosis and outcomes in first-episode psychosis: systematic review and meta-analysis of early detection and intervention strategies. Schizophr Bull 2024;50:771-83.
9. Fusar-Poli P, McGorry PD, Kane JM. Improving outcomes of first-episode psychosis: an overview. World Psychiatry 2017;16:251-65.
10. Correll CU, Galling B, Pawar A et al. Comparison of early intervention services vs treatment as usual for early-phase psychosis a systematic review, meta-analysis, and meta-regression. JAMA Psychiatry 2018;75:555-65.
11. Birchwood M, Todd P, Jackson C. Early intervention in psychosis – The critical period hypothesis. Br J Psychiatry 1998;172:53-9.
12. Bird V, Premkumar P, Kendall T et al. Early intervention services, cognitive-behavioural therapy and family intervention in early psychosis: systematic review. Br J Psychiatry 2010;197:350-6.
13. Page MJ, McKenzie JE, Bossuyt PM et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. PLoS Med 2021;18:e1003583.
14. Stroup DF, Berlin JA, Morton SC et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008-12.
15. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.
16. Egger M, Davey Smith G, Schneider M et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.
17. Lipsey M, Wilson D. Practical meta-analysis. Thousand Oaks: Sage, 2000.
18. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 3rd ed., revised. Washington: American Psychiatric Association, 1987.
19. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261-76.
20. Chang WC, Kwong VWY, Lau ESK et al. Sustainability of treatment effect of a 3-year early intervention programme for first-episode psychosis. Br J Psychiatry 2017;211:37-44.
21. Chang WC, Kwong VWY, Or Chi Fai P et al. Motivational impairment predicts functional remission in first-episode psychosis: 3-year follow-up of the randomized controlled trial on extended early intervention. Aust N Z J Psychiatry 2018;52:1194-201.
22. Borenstein M, Hedges L, Higgins J et al. Comprehensive Meta-Analysis Version 3. Englewood: Biostat, 2013.
23. Higgins J, Altman DG, Gøtzsche PC et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
24. Hastrup LH, Kronborg C, Bertelsen M et al. Cost-effectiveness of early intervention in first-episode psychosis: economic evaluation of a randomised controlled trial (the OPUS study). Br J Psychiatry 2013;202:35-41.
25. Posselt CM, Albert N, Nordentoft M et al. The Danish OPUS early intervention services for first-episode psychosis: a phase 4 prospective cohort study with comparison of randomized trial and real-world data. Am J Psychiatry 2021;178:941-51.
26. Stevens H, Agerbo E, Dean K et al. Reduction of crime in first-onset psychosis: a secondary analysis of the OPUS randomized trial. J Clin Psychiatry 2013;74:e439-44.
27. Nordentoft M, Øhlenschlaeger J, Thorup A et al. Deinstitutionalization revisited: a 5-year follow-up of a randomized clinical trial of hospital-based rehabilitation versus specialized assertive intervention (OPUS) versus standard treatment for patients with first-episode schizophrenia spectrum disorders. Psychol Med 2010;40:1619-26.
28. Secher RG, Hjorthøj CR, Austin SF et al. Ten-year follow-up of the OPUS specialized early intervention trial for patients with a first episode of psychosis. Schizophr Bull 2015;41:617-26.
29. Hansen HG, Starzer M, Nilsson SF et al. Clinical recovery and long-term association of specialized early intervention services vs treatment as usual among individuals with first-episode schizophrenia spectrum disorder: 20-year follow-up of the OPUS trial. JAMA Psychiatry 2023;80:371-9.
30. Bertelsen M, Jeppesen P, Petersen L et al. Five-year follow-up of a randomized multicenter trial of intensive early intervention vs standard treatment for patients with a first episode of psychotic illness: the OPUS trial. Arch Gen Psychiatry 2008;65:762-71.
31. Gafoor R, Nitsch D, McCrone P et al. Effect of early intervention on 5-year outcome in non-affective psychosis. Br J Psychiatry 2010;196:372-6.
32. Sigrúnarson V, Gråwe RW, Morken G. Integrated treatment vs. treatment-as-usual for recent onset schizophrenia; 12 year follow-up on a randomized controlled trial. BMC Psychiatry 2013;13:200.
33. Robinson DG, Schooler NR, Marcy P et al. Outcomes during and after early intervention services for first-episode psychosis: results over 5 years from the RAISE-ETP site-randomized trial. Schizophr Bull 2022;48:1021-31.
34. Pollard JM, Ferrara M, Lin IH et al. Analysis of early intervention services on adult judicial outcomes. JAMA Psychiatry 2020;77:871-2.
35. Rubio JM, Taipale H, Tanskanen A et al. Long-term continuity of antipsychotic treatment for schizophrenia: a nationwide study. Schizophr Bull 2021;47:1611-20.
36. Taipale H, Tanskanen A, Correll CU et al. Real-world effectiveness of antipsychotic doses for relapse prevention in patients with first-episode schizophrenia in Finland: a nationwide, register-based cohort study. Lancet Psychiatry 2022;9:271-9.
37. Takeuchi H, Siu C, Remington G et al. Does relapse contribute to treatment resistance? Antipsychotic response in first- vs. second-episode schizophrenia. Neuropsychopharmacology 2019;44:1036-42.
38. Ricci V, Sarni A, De Berardis D et al. Symptomatic predictors of suicidal behavior in early psychosis: systematic review. J Psychiatr Pract 2025;31:125-38.
39. Correll CU, Solmi M, Croatto G et al. Mortality in people with schizophrenia: a systematic review and meta-analysis of relative risk and aggravating or attenuating factors. World Psychiatry 2022;21:248-71.
40. Vita G, Tavella A, Ostuzzi G et al. Efficacy and safety of long-acting injectable versus oral antipsychotics in the treatment of patients with early-phase schizophrenia-spectrum disorders: a systematic review and meta-analysis. Ther Adv Psychopharmacol 2024;14:20451253241257062.
41. Kishimoto T, Hagi K, Kurokawa S et al. Long-acting injectable versus oral antipsychotics for the maintenance treatment of schizophrenia: a systematic review and comparative meta-analysis of randomised, cohort, and pre-post studies. Lancet Psychiatry 2021;8:387-404.
42. Albert N, Melau M, Jensen H et al. Five years of specialised early intervention versus two years of specialised early intervention followed by three years of standard treatment for patients with a first episode psychosis: randomised, superiority, parallel group trial in Denmark (OPUS II). BMJ 2017;356:i6681.
43. Malla A, Joober R, Iyer S et al. Comparing three-year extension of early intervention service to regular care following two years of early intervention service in first-episode psychosis: a randomized single blind clinical trial. World Psychiatry 2017;16:278-86.
44. Chang WC, Kwong VW, Chan GH et al. Prediction of functional remission in first-episode psychosis: 12-month follow-up of the randomized-controlled trial on extended early intervention in Hong Kong. Schizophr Res 2016;173:79-83.
45. Chang WC, Chan GH, Jim OT et al. Optimal duration of an early intervention programme for first-episode psychosis: randomised controlled trial. Br J Psychiatry 2015;206:492-500.
46. Chang WC, Kwong VW, Chan GH et al. Prediction of motivational impairment: 12-month follow-up of the randomized-controlled trial on extended early intervention for first-episode psychosis. Eur Psychiatry 2017;41:37-41.
47. Norman RM, Manchanda R, Malla AK et al. Symptom and functional outcomes for a 5 year early intervention program for psychoses. Schizophr Res 2011;129:111-5.
48. Galletly C, Castle D, Dark F et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. Aust N Z J Psychiatry 2016;50:410-72.
49. Keating D, McWilliams S, Schneider I et al. Pharmacological guidelines for schizophrenia: a systematic review and comparison of recommendations for the first episode. BMJ Open 2017;7:e013881.
50. Correll CU, Martin A, Patel C et al. Systematic literature review of schizophrenia clinical practice guidelines on acute and maintenance management with antipsychotics. Schizophrenia 2022;8:5.
51. Chan SK, So HC, Hui CL et al. 10-year outcome study of an early intervention program for psychosis compared with standard care service. Psychol Med 2015;45:1181-93.
52. Mihalopoulos C, Harris M, Henry L et al. Is early intervention in psychosis cost-effective over the long term? Schizophr Bull 2009;35:909-18.
53. Cullberg J, Mattsson M, Levander S et al. Treatment costs and clinical outcome for first episode schizophrenia patients: a 3-year follow-up of the Swedish 'Parachute Project' and two comparison groups. Acta Psychiatr Scand 2006;114:274-81.
54. Murphy SM, Kucukgoncu S, Bao Y et al. An economic evaluation of Coordinated Specialty Care (CSC) services for first-episode psychosis in the U.S. public sector. J Ment Health Policy Econ 2018;21:123-30.
55. Valencia M, Juarez F, Ortega H. Integrated treatment to achieve functional recovery for first-episode psychosis. Schizophr Res Treatment 2012;2012:962371.
56. Ruggeri M, Bonetto C, Lasalvia A et al. Feasibility and effectiveness of a multi-element psychosocial intervention for first-episode psychosis: results from the

cluster-randomized controlled GET UP PIANO trial in a catchment area of 10 million inhabitants. Schizophr Bull 2015;41:1192-203.
57. Fusar-Poli P, Cappucciati M, Borgwardt S et al. Heterogeneity of psychosis risk within individuals at clinical high risk: a meta-analytical stratification. JAMA Psychiatry 2016;73:113-20.
58. Salazar de Pablo G, Catalan A, Fusar-Poli P. Clinical validity of DSM-5 attenuated psychosis syndrome advances in diagnosis, prognosis, and treatment. JAMA Psychiatry 2020;77:311-20.
59. Maj M, van Os J, De Hert M et al. The clinical characterization of the patient with primary psychosis aimed at personalization of management. World Psychiatry 2021;20:4-33.

DOI:10.1002/wps.70012

RESEARCH REPORT

Stanford neuromodulation therapy for treatment-resistant depression: a randomized controlled trial confirming efficacy, and an EEG study providing insight into mechanism of action and a potentially predictive biomarker of efficacy

Ian H. Kratter[1], Christopher W. Austelle[1,2], Jennifer I. Lissemore[1], Masataka Wada[1,3], Andrew Geoly[1], Anna Chaiken[1], Irakli Kaloiani[1], Noriah Johnson[1], Stephanie Wan[1], Lena Kozyr[1], Ethan Makarewycz[1], Brendan Wong[1], Malvika Sridhar[1], Flint M. Espil[1], Nick Bassano[1], Bora Kim[1], Jarrod Ehrie[1], Adi Maron-Katz[1], Claudia Tischler[1,4], Romina Nejad[1], Jean-Marie Batail[1,5], Angela L. Phillips[1,2], Eleanor J. Cole[1], Tiffany J. Ford[1], Brandon S. Bentzley[1], Booil Jo[1], Alan F. Schatzberg[1], David Spiegel[1], Cammie Rolle[1,6], Gregory L. Sahlem[1,7], Nolan R. Williams[1]

[1]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, USA; [2]US Department of Veterans Affairs, Palo Alto, CA, USA; [3]Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan; [4]Baylor College of Medicine, Houston, TX, USA; [5]Pôle Hospitalo-Universitaire de Psychiatrie Adulte, Centre Hospitalier G. Régnier, Rennes, France; [6]Wu Tsai Neurosciences Institute, Stanford University, Stanford, CA, USA; [7]Department of Psychiatry and Behavioral Sciences, Behavioral Medicine & Neurosciences Division, Duke University, Durham, NC, USA

Stanford neuromodulation therapy (SNT) is a rapid-acting, high-dose, intermittent theta-burst stimulation protocol. Although it has previously demonstrated efficacy for treatment-resistant depression (TRD) in a randomized controlled trial (RCT), replication in a larger sample is needed. Additionally, the electrophysiological effects of SNT remain unknown. Here we report results from a new double-blind, sham-controlled RCT along with electroencephalography (EEG) findings from the initial and current trials. In the current RCT, 53 participants with TRD were enrolled, and 48 who continued to meet entry criteria were randomized to receive active (N=24) or sham (N=24) SNT. At 1-month, remission (primary outcome) was achieved in 50.0% of active vs. 20.8% of sham participants ($\chi^2_{1,48}$=4.5, p=0.035), and response (secondary outcome) similarly favored active treatment (54.2% vs. 25.0%; $\chi^2_{1,48}$=4.3, p=0.039). Beta band EEG findings converged across trials: frontal beta power decreased significantly following active but not sham SNT in both the initial pilot study and the current trial. Additionally, beta baseline activity and post-SNT changes related to treatment efficacy in the current study. Specifically, greater post-SNT reduction in left anterior cingulate cortex (L-ACC) beta power correlated with greater clinical improvement immediately (rho=0.48, p=0.019) and 1-month after (rho=0.51, p=0.012) active SNT. Moreover, higher pre-treatment L-ACC beta power predicted greater subsequent clinical benefit from active SNT (immediate-post: β=-10.26, p=0.0042; 1-month after: β=-9.00, p=0.024). Neither of these L-ACC beta power findings was observed with sham stimulation. In sum, this study replicates SNT's therapeutic efficacy, identifies left frontal beta suppression as a potential mechanism of action, and highlights baseline L-ACC beta power as a candidate scalable pre-treatment biomarker of efficacy.

Key words: Stanford neuromodulation therapy (SNT), intermittent theta-burst stimulation, repetitive transcranial magnetic stimulation, treatment-resistant depression, beta power, left anterior cingulate cortex, left dorsolateral prefrontal cortex

(World Psychiatry 2026;25:105–116)

Major depressive disorder (MDD) is a leading contributor to global disability, affecting over 280 million people and being responsible for more than 5% of all years lived with disability worldwide[1]. In the US, the economic burden of MDD exceeds $326 billion annually[2].

Approximately 30% of individuals diagnosed with MDD experience treatment-resistant depression (TRD), usually defined as an insufficient response to at least two adequate trials of antidepressant medications[3]. TRD contributes to additional societal costs (more than $90 billion annually) and disability, including lost productivity, unemployment, and further health care costs. It is also associated with an increased all-cause mortality risk compared with MDD that is not treatment-resistant[4].

When patients with TRD do not respond to first-line pharmacological and psychotherapeutic treatments, brain stimulation interventions are often considered. Repetitive transcranial magnetic stimulation (rTMS) is one of a growing number of brain stimulation treatments with proven efficacy for TRD[5-7]. Advances in our understanding of the neurobiology of depression and the mechanisms underlying the clinical effects of rTMS have guided the development of innovative brain stimulation methods for TRD[8-11]. We recently developed an accelerated version of rTMS called Stanford neuromodulation therapy (SNT), based on converging lines of evidence related to the antidepressant effects of rTMS[12,13].

SNT is an accelerated, high-dose, patterned, functional connectivity magnetic resonance imaging (fcMRI)-guided rTMS protocol that utilizes intermittent theta-burst stimulation[12,13]. In an initial randomized controlled trial (RCT), treatment with a 5-day course of active SNT resulted in remission rates of 57.1% immediately post-SNT and 46.2% 1-month post-SNT in participants with moderate to severe TRD[13]. Although this initial trial showed robust clinical effects (Cohen's d of 1.7 and 1.4 immediately post-SNT and 1-month post-SNT, respectively), its limited sample size (N=29) and the ongoing challenge of research reproducibility in psychiatry[14] highlighted the need for replication in a larger trial.

Additionally, our understanding of the therapeutic mechanisms underlying SNT is limited. Increased knowledge of SNT's neurophysiological effects may guide future development of the treatment, potentially allowing for optimization of patient selection and further personalization of treatment to enhance clinical outcomes.

Thus far, functional neuroimaging has yielded fruitful initial insights into the mechanism of action of SNT. Specifically, imaging data from the above-mentioned RCT[13] demonstrated that functional connectivity between the amygdala and the default mode network (DMN) significantly increased following active SNT and was correlated with better clinical outcomes[15]. Further, a seed-based approach identified increased anticorrelation between the left dorsolateral prefrontal cortex (L-DLPFC) and the DMN following active as compared to sham SNT[16]. Finally, a spatiotemporal analysis revealed that SNT induced signaling shifts in the L-DLPFC and bilateral anterior cingulate cortex (ACC), that directional shifts in the ACC predicted improvement in depression symptoms post-treatment, and that pre-treatment ACC signaling predicted the likelihood of subsequent SNT treatment response[17].

Electroencephalography (EEG) offers a cost-effective tool for measuring the effects of SNT on neural activity with sub-millisecond resolution. EEG measures of oscillatory activity within the ~13-30Hz frequency range (i.e., beta power) have been linked to depressive states in humans. For example, an anhedonia symptom subtype in a large transdiagnostic sample (N=420) was specifically associated with elevated frontal beta activity[18], and abnormally high frontal beta power was linked to depressive symptoms in several cross-sectional resting-state EEG studies[19-24]. Similarly, intracranial EEG measurements in the ACC have shown that beta power is related to depressive symptoms in TRD[25] and tracks changes in depressive symptoms after deep brain stimulation[26,27]. Pre-treatment measures of beta power have also been identified as potential predictors of rTMS depressive symptom outcomes[28-30]. Yet, the effects of SNT on beta activity have not been investigated.

In this double-blind, randomized, sham-controlled trial, we assessed SNT's antidepressant efficacy in a newly recruited sample of patients with TRD. We also analyzed the neurophysiological effects of SNT via EEG recorded pre- and post-treatment, examining data both from a subset of the above-mentioned initial RCT[13] as well as from the current trial.

We specifically investigated the effects of active SNT on left frontal beta activity. We further investigated how these effects and pre-treatment beta activity relate to individual treatment outcomes by investigating that activity in cortical regions previously implicated in SNT's therapeutic benefits – L-DLPFC and left ACC (L-ACC) – using EEG co-registered with MRI for source localization. We hypothesized that active SNT would again demonstrate significantly greater antidepressant efficacy than sham SNT, and that only active treatment would modulate left frontal beta activity.

METHODS

Study design

We conducted a double-blind, randomized, sham-controlled trial, prospectively registered in the US Clinical Trials registry (NCT 04739969). All procedures were carried out in accordance with the ethical standards outlined in the Declaration of Helsinki. The study was approved by the Stanford University Institutional Review Board. All participants provided written consent before taking part in any study procedures.

Participants

The study was carried out at the Department of Psychiatry of Stanford University from June 17, 2021 to June 6, 2024. We recruited individuals from the community using media advertisements and from referring clinics both inside and outside of Stanford University.

Included participants had a primary diagnosis of MDD according to the DSM-5, were currently experiencing a moderate to severe depressive episode (score ≥20 on the Montgomery-Åsberg Depression Rating Scale, MADRS[31]), were between 22 and 65 years old, and had moderate-to-severe levels of treatment resistance as measured by the Maudsley Staging Method[32] (score ≥7 required), confirmed by medical records. Adequate treatment failures were defined according to the Antidepressant Treatment History Form (ATHF)[33]. Participants were required to maintain a stable antidepressant regimen for 6 weeks prior to treatment and to remain on this regimen throughout the study (including all follow-up assessments after the 5-day treatment protocol).

Key exclusion criteria were any primary psychiatric diagnosis other than MDD (except for stable comorbid anxiety disorder), unstable symptoms between screening and baseline as defined by a >30% change in MADRS score, intellectual disability, autism spectrum disorder, moderate or severe substance use disorder, active suicidal ideation (defined as a score ≥8 on the Modified Scale for Suicidal Ideation, MSSI[34]), contraindication to MRI[35], or any condition that would increase the risk associated with receiving intermittent theta-burst stimulation[36]. Individuals with prior exposure to rTMS, non-response to electroconvulsive therapy (ECT), or a depth-adjusted SNT treatment dose >65% maximum stimulator output (MSO) were also excluded.

Participants were instructed to continue usual intake patterns of caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) without significant change for the duration of the study, and to abstain from alcohol for at least 24 hours before the start of each rTMS session.

Randomization

Participants were randomized to active vs. sham SNT in a 1:1 ratio in randomly selected block sizes of 2, 4 or 6 as based on a random number generator and without stratification.

Intervention

The SNT paradigm has been previously described[12]. Briefly, a baseline structural and resting-state functional-connectivity MRI (rs-fcMRI) was obtained for each participant. Custom scripts were used to identify the portion of the L-DLPFC maximally anticorrelated with the subgenual ACC, which served as the target for both active and sham stimulation. Stimulation was delivered via a MagVenture MagPro X100 (Skovlunde, Denmark) TMS device equipped with a Cool-B65 A/P coil. The personalized L-DLPFC functional target was localized for each participant using a Localite TMS Navigator (Localite, Bonn, Germany).

Participants were treated with 1,800 pulses of intermittent theta-burst stimulation (3-pulse 50-Hz bursts at 5-Hz for 2-sec trains, with trains every 10 sec) per session at 90% resting motor threshold depth-adjusted to the personalized functional target. Ten sessions were delivered per day (18,000 pulses/day) for 5 consecutive days (90,000 total pulses). The inter-session interval between same-day treatment sessions was 50 min.

To ensure adequate sleep each evening prior to SNT intervention (a safety requirement), study physicians had the option to prescribe certain sleep medications (e.g., zolpidem, zaleplon, eszopiclone, quetiapine) immediately prior to or during the course of SNT. In these cases, participants were instructed to take the medication the night prior to the stimulation session but not during the morning of the sessions or at any time during the intervention day. The use of alternative hypnotics or the short-term use of anxiolytic medications (e.g., hydroxyzine, propranolol) during an intervention day required prior approval by a study physician.

If a participant met the remission criterion according to the MADRS (see below) at the immediate post-SNT visit or a weekly post assessment, but then failed to do so at a subsequent weekly post assessment, he/she was offered additional SNT treatment in blocks of 2 days (6 additional treatments in total maximum allowed) until either reaching the prior lowest total MADRS score or undergoing the 1-month follow-up visit. A minimum of 2 days must have passed between additional SNT treatment and the 1-month follow-up visit. The purpose of these additional days was to return participants who already had achieved remission from the acute SNT intervention to euthymia before transitioning to long-term follow-up, as inspired by the fixed taper schedule utilized in the pivotal ECT Prolonging Remission in Depressed Elderly (PRIDE) study[37]. Three participants in the active group and one in the sham group received additional SNT treatment.

Blinding

All participants, clinical assessors, SNT operators, study physicians, and other study staff were blinded to treatment assignments. Clinical assessors, EEG technicians, and SNT operators were separate individuals.

Clinical outcomes

Assessments were performed at screening, baseline, immediate post-SNT (3-4 days after the final treatment), 1-, 2- and 3-weeks after day 5 of SNT, and 1-month post-SNT, by evaluators blinded to treatment condition. Evaluators also met biweekly with a licensed psychologist to ensure consensus and prevent rater drift. The 1-month visit had to occur between 25 and 35 days after the day 5 of SNT.

The primary outcome was rate of remission 1-month after treatment, as defined by a MADRS score ≤10[38]. The secondary outcome was rate of response, defined as a MADRS score reduction of ≥50% from baseline, at 1-month. As an exploratory outcome, a generalized linear mixed effects model was used to assess the effects of group and time from baseline through 1-month post-treatment on the total MADRS score.

Safety

Adverse events (AEs) were systematically screened for with a series of standardized questions asked at each visit. Any positive response was documented and reported to a study physician for further evaluation and determination of whether or not an AE had occurred. Per protocol, stimulation-based site discomfort was not considered an AE, given that it is expected and normally occurs with rTMS, but pain persisting beyond stimulation would be coded as an AE.

History of suicidal ideation and behavior was assessed with the Columbia-Suicide Severity Rating Scale (C-SSRS)[39], and suicidality was monitored during the trial via the suicidal thoughts item of the MADRS and the MSSI. The Young Mania Rating Scale (YMRS) [40] was administered at the end of each treatment day and at select follow-up visits to monitor for any potential treatment-emergent mania. An independent data safety monitoring board (DSMB) reviewed study progress and safety at regular intervals.

Clinical statistics

A power analysis based on clinical efficacy indicated that 18 participants were required for each arm. However, we initially aimed to enroll a larger sample of 100. Unfortunately, study initiation was substantially delayed by the COVID-19 pandemic, resulting in the study being behind on its milestones. Accordingly, after enrollment of approximately half of the intended sample size, discussion with the DSMB led to a decision to perform an interim analysis. The prespecified stopping rules were to end the trial if both the primary and secondary outcomes were positive, or, conversely, if the difference between active and sham SNT outcomes was minimal (or favoring sham) such that the trial appeared to be futile. As the primary outcome was found to be positive, the study was completed.

Unless otherwise noted, categorical data are presented as percentages and compared using the Pearson chi square test of independence, and Fisher's exact test where necessary. Baseline continuous data are presented as means with standard deviations (SDs) and compared using ANOVA. As no baseline characteristics displayed imbalance between groups or an association with the dependent variable of the primary outcome, no covariates were included in final models.

The primary and secondary outcomes were assessed according to the intent-to-treat principle, and the last observation was carried forward in cases of missing data with no interpolation. For the exploratory analysis, we used a general linear mixed-effects model with group and time as interacting fixed effects and a random intercept for each participant. Because residuals of standard linear mixed-effects models were not normally distributed, exploratory analyses were conducted using a generalized linear mixed-effects model implemented in SAS (PROC GLIMMIX, version 9.4), which applied empirical (sandwich) standard errors (SEs) to ensure robust inference. Fixed effects included treatment group, time, and their interaction. A random intercept was included for each participant. Participant-level autocorrelations were modeled with an autoregressive covariance structure of order 1. Models were estimated using restricted maximum likelihood (REML) with the Satterthwaite approximation for denominator degrees of freedom. Least-squares means were estimated for each group at each time point.

To assess differential changes from baseline between treatment groups, we specified linear contrast statements comparing pre-post change scores across groups at each follow-up time point. Resulting p values were Bonferroni-corrected for five comparisons to control the family-wise error rate. SEs and confidence intervals (CIs) were extracted from the model-estimated covariance structure. All analyses were conducted in SAS Studio (v9.4).

EEG data collection and pre-processing

In both the initial[13] and current RCTs, eyes-open resting state EEG (rs-EEG) recordings were performed at baseline and at the immediate post-SNT visit. We recorded 5 min of rs-EEG per session in the initial trial, and 6 min of rs-EEG (two 3-min recordings) per session in the current trial.

All EEG data were collected using a 64-channel actiCap slim EEG cap with the acti64Champ amplifier (Brain Products GmbH, Germany). During data collection, the EEG signal was referenced to Cz (vertex reference) and sampled at a rate of 10kHz. Channels were positioned according to the 10-10 system. Participants were seated upright during the recording and were instructed to look at a fixation cross while letting their minds wander.

EEG data were pre-processed in MATLAB using a semi-automated approach and open-source functions from EEGLAB[41] and ARTIST[42] toolboxes. All pre-processing was performed by an experienced rater who was blinded to the intervention group and clinical scores associated with each recording (see supplementary information for a detailed list of pre-processing steps).

The 1-50Hz power spectral density was computed using Welch's method with 2-sec Hamming windows (50% overlap). Epochs with 1-50Hz power deviating from the mean by 50 dB or a z-score >1.96 were rejected. The average length of the rs-EEG recordings post-processing was 4.57±0.46 min (range: 2.97-4.97) for the initial RCT pilot data and 5.34±0.58 min (range: 2.97-5.87) for the current trial. Beta power (13-30Hz) was averaged in a left frontal cortical region of interest (Fz, F3, F1, AF3, and AFz).

Source localization was also performed using the open-source Brainstorm toolbox[43] to extract beta power in two frontal cortical regions previously implicated in the antidepressant efficacy of rTMS: L-DLPFC and L-ACC[8,9,11,12,17]. EEG sensor data were first co-registered to individual structural T1-weighted images, and a realistic boundary element method (BEM) forward model was computed from 15,000 cortical vertices (i.e., sources) with unconstrained dipole orientations. To compute the inverse model, we used standardized low-resolution electromagnetic tomography (sLORETA) and the diagonal noise covariance. Beta power in source space was then computed using Welch's method (2-sec windows with 50% overlap) and averaged within L-DLPFC and L-ACC regions using the Desikan-Killiany atlas left rostral middle frontal and left rostral anterior cingulate regions, respectively.

EEG statistics

To account for non-normally distributed beta power values, a log-transform was applied to all power values. To assess whether effects of SNT on beta power differed between active and sham groups, linear mixed-effects models were performed using the R *lme4* package[44]. Beta power was defined as the outcome; time point (pre- vs. post-SNT), treatment group (active vs. sham), and their interaction as fixed effects; age as a covariate; and participant as a random effect.

Post-hoc simple-effects analyses were performed by deriving estimated marginal means for each treatment group (active and sham) at each time point and comparing pre- vs. post-treatment within each treatment group. All statistical analyses were performed using R software[45], version 4.3.1 or newer (in RStudio v. 2023.06.0 or newer[46]).

The relationship between changes in L-DLPFC and L-ACC beta power and improvements in depressive symptoms after treatment was then assessed using Spearman's correlations. Additionally, linear regression models were fitted to the data, adjusted for age, to assess whether baseline L-DLPFC and L-ACC beta power was predictive of SNT clinical outcomes. Histograms and Q-Q plots of all model residuals were checked to assess normality. The variance inflation factor was used to assess for collinearity in the fitted model.

RESULTS

Demographics

From June 17, 2021 to June 6, 2024 we screened 199 participants, of whom 73 (36.7%) were preliminarily eligible, 53 (26.6%) were enrolled, and 48 (24.1%) were ultimately randomized and received active SNT (N=24) or sham SNT (N=24). One participant in the sham group withdrew early (after one day of treatment). All other participants (N=47) completed the study. The CONSORT diagram is presented in Figure 1.

Baseline demographic and clinical characteristics of participants are presented in Table 1. They were similar between the two groups. Among the entire cohort (mean±SD), participants' current depressive episode had lasted for 4.9±5.2 years; they had a history of 3.2±2.6 past depressive episodes; they had failed a total of 4.5±1.8 lifetime adequate antidepressant treatments (2.5±1.5 in the current episode) with a Maudsley staging method score of 8.5±1.4 (moderately treatment resistant), and they presented with a moderately

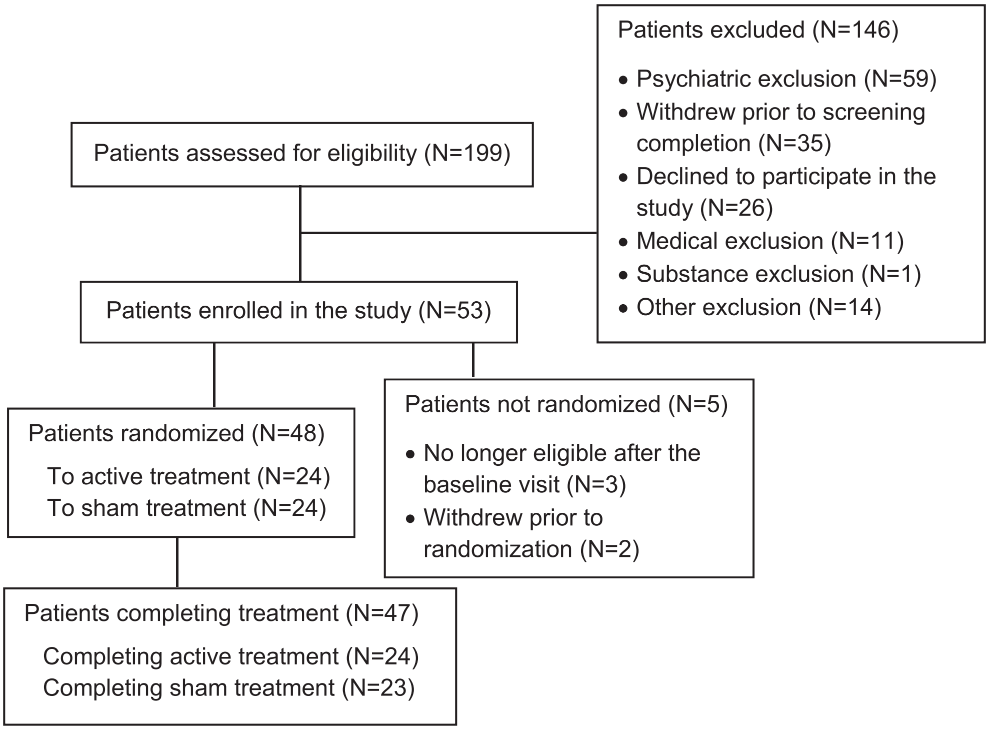


Figure 1 CONSORT diagram

severe current symptom burden (mean MADRS score of 27.9±5.7). Personalized, fcMRI-derived SNT brain targets were obtained for each participant and qualitatively similarly located throughout the L-DLPFC in both groups.

Primary outcome

The pre-defined primary outcome was the rate of remission 1-month after treatment using the MADRS score (remission defined as MADRS ≤10). The remission rates were 50.0% and 20.8% in the active and sham SNT groups, respectively ($X^2_{1,48}$=4.5, p=0.035, odds ratio, OR=3.8, number needed to treat, NNT=3.4) (see Figure 2).

Secondary outcome

The pre-defined secondary outcome was the rate of response (defined as ≥50.0% improvement from baseline) 1-month after treatment using the MADRS. The response rates for active and sham SNT were 54.2% and 25.0%, respectively ($X^2_{1,48}$=4.3, p=0.039, OR=3.5, NNT=3.4) (see Figure 3).

Safety

There were no serious adverse events (SAEs). No AE was significantly more common with active SNT as compared to sham SNT (see supplementary information).

Exploratory clinical outcomes

We assessed whether there were any baseline demographic or clinical differences between participants who responded to or remitted with treatment vs. those who did not. Females were more likely to be responders than males 1-month after treatment ($X^2_{1,48}$= 5.3, p=0.021). There were no other statistically significant demographic or clinical differences between responders and non-responders, nor were there any differences for remitters vs. non-remitters.

Additionally, we assessed the effects of group and time from baseline through 1-month post-treatment on the total MADRS score (see Figure 4). We identified statistically significant effects of group ($F_{1,46}$=5.24, p=0.0267), time ($F_{5,201}$=15.3, p<0.001), and group by time interaction ($F_{5,201}$=3.5, p=0.0047). In post-hoc testing, the change in total MADRS score from baseline was significantly different between the two groups at each time point (see supplementary information).

SNT effects on beta activity

In the initial trial[13], EEG was recorded in a subset of 16 participants (7 active, 9 sham; mean age: 49.6±15.9 years; 12 male). At one month, MADRS scores improved by 57.3% in the active group and 25.9% in the sham group. We used this subset as an initial test of our hypothesis that active and sham treatment would differentially modulate left frontal beta activity. Although the small sample limited statistical power and the overall group x time in-

Table 1 Baseline demographic and clinical characteristics of participants in the trial

	Active SNT (N=24)	Sham SNT (N=24)
Sex, N (%)		
Male	10 (41.6)	15 (62.5)
Female	14 (58.3)	9 (37.5)
Gender, N (%)		
Male	11 (45.8)	15 (62.5)
Female	13 (54.2)	9 (37.5)
Age (years), mean±SD	44.8±11.8	47.3±12.1
Race, N (%)		
White	22 (91.6)	17 (70.8)
Asian	1 (4.2)	6 (25.0)
American Indian/Alaska Native	0	1 (4.2)
Other	2 (8.3)	1 (4.2)
Ethnicity, N (%)		
Hispanic or Latino	1 (4.2)	4 (16.7)
Non-Hispanic or Latino	23 (95.8)	20 (83.3)
N. past episodes, mean±SD	3.1±2.8	3.3±2.5
Duration of current episode (months), mean±SD	64.8±63.7	53.4±60.9
N. adequate antidepressant failures (lifetime), mean±SD	4.5±1.7	4.5±1.9
N. adequate antidepressant trials (current episode), mean ±SD	2.3±1.6	2.6±1.4
Maudsley Staging Method score, mean±SD	8.5±1.4	8.5±1.5
Baseline MADRS score, mean±SD	28.5±5.8	27.3±5.5

SNT – Stanford modulation therapy, MADRS – Montgomery-Åsberg Depression Rating Scale

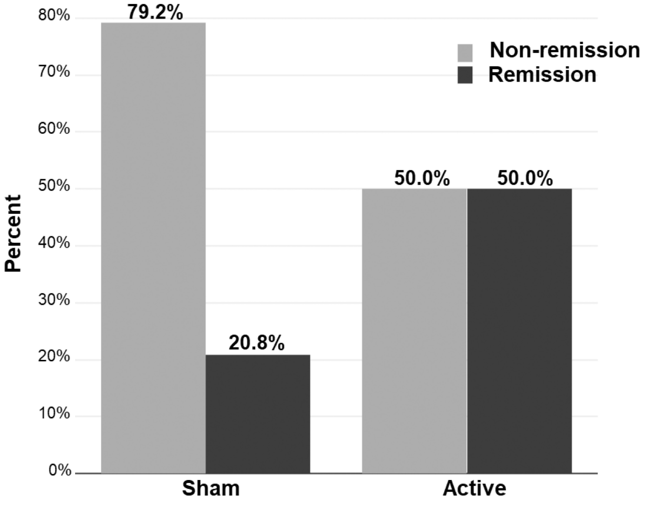


Figure 2 One-month remission rate in individuals receiving active and sham Stanford neuromodulation therapy

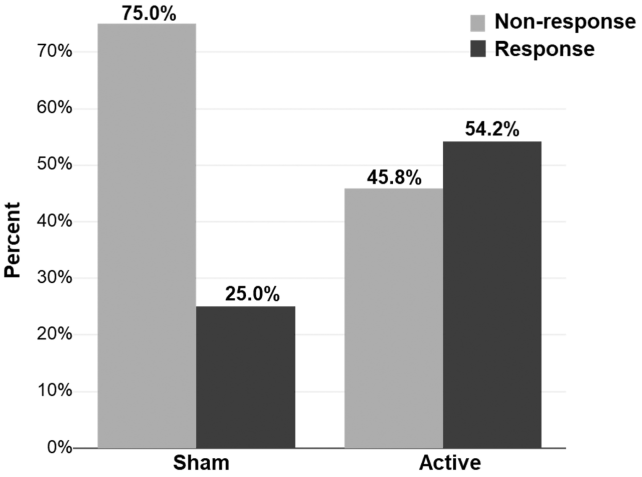


Figure 3 One-month response rate in individuals receiving active and sham Stanford neuromodulation therapy

teraction did not reach significance (β=0.44, t_{15}=1.95, p=0.071), post-hoc analysis showed that left frontal beta power significantly decreased after treatment in the active group (t_{15}=2.41, p=0.030, d=0.62) (see Figure 5).

In the current RCT, EEG was obtained in 45 participants at baseline (age: 45.4±11.8 years; 24 male; N=24 active, N=21 sham) and in 44 participants at the immediate post-SNT visit (N=23 active, N=21 sham; see supplementary information for data exclusion details). The interaction effect between group and time on frontal beta band power was significant (β=0.58, t_{42}=3.69, p<0.001). Replicating the initial trial, post-hoc comparisons revealed a significant decrease in beta power after treatment in the active group (t=2.96, p=0.005, d=0.56) (see Figure 5). Findings persisted in sensitivity analyses excluding participants with concurrent benzodiazepine use (see supplementary information).

Associations between beta activity and SNT outcomes

To investigate how beta activity might be related to clinical outcomes in the current trial, we localized beta activity to two key regions previously implicated in rTMS efficacy: L-ACC and L-DLPFC. A pre-post treatment reduction in beta activity was observed in the L-ACC among responders to active treatment, but not in non-responders (see supplementary information). To further identify whether variance in beta power in L-ACC and L-DLPFC was meaningfully related to clinical improvement, we assessed correlations between treatment-related changes in beta power and reductions in MADRS scores, and used linear regression to model the relationship between baseline beta activity and symptom improvement.

In the active SNT group, greater reductions in L-ACC beta power correlated with greater reductions in MADRS scores both immediately post-SNT (rho=0.48, p=0.019) and 1-month post-SNT (rho=0.51, p=0.012) (see Figure 6). By contrast, in the sham group, changes in L-ACC beta power were not significantly correlated with MADRS score improvements at either time point (immedi-

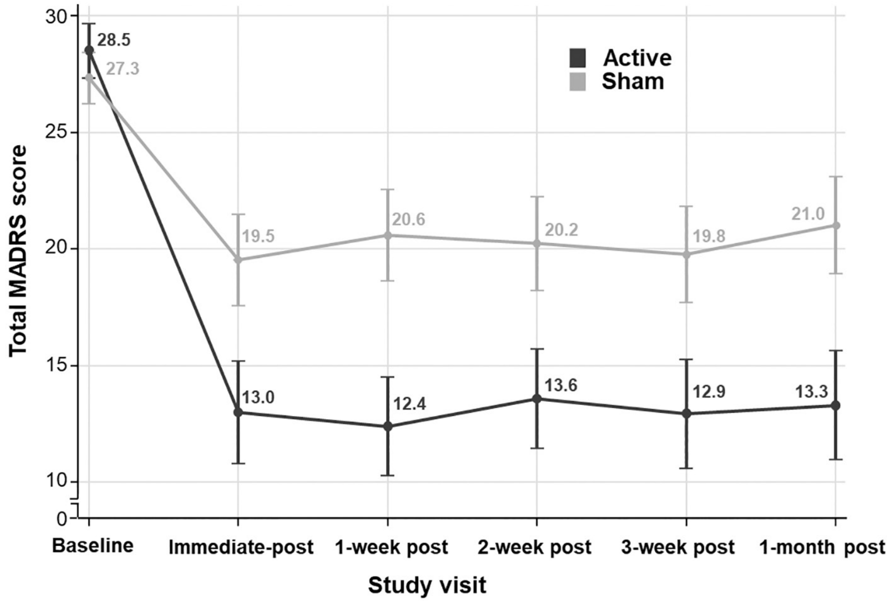


Figure 4 Longitudinal clinical outcomes by mean score on the Montgomery-Åsberg Depression Rating Scale (MADRS) in participants receiving active and sham Stanford neuromodulation therapy. Solid circles represent generalized mixed-effects model-estimated marginal means. Error bars represent model-based standard errors.

ately post-SNT: rho=0.13, p=0.57; 1-month post-SNT: rho=0.17, p=0.45) (see Figure 6). Changes in L-DLPFC beta power were not correlated with MADRS score improvements in either group.

In the active SNT group, higher pre-treatment L-ACC beta power was a significant predictor of greater reductions in MADRS scores immediately post-SNT (R^2=0.40; β=–10.26, 95% CI: –17.60 to –3.76, p=0.0042) and 1-month post-SNT (R^2=0.30; β=–9.00, 95% CI: –17.37 to –1.38, p=0.024) (see Figure 7). In contrast, greater pre-treatment L-ACC beta power was not a significant predictor of reductions in MADRS scores after sham treatment (immediate post-SNT, p=0.20; 1-month post-SNT, p=0.22) (see Figure 7). Associations between baseline L-DLPFC beta power and clinical outcomes were weaker and not persistent (see supplementary information).

DISCUSSION

The present study examined the antidepressant effects of SNT and investigated its underlying neurophysiological mechanisms. Clinically, SNT produced significantly greater antidepressant effects in participants with TRD than sham treatment, with a particularly notable 50% rate of remission with active SNT at 1-month.

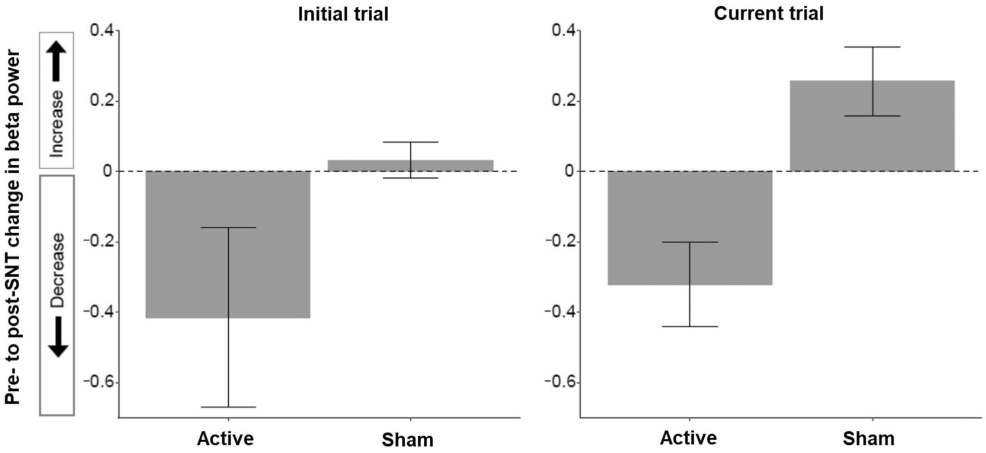


Figure 5 Pre-post changes in left frontal beta power in patients receiving active and sham Stanford neuromodulation therapy (SNT) in the initial and current trial. The group x time interaction was not significant (p=0.071) in the initial trial (N=16), whereas it was significant (p<0.001) in the current trial (N=44). In post-hoc tests, frontal beta power was significantly reduced after active SNT compared to baseline in the initial (p=0.030) and current (p=0.005) trial. Error bars reflect standard error of the mean.

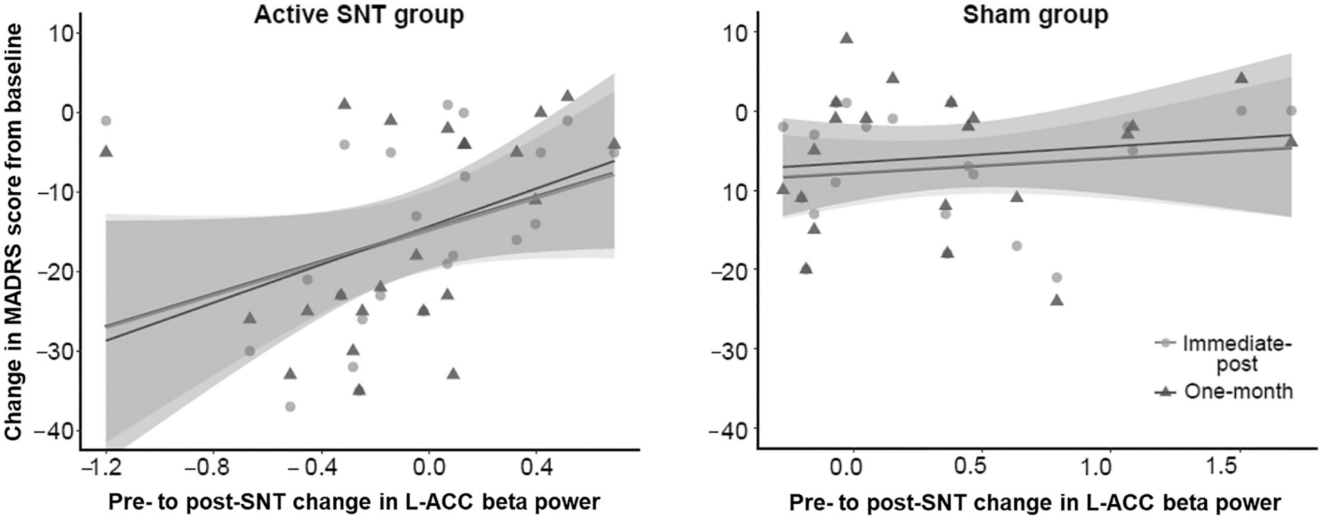


Figure 6 Scatterplots of individual data showing that greater reductions in left anterior cingulate cortex (L-ACC) beta power after Stanford neuromodulation therapy (SNT) were associated with greater improvements in depressive symptoms both at the immediate post-SNT visit (rho=0.48, p=0.019) and 1-month (rho=0.51, p=0.012) after active SNT, but not sham treatment (immediate-post: rho=0.13, p=0.57; one-month: rho=0.17, p=0.45). MADRS – Montgomery-Åsberg Depression Rating Scale.

Using rs-EEG to probe neurophysiological changes, we found that SNT consistently reduced frontal beta power. Greater reductions in L-ACC beta activity following active SNT were associated with greater improvements in depressive symptoms, both at the immediate post-SNT visit and 1-month post-treatment. Additionally, higher baseline beta power in the L-ACC predicted greater symptom improvement at both time points. These findings suggest that L-ACC beta activity may play a mechanistic role in the therapeutic benefit of SNT, and that baseline beta power could serve as a scalable neurophysiological predictor of treatment response.

This trial marks the largest SNT RCT to date, and the 50% remission rate with active treatment is notable for several reasons. First, it is very similar to the 46.2% one-month remission rate from the initial RCT[13]. Research into the development of more effective antidepressants faces a number of challenges[47], which may contribute to difficulties with reproducibility. According to one report, out of 43 highly cited psychiatric studies, only 16 (37%) replicated[14]. The fact that both SNT RCTs demonstrated significantly greater antidepressant efficacy with active as compared to sham treatment and a similar remission rate lends confidence to the veracity of these results in a double-blind trial setting.

Second, these remission rates allow for meaningful comparisons of efficacy between SNT and other common interventions for TRD. Conventional rTMS, for example, is approved by the US

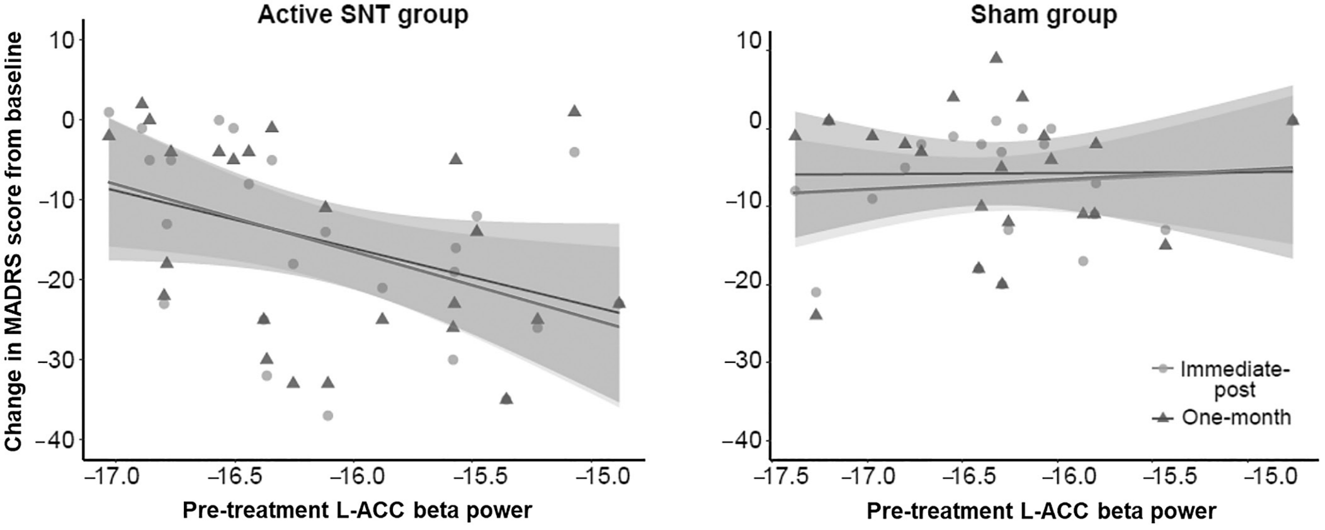


Figure 7 Scatterplots of individual data showing an association between higher left anterior cingulate cortex (L-ACC) beta power before Stanford neuromodulation therapy (SNT) and greater improvement in depressive symptoms both at the immediate post-SNT visit (β=–10.26, p=0.0042) and 1-month (β=–9.00, p=0.024) after active SNT, but not sham treatment (immediate-post: p=0.20; 1-month: p=0.22). MADRS – Montgomery-Åsberg Depression Rating Scale.

Food and Drug Administration (FDA) for TRD, commonly utilized in this population, and demonstrates relatively modest efficacy. In RCTs, rTMS typically yields remission rates of around 15%[7], with somewhat higher rates – up to 37% – reported in open-label studies[48-50].

Similarly, esketamine, another intervention approved by the FDA for TRD, has demonstrated moderate efficacy, with response rates between 50% and 70%, and remission rates ranging from 36% to 52.5%[51,52]. However, esketamine requires frequent in-person visits for administration and monitoring, especially during the acute phase, and patients are unable to drive themselves home afterward due to transient side effects. These logistical challenges, along with the potential need for ongoing maintenance treatments, can pose significant barriers to access and adherence.

SNT, by comparison, offers a non-pharmacological alternative with a favorable side effect profile and a shorter course of treatment. Indeed, its tolerability appears to be comparable to that of conventional rTMS[36]. Perhaps most striking is that the antidepressant outcomes reported in SNT trials appear comparable to those achieved with ECT[53], which remains the gold standard for TRD. In a meta-analysis of ECT outcomes in TRD, the acute remission rate was found to be approximately 48%[53], suggesting that SNT may offer similar therapeutic benefits but with far fewer associated risks.

Notably, in a recent trial comparing intravenous ketamine with ECT for non-psychotic TRD, the ketamine arm achieved a remission rate of 37.9%, while the ECT arm only reached 21.8% remission[54]. Both these rates are lower than those observed in the initial SNT trial[13] and in the current RCT. Unlike ECT[54], SNT does not carry risks of cognitive side effects, nor is there the potential for anesthesia-related complications.

Taken together, these comparisons highlight SNT's potential as a highly effective and better-tolerated treatment option for individuals with TRD, particularly since re-treatment appears to be highly effective for previous treatment responders who experience a subsequent relapse[55].

Third, the efficacy of SNT reinforces the potential of neuroscience-informed principles to guide the development of novel treatment paradigms and further refine those that exist already. Indeed, rTMS has been described as perhaps the most important advancement in TRD management, due to both its demonstrated efficacy and its potential for further optimization[56]. Regarding the latter, a number of different treatment paradigms have been described in recent years[57-59]. For SNT, the relative therapeutic contribution of each of the modified elements remains unknown and requires further study. In the case of functional imaging-derived targeting, however, such evidence is beginning to emerge. A recent analysis of a large dataset demonstrated that individualized rTMS targets show stronger association with clinical efficacy than TMS targets based on group functional connectivity profiles[60]. Furthermore, a prospective randomized trial observed that the use of functional connectivity-guided targeting in an accelerated course of rTMS resulted in superior outcomes as compared to scalp-based targeting, with a large effect size[61].

These developments underscore how a deeper understanding of the neural mechanisms underlying the therapeutic effects of SNT may facilitate the further optimization of treatment outcomes. Towards that end, this study is the first to investigate the effects of SNT on EEG-based neurophysiological measures. We validate prior conventional rTMS EEG findings through both replication in two independent samples and the use of high-density EEG with source reconstruction in a double-blind, randomized, sham-controlled design. While earlier studies using fMRI have linked SNT efficacy to changes in functional connectivity in frontal cortical networks, our EEG findings provide complementary mechanistic insight by capturing neural dynamics at distinct oscillatory frequencies with high temporal resolution. The current EEG findings provide novel evidence that L-ACC beta activity is involved in SNT's underlying mechanism of action, and identify baseline beta activity in targeted prefrontal regions as a potential predictive biomarker of subsequent SNT efficacy.

Specifically, we found that active SNT reduced left frontal beta power, with greater reductions in the L-ACC associated with greater symptom improvement both immediately and 1-month after treatment – a relationship that was observed for active but not sham treatment. These results replicate and extend findings from conventional 5Hz rTMS studies linking frontocentral beta power reductions to symptom improvement[62,63], and parallel evidence from deep brain stimulation trials in TRD showing acute beta power reductions in the anterior cingulate alongside clinical response[26,27]. Additionally, the inhibition of ACC activity has been shown to induce antidepressant-like effects in mice, indicating potential causality of this mechanism[64,65]. These findings also complement fMRI evidence that SNT alters directed ACC connectivity, as beta oscillations have previously been implicated in the large-scale integration of prefrontal network interactions[66]. L-ACC beta power may therefore represent a complementary, scalable neurophysiological measure of SNT's mechanism of action, with the potential to support real-time monitoring of neural engagement and individualized dosing.

We also found that higher pre-treatment beta activity in the L-ACC predicted greater symptom improvement following active SNT. In contrast, pre-treatment beta activity was unrelated to outcomes in the sham group, suggesting a specific association with SNT's therapeutic mechanism. While previous open-label studies have linked pre-treatment beta power to clinical response following conventional rTMS protocols[29,67-69], this is, to our knowledge, the first demonstration that pre-treatment beta power is a predictor of response to an intermittent theta-burst stimulation treatment protocol. This finding aligns with neuroimaging studies demonstrating that higher pre-treatment activity in the anterior cingulate predicts more favorable outcomes with conventional high-frequency rTMS[70-73]. Notably, simultaneous EEG-fMRI research has shown that higher EEG beta power correlates with greater fMRI activity in the anterior cingulate[74], supporting the use of EEG beta power as a proxy for underlying regional activity.

As an accessible, cost-effective and temporally precise tool, EEG is well-suited for translation into the clinic, and may offer a practical supplement to fMRI for applying biomarkers to personalize SNT. For example, patients with elevated baseline L-ACC beta power could be prioritized for SNT earlier in a treatment algorithm for

TRD[56], potentially improving treatment outcomes and cost-effectiveness. In addition, emerging evidence from studies of motor circuits suggests that higher pre-stimulation frontocentral beta power facilitates TMS target engagement, as measured by increased propagation of neural signals from targeted cortical regions to subcortical regions[75]. Given fMRI findings that greater modulation of downstream functional connections following SNT is associated with clinical response[15-17], beta-related facilitation of downstream target engagement may translate into improved clinical outcomes.

In line with this idea, closed-loop deep brain stimulation protocols that stimulate based on real-time beta activity may improve treatment outcomes for Parkinson's disease, as compared to standard open-loop, biomarker-naive stimulation protocols[76]. These results raise the possibility that EEG beta activity could similarly inform the development of adaptive or closed-loop SNT paradigms. In addition to personalizing *where* we stimulate with SNT, such approaches could use real-time EEG to optimize *when* we stimulate [77], potentially enhancing therapeutic outcomes by targeting brain states characterized by elevated beta activity.

Altogether, these findings identify L-ACC beta power as a candidate biomarker for both patient stratification and SNT treatment optimization. Future studies should explore the application of EEG-based biomarkers in prospective, biomarker-guided SNT trials.

This study has some limitations. First, although this is the largest RCT of SNT to date, further replication with a greater sample size would be of benefit. Additionally, as in the prior RCT, this study was performed at a single site with participants who were primarily highly educated, White or Asian, and non-Hispanic or Latino persons. Additional study in other demographic groups is needed to further assess the generalizability of these findings, although we note that a SNT study in bipolar depression at two other academic sites also reported positive findings[78].

All participants in this trial had a primary diagnosis of MDD (although a stable, co-primary anxiety disorder was allowed), and so the efficacy of SNT in patients in whom depression is co-primary or secondary remains unknown. While the remission rates achieved by SNT in the initial and current RCTs compare favorably to those reported in traditional rTMS RCTs[4,5], SNT remains to be tested against rTMS (or another active comparator) to address comparative efficacy. Similarly, although a recent study found that 47% of participants who achieved remission with SNT were still in remission 12 weeks after treatment[79], the longer-term durability of its antidepressant effect remains unknown.

Additionally, comparisons with healthy controls are needed to determine whether the observed reductions in beta activity following active SNT reflect normalization of neural activity or the engagement of compensatory mechanisms. The current work also focused specifically on beta activity in frontal cortical regions, based on extensive prior evidence linking frontal beta rhythms to depression and neuromodulation outcomes. While this hypothesis-driven approach helped minimize the issue of multiple comparisons, future work should explore whether other EEG measures and cortical regions also play a role in the therapeutic effects of SNT.

In conclusion, active SNT was more effective than sham in achieving remission of TRD in a double-blind RCT, replicating the initial RCT in an independent, larger sample. Further, we provide the first report of the electrophysiological effects of SNT, including the identification of a potential pre-treatment biomarker. The EEG data reported here, in combination with previously reported neuroimaging findings[15-17], provide an opportunity to build on our understanding of SNT's therapeutic mechanism of action and the pathophysiology of TRD more generally.

ACKNOWLEDGEMENTS

The authors are grateful to all study participants, and to the Stanford Brain Stimulation Lab members who played a role in the study: M. Husain, K. Marchione, N. Keynan, T. Pope, A. Shamma, S. Dronavalli, L. Crowe, S. Ninomiya, S. Hunegnaw, L. Anker, K. Hollingsworth, K.L. Juskiewicz, K. Cherian, M. Gholmieh, T. Knightly, A.H. Musleh, N.B.H. Alnajjar, N. Dannawi, R. Shaibani, P. Singal, E. Sonnelid, C. Daye, Q. Pham, R. Ash, O. Kenyan, P. Crittenden, I.D. Bandeira, C. Veerapal, M. Mattos, T. Dinh, and S. O'Sullivan. This work was supported by the US National Institute of Mental Health (grant no. R01 MH122754), a Brain and Behavior Research Foundation Young Investigator Award (to N.R. Williams), C.R. Schwab, the D. and A. Chao Fund II, the A. Roth PhD Fund, the Neuromodulation Research Fund, the Lehman Family, the Still Charitable Trust, the Marshall and D.A. Payne Fund, and the Gordie Brookstone Fund. Additional support was provided by J. Lack, D. and M. Williams, D. Meine, T.L. Lane, S. and G. Spessard, J. and R. Kadlubar, A. and E. Rausch, A. Atwood Reimer, S. and M. Charles, C.M. Beyer, C. and V. Spessard, K. Riebe, K. and C. Buckner and the D. Buckner Foundation, H. Shelton, N. and R. Koppikar, F.D. Speno, Scicomm Media, the Tiny Foundation, the Saks Foundation, S. Brookstone-Mirbach and H.W. Mirbach, M. and D.A. Payne, J. and K. Crabbe, J. Mirbach, E. and N. Fong, T. and A. Nation, B. Stevens, Central Computers, D.J. Stinchfield, B. Moreton; J.C. Lehman, D.A. Aaker, L. Wolfson Keller, the Mellam Family Foundation, A. Lack, M. and K. Jerstad, S. Shin and C. Sherman, E. and A. Klump, M.A. Klump, E.M. Wallace, Y.R. Torrez, V.W. Woodgett, D. Wheeler, and C. Tager. I.H. Kratter, C.W. Austelle and J.I. Lissemore are shared first authors of this paper; M. Wada and A. Geoly are shared second authors; C. Rolle, G.L. Sahlem and N.R. Williams are shared last authors. Supplementary information on this study is available at https://osf.io/emkdq.

REFERENCES

1. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020;396:1204-22.
2. Greenberg PE, Fournier AA, Sisitsky T et al. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). J Clin Psychiatry 2015;76:155-62.
3. Rush AJ, Trivedi MH, Wisniewski SR et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006;163:1905-17.
4. Chan JKN, Solmi M, Lo HKY et al. All-cause and cause-specific mortality in people with depression: a large-scale systematic review and meta-analysis of relative risk and aggravating or attenuating factors, including antidepressant treatment. World Psychiatry 2025;24:404-21.
5. O'Reardon JP, Solvason HB, Janicak PG et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry 2007;62:1208-16.
6. George MS, Lisanby SH, Avery D et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry 2010;67:507-16.
7. Li H, Cui L, Li J et al. Comparative efficacy and acceptability of neuromodulation procedures in the treatment of treatment-resistant depression: a network meta-analysis of randomized controlled trials. J Affect Disord 2021;287:115-24.
8. Fox MD, Buckner RL, White MP et al. Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. Biol Psychiatry 2012;72:595-603.
9. Weigand A, Horn A, Caballero R et al. Prospective validation that subgenual connectivity predicts antidepressant efficacy of transcranial magnetic stimulation sites. Biol Psychiatry 2018;84:28-37.
10. Modak A, Fitzgerald PB. Personalising transcranial magnetic stimulation for depression using neuroimaging: a systematic review. World J Biol Psychiatry 2021;22:647-69.
11. Rosen AC, Bhat JV, Cardenas VA et al. Targeting location relates to treatment

response in active but not sham rTMS stimulation. Brain Stimul 2021;14:703-9.
12. Cole EJ, Stimpson KH, Bentzley BS et al. Stanford Accelerated Intelligent Neuromodulation Therapy for treatment-resistant depression. Am J Psychiatry 2020;177:716-26.
13. Cole EJ, Phillips AL, Bentzley BS et al. Stanford Neuromodulation Therapy (SNT): a double-blind randomized controlled trial. Am J Psychiatry 2022;179:132-41.
14. Tajika A, Ogawa Y, Takeshima N et al. Replication and contradiction of highly cited research papers in psychiatry: 10-year follow-up. Br J Psychiatry 2015;207:357-62.
15. Batail JM, Xiao X, Azeez A et al. Network effects of Stanford Neuromodulation Therapy (SNT) in treatment-resistant major depressive disorder: a randomized, controlled trial. Transl Psychiatry 2023;13:240.
16. Gajawelli N, Geoly AD, Batail JM et al. Increased anti-correlation between the left dorsolateral prefrontal cortex and the default mode network following Stanford Neuromodulation Therapy (SNT): analysis of a double-blinded, randomized, sham-controlled trial. npj Ment Health Res 2024;3:35.
17. Mitra A, Raichle ME, Geoly AD et al. Targeted neurostimulation reverses a spatiotemporal biomarker of treatment-resistant depression. Proc Natl Acad Sci USA 2023;120:e2218958120.
18. Grisanzio KA, Goldstein-Piekarski AN, Wang MY et al. Transdiagnostic symptom clusters and associations with brain, behavior, and daily function in mood, anxiety, and trauma disorders. JAMA Psychiatry 2018;75:201-9.
19. Newson JJ, Thiagarajan TC. EEG frequency bands in psychiatric disorders: a review of resting state studies. Front Hum Neurosci 2019;12:521.
20. Jaworska N, De La Salle S, Schryver B et al. Electrocortical profiles in relation to childhood adversity and depression severity: a preliminary report. Clin EEG Neurosci 2025;56:230-8.
21. Ellis CA, Sancho ML, Miller RL et al. Identifying EEG biomarkers of depression with novel explainable deep learning architectures. In: Longo L, Lapuschkin S, Seifert C (eds). Explainable artificial intelligence. Cham: Springer, 2024:102-24.
22. Liu X, Zhang H, Cui Y et al. EEG-based major depressive disorder recognition by neural oscillation and asymmetry. Front Neurosci 2024;18:1362111.
23. Matousek M. EEG patterns in various subgroups of endogenous depression. Int J Psychophysiol 1991;10:239-43.
24. Chang J, Choi Y. Depression diagnosis based on electroencephalography power ratios. Brain Behav 2023;13:e3173.
25. Clark DL, Brown EC, Ramasubbu R et al. Intrinsic local beta oscillations in the subgenual cingulate relate to depressive symptoms in treatment-resistant depression. Biol Psychiatry 2016;80:e93-4.
26. Alagapan S, Choi KS, Heisig S et al. Cingulate dynamics track depression recovery with deep brain stimulation. Nature 2023;622:130-8.
27. Sendi MSE, Waters AC, Tiruvadi V et al. Intraoperative neural signals predict rapid antidepressant effects of deep brain stimulation. Transl Psychiatry 2021;11:551.
28. Hasanzadeh F, Mohebbi M, Rostami R. Prediction of rTMS treatment response in major depressive disorder using machine learning techniques and nonlinear features of EEG signal. J Affect Disord 2019;256:132-42.
29. Arteaga A, Tong X, Zhao K et al. Multiband EEG signature decoded using machine learning for predicting rTMS treatment response in MDD. J Affect Disord 2025;388:119483.
30. Ebrahimzadeh E, Fayaz F, Rajabion L et al. Machine learning approaches and non-linear processing of extracted components in frontal region to predict rTMS treatment response in major depressive disorder. Front Syst Neurosci 2023;17:919977.
31. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382-9.
32. Fekadu A, Wooderson S, Donaldson C et al. A multidimensional tool to quantify treatment resistance in depression: the Maudsley Staging Method. J Clin Psychiatry 2009;70:177-84.
33. Sackeim HA. The definition and meaning of treatment-resistant depression. J Clin Psychiatry 2001;62(Suppl. 16):10-7.
34. Miller IW, Norman WH, Bishop SB et al. The Modified Scale for Suicidal Ideation: reliability and validity. J Consult Clin Psychol 1986;54:724-5.
35. ACR Committee on MR Safety, Greenberg TD, Hoff MN et al. ACR guidance document on MR safe practices: updates and critical information 2019. J Magn Reson Imaging 2020;51:331-8.
36. Rossi S, Antal A, Bestmann S et al. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: expert guidelines. Clin Neurophysiol 2021;132:269-306.
37. Kellner CH, Husain MM, Knapp RG et al. Right unilateral ultrabrief pulse ECT in geriatric depression: phase 1 of the PRIDE study. Am J Psychiatry 2016;173:1101-9.
38. Zimmerman M, Posternak MA, Chelminski I. Derivation of a definition of remission on the Montgomery-Åsberg depression rating scale corresponding to the definition of remission on the Hamilton rating scale for depression. J Psychiatr Res 2004;38:577-82.
39. Posner K, Brown GK, Stanley B et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 2011;168:1266-77.
40. Young RC, Biggs JT, Ziegler VE et al. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 1978;133:429-35.
41. Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods 2004;134:9-21.
42. Wu W, Keller CJ, Rogasch NC et al. ARTIST: a fully automated artifact rejection algorithm for single-pulse TMS-EEG data. Hum Brain Mapp 2018;39:1607-25.
43. Tadel F, Baillet S, Mosher JC et al. Brainstorm: a user-friendly application for MEG/EEG analysis. Comput Intell Neurosci 2011;2011:879716.
44. Bates D, Mächler M, Bolker B et al. Fitting linear mixed-effects models using lme4. J Stat Softw 2015;67:1-48.
45. R Core Team. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing, 2023.
46. Posit team. RStudio: integrated development environment for R. Boston: Posit Software, 2023.
47. Rush AJ, Thase ME, Dubé S. Research issues in the study of difficult-to-treat depression. Biol Psychiatry 2003;53:743-53.
48. Blumberger DM, Vila-Rodriguez F, Thorpe KE et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. Lancet 2018;391:1683-92.
49. Carpenter LL, Janicak PG, Aaronson ST et al. Transcranial magnetic stimulation (TMS) for major depression: a multisite, naturalistic, observational study of acute treatment outcomes in clinical practice. Depress Anxiety 2012;29:587-96.
50. Janicak PG, Nahas Z, Lisanby SH et al. Durability of clinical benefit with transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant major depression: assessment of relapse during a 6-month, multisite, open-label study. Brain Stimul 2010;3:187-99.
51. Fedgchin M, Trivedi M, Daly EJ et al. Efficacy and safety of fixed-dose esketamine nasal spray combined with a new oral antidepressant in treatment-resistant depression: results of a randomized, double-blind, active-controlled study (TRANSFORM-1). Int J Neuropsychopharmacol 2019;22:616-30.
52. Popova V, Daly EJ, Trivedi M et al. Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: a randomized double-blind active-controlled study. Am J Psychiatry 2019;176:428-38.
53. Heijnen WT, Birkenhäger TK, Wierdsma AI et al. Antidepressant pharmacotherapy failure and response to subsequent electroconvulsive therapy: a meta-analysis. J Clin Psychopharmacol 2010;30:616-9.
54. Anand A, Mathew SJ, Sanacora G et al. Ketamine versus ECT for nonpsychotic treatment-resistant major depression. N Engl J Med 2023;388:2315-25.
55. Geoly AD, Kratter IH, Toosi P et al. Sustained efficacy of Stanford Neuromodulation Therapy (SNT) in open-label repeated treatment. Am J Psychiatry 2024;181:71-3.
56. Kaster TS, Blumberger DM. Positioning rTMS within a sequential treatment algorithm of depression. Am J Psychiatry 2024;181:781-3.
57. Luehr JG, Fritz E, Turner M et al. Accelerated transcranial magnetic stimulation: a pilot study of safety and efficacy using a pragmatic protocol. Brain Stimul 2024;17:860-3.
58. Goodman MS, Trevizol AP, Konstantinou GN et al. Extended course accelerated intermittent theta burst stimulation as a substitute for depressed patients needing electroconvulsive therapy. Neuropsychopharmacology 2025;50:685-94.
59. Vaughn DA, Marino B, Engelbertson A et al. Real-world effectiveness of a single-day regimen for transcranial magnetic stimulation using Optimized, Neuroplastogen-Enhanced techniques in Depression (ONE-D). https://www.researchsquare.com/article/rs-5679327/v1.
60. Chen X, Lu B, Wang YW et al. Subgenual anterior cingulate cortex functional connectivity abnormalities in depression: insights from brain imaging big data and precision-guided personalized intervention via transcranial magnetic stimulation. Sci Bull 2025;70:2676-90.
61. Taylor J, Haj-Darwish D, Kare M et al. The AINT trial: imaging- versus scalp-targeted accelerated TMS for depression. Brain Stimul 2025;18:245.
62. Morris AT, Temereanca S, Zandvakili A et al. Fronto-central resting-state 15-29 Hz transient beta events change with therapeutic transcranial magnetic stimulation for posttraumatic stress disorder and major depressive disorder. Sci Rep 2023;13:6366.

63. Cosmo C, Zandvakili A, Petrosino NJ et al. Examining the neural mechanisms of rTMS: a naturalistic pilot study of acute and serial effects in pharmacoresistant depression. Front Neural Circuits 2023;17:1161826.
64. Yuan Z, Yang H, Wang P et al. Optimized deep brain stimulation for anterior cingulate cortex inhibition produces antidepressant-like effects in mice. Neuron 2025;113:1-11.
65. Yuan Z, Qi Z, Wang R et al. A corticoamygdalar pathway controls reward devaluation and depression using dynamic inhibition code. Neuron 2023;111:3837-53.
66. Siegel M, Donner TH, Engel AK. Spectral fingerprints of large-scale neuronal interactions. Nat Rev Neurosci 2012;13:121-34.
67. Vlcek P, Bares M, Novak T et al. Baseline difference in quantitative electroencephalography variables between responders and non-responders to low-frequency repetitive transcranial magnetic stimulation in depression. Front Psychiatry 2020;11:83.
68. Kaewpijit P, Fitzgerald PB, Hoy K et al. Baseline resting EEG measures differentiate rTMS treatment responders and non-responders. medRxiv 2023;2023. 11.16.23298445.
69. Stolz LA, Kohn JN, Smith SE et al. Predictive biomarkers of treatment response in major depressive disorder. Brain Sci 2023;13:1570.
70. Baeken C, Marinazzo D, Everaert H et al. The impact of accelerated HF-rTMS on the subgenual anterior cingulate cortex in refractory unipolar major depression: insights from 18FDG PET brain imaging. Brain Stimul 2015;8:808-15.
71. Langguth B, Wiegand R, Kharraz A et al. Pre-treatment anterior cingulate activity as a predictor of antidepressant response to repetitive transcranial magnetic stimulation (rTMS). Neuro Endocrinol Lett 2007;28:633-8.
72. Baeken C, De Raedt R, Van Hove C et al. HF-rTMS treatment in medication-resistant melancholic depression: results from 18FDG-PET brain imaging. CNS Spectr 2009;14:439-48.
73. Li CT, Wang SJ, Hirvonen J et al. Antidepressant mechanism of add-on repetitive transcranial magnetic stimulation in medication-resistant depression using cerebral glucose metabolism. J Affect Disord 2010;127:219-29.
74. Laufs H, Krakow K, Sterzer P et al. Electroencephalographic signatures of attentional and cognitive default modes in spontaneous brain activity fluctuations at rest. Proc Natl Acad Sci USA 2003;100:11053-8.
75. Sack AT, Paneva J, Küthe T et al. Target engagement and brain state dependence of transcranial magnetic stimulation: implications for clinical practice. Biol Psychiatry 2024;95:536-44.
76. Little S, Pogosyan A, Neal S et al. Adaptive deep brain stimulation in advanced Parkinson disease. Ann Neurol 2013;74:449-57.
77. Zrenner C, Ziemann U. Closed-loop brain stimulation. Biol Psychiatry 2024; 95:545-52.
78. Li K, Bichlmeier A, DuPont C et al. Fast depressive symptoms improvement in bipolar I disorder after Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT): a two-site feasibility and safety open-label trial. J Affect Disord 2024;365:359-63.
79. Geoly AD, Stimpson KH, Espil FM et al. Durability of clinical benefit with Stanford Neuromodulation Therapy (SNT) in treatment-resistant depression. Brain Stimul 2025;18:875-81.

DOI:10.1002/wps.70032

Representation and outcomes of individuals with major depression in routine care who are ineligible for randomized controlled trials: a nationwide register-based study

Aleksi Hamina[1,2], Justo Pinzón-Espinosa[3-6], Heidi Taipale[1,7,8], Johannes Schneider-Thoma[9,10], Joaquim Radua[11-13], Orestis Efthimiou[14,15], Narcís Cardoner[16-19], Christoph U. Correll[20-24], Paolo Fusar-Poli[25-28], Ellenor Mittendorfer-Rutz[29], Brenda W.J.H. Penninx[30], Henricus G. Ruhe[31,32], Antti Tanskanen[1,7], Christiaan H. Vinkers[3,33-35], Stefan Leucht[9,10], Eduard Vieta[18,36-38], Andrea Cipriani[39-41], Jari Tiihonen[1,7,42], Jurjen J. Luykx[3,33-35,43]

[1]Department of Forensic Psychiatry, University of Eastern Finland, Niuvanniemi Hospital, Kuopio, Finland; [2]Norwegian Centre for Addiction Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway; [3]Department of Psychiatry, Amsterdam University Medical Center, Amsterdam, The Netherlands; [4]Department of Clinical Psychiatry, School of Medicine, University of Panama, Panama City, Panama; [5]Center of Population Sciences for Health Empowerment, Florida State University, Tallahassee, FL, USA; [6]Instituto de Investigaciones Científicas y Servicios de Alta Tecnología, Panama City, Panama; [7]Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden; [8]School of Pharmacy, University of Eastern Finland, Kuopio, Finland; [9]Department of Psychiatry and Psychotherapy, School of Medicine and Health, Technical University of Munich, Munich, Germany; [10]German Center for Mental Health, partner site Munich-Augsburg, Germany; [11]Imaging of Mood- and Anxiety-Related Disorders Group, Institut d'Investigacions Biomèdiques August Pi i Sunyer, CIBERSAM, Barcelona, Spain; [12]Centre for Psychiatric Research and Education, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden; [13]Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; [14]Institute of Primary Health Care, University of Bern, Bern, Switzerland; [15]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland; [16]Psychiatry Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [17]Institut d'Investigació Biomèdica Sant Pau, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [18]Centro de Investigación Biomédica En Red en Salud Mental, Instituto de Salud Carlos III, Madrid, Spain; [19]Department of Psychiatry and Forensic Medicine, School of Medicine Bellaterra, Universitat Autònoma de Barcelona, Barcelona, Spain; [20]Department of Psychiatry, Zucker Hillside Hospital, Glen Oaks, NY, USA; [21]Department of Psychiatry and Molecular Medicine, Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA; [22]Center for Psychiatric Neuroscience, Feinstein Institute for Medical Research, New Hyde Park, NY, USA; [23]Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin Berlin, Berlin, Germany; [24]German Center for Mental Health, partner site Berlin, Germany; [25]Department of Brain and Behavioral Sciences, University of Pavia, Italy; [26]Early Psychosis: Interventions and Clinical-detection (EPIC) Lab, Department of Psychosis Studies, King's College London, London, UK; [27]Outreach and Support in South-London (OASIS) Service, South London and Maudlsey NHS Foundation Trust, London, UK; [28]Department of Psychiatry and Psychotherapy, University Hospital, Ludwig-Maximilian-University, Munich, Germany; [29]Division of Insurance Medicine, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden; [30]Department of Psychiatry and Amsterdam Public Health, Amsterdam UMC, Vrije Universiteit, Amsterdam, The Netherlands; [31]Department of Psychiatry, Radboudumc, Nijmegen, The Netherlands; [32]Donders Institute for Brain, Cognition and Behavior, Radboud University, Nijmegen, The Netherlands; [33]GGZ inGeest Mental Health Care, Amsterdam, The Netherlands; [34]Amsterdam Neuroscience and Public Health Research Institutes, Amsterdam, The Netherlands; [35]Department of Anatomy and Neurosciences, Amsterdam University Medical Center, Amsterdam, The Netherlands; [36]Departament de Medicina, Facultat de Medicina i Ciències de la Salut, Universitat de Barcelona, Barcelona, Spain; [37]Bipolar and Depressive Disorders Unit, Hospital Clinic de Barcelona, Barcelona, Spain; [38]Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain; [39]Department of Psychiatry, University of Oxford, Oxford, UK; [40]Oxford Precision Psychiatry Lab, NIHR Oxford Health Biomedical Research Centre, Oxford, UK; [41]Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, UK; [42]Neuroscience Center, University of Helsinki, Helsinki, Finland; [43]Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University Medical Center, Maastricht, The Netherlands

Randomized controlled trials (RCTs) are the foundation of current clinical treatment guidelines. However, they may not reflect real-world populations, due to strict eligibility criteria. We determined the proportion of individuals with major depressive disorder (MDD) receiving maintenance antidepressant treatment in routine care who would be ineligible for RCTs, and compared their outcomes with those who were eligible. Utilizing specialized health care registers in Finland (2004-2018) and Sweden (2006-2021), we identified adults diagnosed with non-psychotic MDD (ICD-10: F32, F33) who were stabilized on maintenance antidepressant monotherapy. Through multidisciplinary expert consensus on latest meta-analytic evidence, we derived a standardized list of RCT inclusion and exclusion criteria. These criteria were systematically applied to classify individuals as RCT-eligible or RCT-ineligible. We then used Cox proportional models to derive hazard ratios (HRs) of a composite primary outcome of hospitalization due to any psychiatric reason or suicide attempt, and all-cause mortality, during a 6-month follow-up. Secondary outcomes were treatment changes (i.e., discontinuation, switch or augmentation) and psychiatric sick leave ≥2 weeks. A total of 73,720 individuals in Finland and 135,092 in Sweden were included. More than one third of patients with MDD (33.5% in Finland and 35.3% in Sweden) were found to be ineligible for RCTs. The most common reasons for ineligibility were comorbidities (serious somatic disease, other psychiatric disorders, or substance use disorder). RCT-ineligible individuals had more than twice the risk of the composite primary outcome compared to eligible individuals (HR=2.44, 95% CI: 2.15-2.76 in Finland; HR=2.61, 95% CI: 2.37-2.87 in Sweden). Approximately one third of the composite primary outcome was attributable to RCT-ineligibility factors (32.5%, 95% CI: 27.9-37.1 for Finland; 36.2%, 95% CI: 32.6-39.8 for Sweden). Risk of treatment change was slightly but significantly higher in ineligible individuals. Findings were consistent in a wide range of sensitivity analyses. We conclude that more inclusive eligibility criteria for RCTs, and their integration with real-world data, are needed to improve the generalizability of antidepressant trial evidence and MDD clinical treatment guidelines.

Key words: RCT eligibility, major depressive disorder, maintenance treatment, hospitalization, mortality, generalizability, treatment guidelines

(World Psychiatry 2026;25:117–124)

Major depressive disorder (MDD) is a common, often recurrent, and potentially severe psychiatric disorder marked by emotional, cognitive and physical symptoms[1-3]. Affecting up to 20% of individuals over a lifetime[1,2,4], it is one of the most prevalent mental disorders globally, and a leading cause of disability. Its impact includes substantial psychosocial impairment, reduced quality of life[2,4], and a profound disruption of the subjective experience[5]. MDD frequently co-occurs with anxiety disorders, substance use disorders, and a range of chronic somatic diseases[6-8].

Maintenance treatment with antidepressants can effectively reduce the risk of early relapse and later recurrence rates compared to placebo[9-11], with a number needed to treat to prevent one recurrence of approximately 3.8[9,12]. A randomized controlled trial (RCT) showed relapse in nearly 50% of patients with MDD continuing antidepressant treatment versus 74% in those discontinuing treatment (odds ratio, OR=2.54, 95% CI: 1.37-4.84) across a 3-year maintenance period[13].

However, these findings are derived from RCTs, which often use strict inclusion and exclusion criteria for participants[14,15]. While necessary for internal validity, these criteria can limit the generalizability of results to routine clinical settings, particularly when they exclude individuals with characteristics that also modify treatment effects. For example, if substance use disorder is an exclusion criterion in RCTs and also reduces the effects of antidepressants, treatment efficacy estimated in RCTs is not applicable to individuals with that disorder, and real-world antidepressant effectiveness in routine clinical care may be overestimated.

We previously demonstrated that nearly 80% of individuals with schizophrenia would be excluded from RCTs assessing antipsychotic efficacy in relapse prevention[16,17]. Our real-world data indicated that the beneficial effects of antipsychotics compared to no treatment were greater in RCT-eligible individuals compared to ineligible ones[16]. Furthermore, a Swedish registry study found that approximately half of individuals initiating medication for attention-deficit/hyperactivity disorder (ADHD) would have been ineligible for RCT participation, and that ineligible individuals had higher risks of adverse outcomes[18]. These studies suggest that RCT findings may not be fully generalizable to routine clinical practice for several psychiatric disorders, and underscore the critical impact of trial representativeness on the validity and applicability of psychiatric treatment guidelines.

Similar concerns about representation and potential differences in outcomes between RCT-eligible and ineligible individuals have been raised for MDD treatment. A study on duloxetine and venlafaxine found larger effect sizes in RCTs compared to observational research[19]. A study utilizing primary care data indicated that antidepressants have small-to-moderate effectiveness in real-world settings, consistent with findings from RCTs[20]. However, as none of these studies examined representation and outcomes of all people with MDD seen in routine care, it remains unclear to what extent individuals with MDD in routine care are represented in RCTs.

To address this knowledge gap, we examined the impact of applying typical RCT exclusion criteria on the representation and clinical outcomes of individuals on antidepressant maintenance treatment for MDD, using data from two nationwide real-world cohorts.

METHODS

Our study protocol was registered prior to data analysis[21]. This paper adheres to RECORD-PE reporting guidelines[22].

Study population

The Finnish cohort was gathered from Finnish inpatient care, specialized outpatient care, sickness absence, and disability pension registers between 2004 and 2017, with follow-up until the end of 2018. We utilized the Finnish Care Register for Health Care, which contains data on all inpatient and specialized outpatient care, as well as the registers maintained by the Social Insurance Institution and the Centre for Pensions, which provide information on disability-related benefits, including sickness allowances and disability pensions. These data were linked with other nationwide registries, including the Prescription Register, which contains information on all reimbursed drug dispensations from Finnish community pharmacies.

The Swedish cohort was gathered from the National Patient Register (inpatient, specialized outpatient care) and the MiDAS (MicroData for Analysis of the Social Insurance System) register (sickness absence, disability pension) between 2006 and 2020, with follow-up until the end of 2021. In addition to the patient register and prescribed drug register data, we also used data on disability pensions (from MiDAS).

Cohort inclusion required a primary diagnosis of single-episode or recurrent MDD (ICD-10: F32 or F33), excluding psychotic depression (F32.3 and F33.3). All individuals were required to be between 18 and 65 years old, and without a diagnosis of schizophrenia-spectrum disorder (F20-F29), bipolar disorder (F30-F31) and/or dementias (F00-F09, G30) prior to cohort entry.

Data were extracted by register maintenance personnel using personal identity numbers, and were anonymized before sharing with researchers. Approvals for the research project were obtained from the Regional Ethics Board of Stockholm (2007/762-31 and 2021-06441-02), and relevant authorities at FinData (THL/5279/14.06.00/2023), the Finnish National Institute for Health and Welfare (THL/635/5.05.00/2019), Social Insurance Institution of Finland (31/522/2019), Finnish Centre for Pensions (19023), and Statistics Finland (TK-53-569-19).

According to regulations in Sweden and Finland, obtaining informed consent from participants is not required for register-based studies when the participants are not contacted.

RCT eligibility

We gathered typical inclusion and exclusion criteria from published RCTs on the efficacy of antidepressants for the maintenance treatment of adults with MDD, and finalized the list through multiple consensus exercises (in meetings and writing) (see also supplementary information).

Inclusion criteria were: a) a primary diagnosis of single episode or recurrent MDD, except psychotic depressive disorder, within the previous six months; b) no use of antidepressants, mood stabilizers and/or antipsychotics in the six months before antidepressant initiation; and c) continuous use of an antidepressant monotherapy for at least 15 weeks (105 days). Continuous antidepressant use was established by the validated PRE2DUP method from dispensed prescription drugs[23].

Exclusion criteria were: a) any substance use disorder diagnosed at any time before start of follow-up, except tobacco dependence; b) any diagnosis of intellectual disability at any time before start of follow-up; c) any diagnosis of other psychiatric disorder before start of follow-up (including obsessive-compulsive disorder, post-traumatic stress disorder, eating disorders, neurodevelopmental disorders, and personality disorders); d) use of non-pharmacological somatic therapies (i.e., electroconvulsive therapy or other neuromodulation interventions) reported ever before start of follow-up;

e) being pregnant or breastfeeding in the year before cohort entry; f) any suicide attempt recorded ever before start of follow-up; and g) any comorbid somatic disease.

For somatic disease, we applied both a broad and a narrow definition. The broad definition was "any comorbid somatic disease, including seizures and urinary retention, during two years before start of follow-up". The narrow definition excluded any neurological disease except migraine; head injuries; cardiac disorders (ischaemic heart disease, other heart diseases); cerebrovascular diseases; diseases of arteries, arterioles and capillaries; major hematopoietic disorders, neoplasms and hypothyroidism in the two years before start of follow-up; and any lifetime history of cardiac arrythmias, renal failure, hepatic disorders, peptic ulcer, glaucoma, urinary retention, and seizures (see also supplementary information).

Outcomes and follow-up

We defined the primary outcome as the composite of hospitalization due to any psychiatric reason or suicide attempt, and all-cause mortality. We further considered each component as a separate outcome. The first secondary outcome was ≥2 weeks of sick leave due to psychiatric reasons, analyzed among those individuals who were not pensioned or already on sick leave upon cohort entry. The other secondary outcome was therapeutic regimen change, which we defined as discontinuation of antidepressant use, switch to another antidepressant agent, or therapy augmentation with another antidepressant, one or more antipsychotics, or one or more mood stabilizers.

The duration of follow-up was 6 months in the main analysis, which, in addition to the stabilization phase prior to cohort entry, corresponds to the typical duration of antidepressant RCTs[24]. Time zero was set to the first day of the maintenance treatment, i.e., the day when the stabilization phase ended. Follow-up ended at treatment regimen change (i.e. discontinuation of antidepressants, switch or augmentation), death, or end of the 6-month follow-up, whichever came first.

Statistical analyses

All analyses were conducted using R v4.4.1. First, we computed several descriptive statistical measures, applying the above RCT inclusion and exclusion criteria and dividing the study population into two groups: a) individuals eligible for standard RCTs on maintenance treatment with antidepressants, i.e., those meeting RCT inclusion criteria and none of the exclusion criteria; and b) individuals who would be ineligible for standard RCTs, i.e., those meeting RCT inclusion criteria but also ≥1 exclusion criteria. We then computed the percentages of individuals in our study population in both countries belonging to the RCT-eligible and RCT-ineligible groups. We further analyzed the proportion and the effects of each exclusion criterion on RCT eligibility separately, i.e. comparing those who would be ineligible due to that criterion to individuals who did not meet that specific RCT exclusion criterion.

Second, to compare the risks of the primary outcome and secondary outcomes between eligible and ineligible individuals, we conducted Cox regression analyses. We used RCT eligibility as the single exposure (with eligible individuals as the reference), deriving hazard ratios (HRs) with 95% confidence intervals (CIs). Additionally, we investigated the effects of each exclusion criterion on the risk of the primary outcome by comparing individuals with a given exclusion criterion (irrespective of other exclusion criteria) to eligible individuals. For the main analysis, we used the narrow definition of serious somatic disease.

Third, we estimated the proportion of cases for each outcome attributable to the ineligibility factors, by applying Levin's formula, with ineligible and eligible risks derived from the survival curves and CIs estimated via Monte Carlo simulation[25].

Finally, we ran several sensitivity analyses to corroborate the robustness of our findings. We first extended the outcome follow-up assessment to 9 months and repeated the analyses. In a second analysis, aiming to exclude individuals using mirtazapine for possible other indications than MDD (primarily sleep disorders), we repeated the main analysis only in those who used mirtazapine at a dose of >15 mg/day during their stabilization period, and then limiting to those who used a selective serotonin uptake inhibitor (SSRI). In a third sensitivity analysis, we applied the broad definition of serious somatic disease to the main analysis. In the last sensitivity analysis, follow-up was not censored to antidepressant treatment change, but only at death or end of follow-up.

RESULTS

Characteristics of RCT-eligible and RCT-ineligible populations

The Finnish cohort included 73,720 individuals with MDD (mean age: 40.2±12.5 years; 67.9% female). The Swedish cohort included 135,092 individuals with MDD (mean age: 38.5±12.8 years, 63.4% female). The age and sex distributions for RCT-eligible and RCT-ineligible individuals were similar (see Table 1).

In our main analysis, at least one exclusion criterion was met by 33.5% (N=24,677) and 35.3% (N=47,695) of individuals in the Finnish and Swedish study cohorts, respectively. These individuals were ineligible to participate in a standard RCT on maintenance treatment for MDD. When applying the broad instead of the narrow definition of serious somatic disease, these percentages increased to 52.2% (N=38,505) in the Finnish cohort and 56.7% (N=76,563) in the Swedish cohort.

The most frequently used antidepressants in the stabilization period in the Finnish cohort were SSRIs, although their use was more frequent among RCT-eligible (72.6%) than RCT-ineligible (67.5%) individuals. Escitalopram was the most frequent agent in both groups (RCT-eligible: 34.1%; RCT-ineligible: 29.1%). Similarly, in the Swedish cohort, SSRIs were the most frequently used antidepressants, with more frequent use among the RCT-eligible (82.2%) compared to the RCT-ineligible (74.3%) individuals. The most fre-

Table 1 Characteristics of RCT-ineligible and eligible individuals in the Finnish and Swedish cohorts

	Finnish cohort		Swedish cohort	
	Ineligible (N=24,677)	**Eligible (N=49,043)**	**Ineligible (N=47,695)**	**Eligible (N=87,397)**
Women, N (%)	16,318 (66.1)	33,723 (68.8)	30,377 (63.7)	55,306 (63.3)
Men, N (%)	8,359 (33.9)	15,320 (31.2)	17,318 (36.3)	32,091 (36.7)
Age, years (mean±SD)	40.9±12.9	39.9±12.3	38.1±13.1	38.7±12.6
Age, years, N (%)				
<25	3,446 (14.0)	7,053 (14.4)	8,554 (17.9)	14,418 (16.5)
25-34	5,212 (21.1)	10,673 (21.8)	13,129 (27.5)	21,238 (24.3)
35-44	5,184 (21.0)	12,022 (24.5)	10,245 (21.5)	21,960 (25.1)
45-54	6,214 (25.2)	12,042 (24.6)	8,604 (18.0)	17,769 (20.3)
≥55	4,621 (18.7)	7253 (14.8)	7,163 (15.0)	12,012 (13.7)

RCT – randomized controlled trials

quent agent in both groups was sertraline (RCT-eligible: 36.3%, RCT-ineligible: 34.5%) (see also supplementary information).

Reasons for RCT ineligibility

Reasons for RCT ineligibility were similar in the two cohorts. The most common reason was serious somatic disease (broad definition: 42.6% in Finland and 45.1% in Sweden; for the narrow definition these percentages were 18.9% and 16.0%, respectively). Other reasons for RCT ineligibility were comorbid psychiatric disorder diagnoses (11.9% in Finland; 15.0% in Sweden) and substance use disorders (5.6% in Finland; 7.6% in Sweden) (see Table 2).

Across the two countries, very similar percentages of individuals met one exclusion criterion (26.2% in Finland; 26.4% in Sweden) and two exclusion criteria (6.0% in Finland; 6.9% in Sweden). These percentages were also similar in Finland and Sweden when applying the broad instead of the narrow definition of serious somatic disease (see supplementary information).

Table 2 Prevalence of RCT exclusion criteria in the Finnish and Swedish cohorts

	Finnish cohort (N=73,720)	**Swedish cohort (N=135,092)**
Serious somatic disease, narrow definition	18.9%	16.0%
Serious somatic disease, broad definition	42.6%	45.1%
Other psychiatric disorders	11.9%	15.0%
Substance use disorders	5.6%	7.6%
Pregnancy or breastfeeding	3.2%	3.9%
Prior suicide attempt	2.8%	3.6%
Intellectual disability	0.1%	0.3%
Prior ECT/neuromodulation	0.1%	0.2%

RCT – randomized controlled trials, ECT – electroconvulsive therapy

Risks of primary and secondary outcomes in RCT-eligible and ineligible individuals

RCT-ineligible individuals were at higher risk of the composite primary outcome compared to RCT-eligible ones during the 6-month follow-up (Finland: HR=2.44, 95% CI: 2.15-2.76; Sweden: HR=2.61, 95% CI: 2.37-2.87; both p<0.001) (see Table 3 and Figures 1-2).

The risks of all components of the primary outcome were higher among the RCT-ineligible than the RCT-eligible patients (psychiatric hospitalization: HR=2.28, 95% CI: 1.97-2.63 in Finland, HR=2.76, 95% CI: 2.48-3.07 in Sweden; suicide attempt or death: HR=3.11, 95% CI: 2.37-4.07 in Finland, HR=2.04, 95% CI: 1.69-2.46 in Sweden; all-cause mortality: HR=2.74, 95% CI: 1.58-4.75 in Finland, HR=2.92, 95% CI: 1.75-4.89 in Sweden; all p<0.001) (see Table 3).

Concerning secondary outcomes, being RCT-ineligible was associated with a slightly but significantly higher risk of all-cause antidepressant treatment change (Finland: HR=1.03, 95% CI: 1.01-1.05, p=0.019; Sweden: HR=1.13, 95% CI: 1.11-1.15, p<0.001). As for sick leave, only in Sweden RCT ineligibility was associated with a slightly but significantly increased risk (HR=1.20, 95% CI: 1.11-1.29, p<0.001), while no evidence of an association was found in Finland (HR=0.94, 95% CI: 0.87-1.02, p<0.2) (see Table 3).

Primary outcome among individuals ineligible for specific criteria

When comparing RCT-ineligible individuals grouped according to each specific exclusion criterion they met vs. those who did not meet that specific criterion, the largest risk for the composite primary outcome was found for those with a history of suicide attempt (Finland: HR=5.76, 95% CI: 4.79-6.91; Sweden: HR=5.20, 95% CI: 4.56-5.93; both p<0.001) (see Table 4).

We found higher risks of the primary outcome for individuals with substance use disorders compared to eligible patients, with

Table 3 Risk of the primary and secondary outcomes for RCT-ineligible vs. eligible individuals in the Finnish and Swedish cohorts during the 6-month follow-up

	Finnish cohort			Swedish cohort		
	Events in ineligible individuals (%)	Events in eligible individuals (%)	HR (95% CI)	Events in ineligible individuals (%)	Events in eligible individuals (%)	HR (95% CI)
Composite primary outcome	547 (2.2)	452 (0.9)	2.44 (2.15-2.76)	1,003 (2.1)	728 (0.8)	2.61 (2.37-2.87)
Psychiatric hospitalization	402 (1.6)	355 (0.7)	2.28 (1.97-2.63)	815 (1.7)	559 (0.6)	2.76 (2.48-3.07)
Suicide attempt or death	133 (0.5)	86 (0.2)	3.11 (2.37-4.07)	224 (0.5)	208 (0.2)	2.04 (1.69-2.46)
All-cause mortality	30 (0.1)	22 (0.0)	2.74 (1.58-4.75)	37 (0.1)	24 (0.0)	2.92 (1.75-4.89)
Change in AD therapy	11,943 (48.4)	23,281 (47.5)	1.03 (1.01-1.05)	20,701 (43.4)	34,711 (39.7)	1.13 (1.11-1.15)
Sick leave	833 (5.3)	1,944 (5.8)	0.94 (0.87-1.02)	1,206 (4.3)	1,980 (3.7)	1.20 (1.11-1.29)

RCT – randomized controlled trials, HR – hazard ratio, AD – antidepressant

HRs being similar in the two countries (Finland: HR=5.05, 95% CI: 4.34-5.87; Sweden: HR=5.13, 95% CI: 4.62-5.70; both p<0.001). History of ECT or other neuromodulation treatments was also associated with a higher risk of the primary outcome compared to eligible individuals in Sweden (HR=5.07, 95% CI: 3.30-7.80), and also in Finland, albeit with increased uncertainty (HR=3.66, 95% CI: 0.91-14.70) (see Table 4).

Proportion of outcomes attributable to RCT ineligibility

RCT ineligibility accounted for 32.5% (95% CI: 27.9-37.1) of cases of the composite primary outcome in Finland, and 36.2% of cases (95% CI: 32.6-39.8) in Sweden. The proportions of cases for each component of the primary outcome attributable to RCT ineligibility were the following: for psychiatric hospitalization, 30.0% (95% CI: 24.6-35.4) in Finland and 38.3% (95% CI: 34.3-42.2) in Sweden; for suicide attempt or death, 41.4% (95% CI: 31.4-50.7) in Finland and 26.9% (95% CI: 19.6-34.0) in Sweden; for all-cause mortality, 36.8% (95% CI: 16.3-55.7) in Finland and 40.4% (95% CI: 20.9-57.9) in Sweden (see Table 5).

RCT-ineligibility factors explained only a small fraction of secondary outcomes. Changes in antidepressant therapy were attributable to ineligibility in just 1.0% (95% CI: 0.3-1.7) of cases in Finland and 4.4% (95% CI: 3.7-5.0) in Sweden. The corresponding figures for psychiatric sick leave were 0% (95% CI: 0-0.6) in Finland and 6.4% (95% CI: 3.7-9.2) in Sweden (see Table 5).

Sensitivity analyses

All results in both countries were similar for the 9-month follow-up period (see supplementary information). When limiting the analysis to individuals who used mirtazapine at doses >15 mg/day during their stabilization period, the risk of the primary outcome among RCT-ineligible persons was higher compared to eligible per-

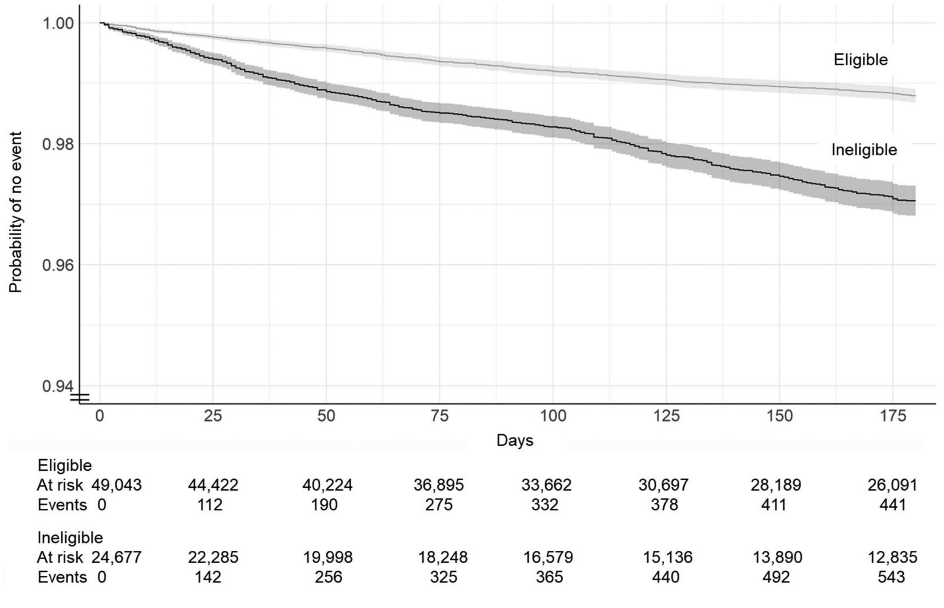


Figure 1 Kaplan-Meier curves of the composite primary outcome (hospitalization due to any psychiatric reason or suicide attempt; all-cause mortality) for RCT-ineligible and eligible individuals in the Finnish cohort. RCT – randomized controlled trials.

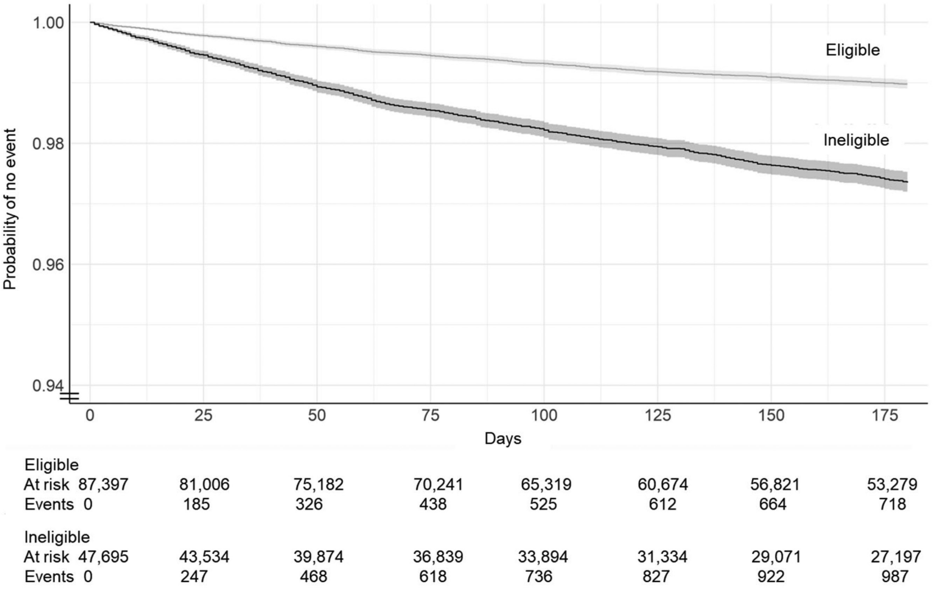


Figure 2 Kaplan-Meier curves of the composite primary outcome (hospitalization due to any psychiatric reason or suicide attempt; all-cause mortality) for RCT-ineligible and eligible individuals in the Swedish cohort. RCT – randomized controlled trials.

sons (Finland: HR=3.22, 95% CI: 2.17-4.77; Sweden: HR=3.55, 95% CI: 2.55-4.93; both p<0.001). This also held for the analysis limited to those on SSRIs, but the strength of the association was lower (Finland: HR=2.27, 95% CI: 1.95-2.64, Sweden: HR=2.21, 95% CI: 1.98-2.48, both p<0.001) (see supplementary information).

After applying the broad instead of the narrow somatic disease definition, the risk of the composite primary outcome was still higher among RCT-ineligible individuals (Finland: HR=2.06, 95% CI: 1.80-2.36; Sweden: HR=2.02, 95% CI: 1.82-2.24; both p<0.001). RCT ineligibility was associated with increased risk of sick leave in Sweden (HR=1.29, 95% CI: 1.20-1.38, p<0.0001), but not in Finland (HR=1.02, 95% CI: 0.94-1.10, p=0.6). In the sensitivity analysis not censoring for follow-up to antidepressant treatment change, the risks of the outcomes were similar to the main results (see supplementary information).

DISCUSSION

This study applied RCT inclusion and exclusion criteria for antidepressant maintenance treatment to over 200,000 adults diagnosed with MDD in nationwide Finnish and Swedish health care registers. We provide the first quantification of the proportion of individuals with MDD in routine care who would be excluded from participating in an antidepressant maintenance treatment RCT. Under a narrow definition of serious somatic disease, more than one third of these individuals were deemed ineligible to participate in an RCT. When broadening the definition of serious somatic disease, over half of the individuals with MDD in both cohorts would have been ineligible for RCT participation.

Serious somatic disease was the most common reason for exclusion, affecting 42.6% of individuals with MDD in Finland and 45.1%

Table 4 Risk of the composite primary outcome in RCT-ineligible individuals grouped according to each specific exclusion criterion they met compared to individuals who did not meet that criterion

	Finnish cohort		Swedish cohort	
	N (%)	HR (95% CI)	N (%)	HR (95% CI)
History of suicide attempt	2,050 (2.8)	5.76 (4.79-6.91)	4,863 (3.6)	5.20 (4.56-5.93)
Substance use disorder	4,073 (5.5)	5.05 (4.34-5.87)	10,270 (7.6)	5.13 (4.62-5.70)
History of ECT or other neuromodulation	40 (0.1)	3.66 (0.91-14.70)	336 (0.2)	5.07 (3.30-7.80)
Intellectual disability	79 (0.1)	2.88 (0.93-8.94)	417 (0.3)	2.33 (1.32-4.10)
Other psychiatric disorders	8,651 (11.7)	2.09 (1.80-2.43)	20,286 (15.0)	2.18 (1.96-2.42)
Serious somatic disease, narrow definition	13,814 (18.7)	1.47 (1.28-1.70)	21,653 (16.0)	1.28 (1.14-1.44)
Serious somatic disease, broad definition	31,208 (42.3)	1.33 (1.17-1.50)	60,936 (45.1)	1.13 (1.03-1.24)
Pregnancy or breastfeeding	2,375 (3.2)	0.89 (0.62-1.28)	5.301 (3.9)	0.74 (0.56-0.98)

RCT – randomized controlled trials, HR – hazard ratio, ECT – electroconvulsive therapy

Table 5 Proportion of cases for each outcome attributable to RCT-ineligibility criteria

	Finnish cohort	Swedish cohort
Composite primary outcome	32.5% (95% CI: 27.9-37.1)	36.2% (95% CI: 32.6-39.8)
Psychiatric hospitalization	30.0% (95% CI: 24.6-35.4)	38.3% (95% CI: 34.3-42.2)
Suicide attempt or death	41.4% (95% CI: 31.4-50.7)	26.9% (95% CI: 19.6-34.0)
All-cause mortality	36.8 (95% CI:16.3-55.7)	40.4% (95% CI: 20.9-57.9)
Change in AD therapy	1.0% (95% CI: 0.3-1.7)	4.4% (95% CI: 3.7-5.0)
Sick leave	0% (95% CI: 0-0.6)	6.4% (95% CI: 3.7-9.2)

RCT – randomized controlled trials, AD – antidepressant

in Sweden, followed by psychiatric comorbidities (Finland: 11.9%; Sweden: 15.0%) and substance use disorders (5.6% and 7.6%, respectively).

Moreover, RCT ineligibility was associated with worse results across a range of clinically relevant outcomes. Overall, approximately one third of our primary outcome, consisting of a composite of hospitalization due to any psychiatric reason or suicide attempt, and all-cause mortality, was found to be attributable to RCT-ineligibility factors.

Our results reinforce concerns about a lack of translatability of the results from clinical trials in psychiatry to real-world care settings and individuals. The findings align with evidence from fields such as oncology[26-30] and internal medicine[31], where restrictive eligibility criteria in RCTs also limit generalizability. This creates a critical representational gap, as particularly RCT results are translated into clinical guidelines[32-35]. Our findings emphasize the need for broader inclusion criteria in future trials and for complementing RCT evidence with robust real-world data, to ensure that clinical treatment guidelines are both evidence-based and context-appropriate for the realities of everyday psychiatric care.

Applying current exclusion criteria (e.g., histories of somatic disease, suicidality, or substance use disorders) may be particularly problematic as these conditions are highly prevalent among individuals with MDD, and often exacerbate the severity of depressive episodes[36], and attenuate antidepressant effectiveness in the real world[37-44]. We found a five-fold increased risk of hospitalization or mortality among individuals with a history of suicide attempts. Accordingly, excluding individuals with complex or severe presentations of MDD from maintenance treatment RCTs creates a critical evidence gap on the long-term maintenance effectiveness of antidepressants, particularly in individuals with multimorbidity[45]. This limitation not only restricts the generalizability and external validity of RCT findings, but may also contribute to health inequities, by failing to address the treatment needs of those most at risk of poorer outcomes.

Importantly, our results do not undermine the well-established efficacy of antidepressants in treating MDD, particularly in maintenance therapy[11]. The worse outcomes that we observed in RCT-ineligible individuals should not be misconstrued as evidence that antidepressants are ineffective in this population. Rather, these individuals may present with a greater burden of illness, higher baseline risk, and complex biopsychosocial factors that inherently contribute to poorer clinical treatment outcomes/trajectories. Our findings highlight the limitations of current trial designs in capturing the full spectrum of individuals with MDD encountered in routine clinical practice.

Strengths of this study include the comprehensive, nationwide database from large and well-curated national registers. Our use of the PRE2DUP method also strengthens our medication-exposure accuracy[23]. Sensitivity analyses (e.g., extended follow-up to 9 months, limiting the analysis to individuals who used mirtazapine at doses >15 mg/day) confirmed the consistency of the findings.

However, some limitations must be acknowledged. First, since register data rely on coded diagnoses, they may not fully capture suicidal ideation or attempts nor substance use disorders at treatment initiation, potentially leading to an underestimation of RCT-ineligible individuals[46]. Second, although 6-9 months of follow-up aligns with common RCT durations, this duration may not reflect longer-term trajectories of antidepressant effectiveness or relapse patterns in the real-world. Third, because RCT inclusion/exclusion criteria vary across studies and since detailed study protocols listing all specific exclusion criteria were unavailable, our set of criteria may not represent the inclusion/exclusion criteria of all RCTs, and differences in criteria might yield slightly variable estimates of ineligible individuals. Fourth, while our results contribute to the broader discourse on the efficacy-effectiveness gap – the disconnect between RCT findings and real-world clinical impact[47] – this gap is likely not solely due to trial exclusion criteria. For example, other factors such as treatment adherence, frequency of clinical monitoring, and variability in treatment practices may also play important roles. Finally, results from Finland and Sweden may not generalize to other health care settings or populations.

In conclusion, approximately one third to half of individuals with MDD in routine care are excluded from participating in antidepressant maintenance treatment RCTs, and these individuals are at higher risk of unfavorable outcomes than eligible individuals. Our findings underscore the need for increased representation in maintenance RCTs to better align with real-world populations, so that evidence-based treatment and clinical guidelines can better serve a more representative, larger population of individuals with MDD seen in routine care.

Expanding eligibility criteria, incorporating real-world outcome measures, including patient-reported outcomes, and extending follow-up periods all carry the potential to enhance the translational value of RCT findings, making them more reflective of routine clinical practice[48,49].

ACKNOWLEDGEMENTS

Finnish data collected for this study are proprietary to the Social Insurance Institution of Finland, National Institute for Health and Welfare, Finnish Centre of Pensions and Welfare, and Statistics Finland. For the Swedish cohort, we used data from the REWHARD consortium, supported by the Swedish Research Council (grant no. 2021-

00154). O. Efthimiou was supported by the Swiss National Science Foundation (grant no. 10002053). A. Hamina and J. Pinzón-Espinosa are joint first authors of this paper. Supplementary information on this study is available at https://osf.io/b8w25.

REFERENCES

1. Barnett R. Depression. Lancet 2019;393:2113.
2. Malhi GS, Mann JJ. Depression. Lancet 2018;392:2299-312.
3. Belzung C, Willner P, Philippot P. Depression: from psychopathology to pathophysiology. Curr Opin Neurobiol 2015;30:24-30.
4. Brody D, Pratt LA, Hughes JP. Prevalence of depression among adults aged 20 and over: United States, 2013-2016. NCHS Data Brief 2018;303:1-8.
5. Fusar-Poli P, Estradé A, Stanghellini G et al. The lived experience of depression: a bottom-up review co-written by experts by experience and academics. World Psychiatry 2023;22:352-65.
6. Berk M, Köhler-Forsberg O, Turner M et al. Comorbidity between major depressive disorder and physical diseases: a comprehensive review of epidemiology, mechanisms and management. World Psychiatry 2023;22:366-87.
7. Gold SM, Köhler-Forsberg O, Moss-Morris R et al. Comorbid depression in medical diseases. Nat Rev Dis Primer 2020;6:1-22.
8. Moussavi S, Chatterji S, Verdes E et al. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet 2007;370:851-8.
9. Sim K, Lau WK, Sim J et al. Prevention of relapse and recurrence in adults with major depressive disorder: systematic review and meta-analyses of controlled trials. Int J Neuropsychopharmacol 2015;19:pyv076.
10. Glue P, Donovan MR, Kolluri S et al. Meta-analysis of relapse prevention antidepressant trials in depressive disorders. Aust N Z J Psychiatry 2010;44:697-705.
11. Cipriani A, Furukawa TA, Salanti G et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet 2018;391:1357-66.
12. Hansen R, Gaynes B, Thieda P et al. Meta-analysis of major depressive disorder relapse and recurrence with second-generation antidepressants. Psychiatr Serv 2008;59:1121-30.
13. DeRubeis RJ, Zajecka J, Shelton RC et al. Prevention of recurrence after recovery from a major depressive episode with antidepressant medication alone or in combination with cognitive behavioral therapy. JAMA Psychiatry 2020;77:237-45.
14. Zimmerman M, Clark HL, Multach MD et al. Have treatment studies of depression become even less generalizable? A review of the inclusion and exclusion criteria used in placebo-controlled antidepressant efficacy trials published during the past 20 years. Mayo Clin Proc 2015;90:1180-6.
15. Zimmerman M, Clark HL, Multach MD et al. Inclusion/exclusion criteria in placebo-controlled studies of vortioxetine: comparison to other antidepressants and implications for product labeling. J Affect Disord 2016;190:357-61.
16. Efthimiou O, Taipale H, Radua J et al. Efficacy and effectiveness of antipsychotics in schizophrenia: network meta-analyses combining evidence from randomised controlled trials and real-world data. Lancet Psychiatry 2024;11:102-11.
17. Taipale H, Schneider-Thoma J, Pinzón-Espinosa J et al. Representation and outcomes of individuals with schizophrenia seen in everyday practice who are ineligible for randomized clinical trials. JAMA Psychiatry 2022;79:210-8.
18. Garcia-Argibay M, Chang Z, Brikell I et al. Evaluating ADHD medication trial representativeness: a Swedish population-based study comparing hypothetically trial-eligible and trial-ineligible individuals. Lancet Psychiatry 2025;12:131-9.
19. Schneider C, Breilmann J, Reuter B et al. Systematic evaluation of the 'efficacy-effectiveness gap' in the treatment of depression with venlafaxine and duloxetine. Acta Psychiatr Scand 2021;144:113-24.
20. De Crescenzo F, De Giorgi R, Garriga C et al. Real-world effects of antidepressants for depressive disorder in primary care: population-based cohort study. Br J Psychiatry 2024; doi: 10.1192/bjp.2024.194.
21. Taipale H, Hamina A, Pinzón-Espinosa J et al. Representation and outcomes of people with major depressive disorder seen in everyday clinical practice who are ineligible for randomized clinical trials. OSF Registries, https://osf.io/h6z93.
22. Langan SM, Schmidt SA, Wing K et al. The reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE). BMJ 2018;363:k3532.
23. Tanskanen A, Taipale H, Koponen M et al. From prescription drug purchases to drug use periods – A second generation method (PRE2DUP). BMC Med Inform Decis Mak 2015;15:21.
24. Kishi T, Ikuta T, Sakuma K et al. Antidepressants for the treatment of adults with major depressive disorder in the maintenance phase: a systematic review and network meta-analysis. Mol Psychiatry 2022;28:402-9.
25. Dragioti E, Radua J, Solmi M et al. Global population attributable fraction of potentially modifiable risk factors for mental disorders: a meta-umbrella systematic review. Mol Psychiatry 2022;27:3510-9.
26. Szlezinger K, Pogoda K, Jagiełło-Gruszfeld A et al. Eligibility criteria in clinical trials in breast cancer: a cohort study. BMC Med 2023;21:240.
27. Duma N, Kothadia SM, Azam TU et al. Characterization of comorbidities limiting the recruitment of patients in early phase clinical trials. Oncologist 2018;24:96-102.
28. Gerber DE, Laccetti AL, Xuan L et al. Impact of prior cancer on eligibility for lung cancer clinical trials. J Clin Oncol 2014;32(Suppl. 15):6566.
29. Rodríguez-Lobato LG, Tovar N, de Daniel A et al. Outcomes of patients with newly diagnosed transplant-ineligible multiple myeloma according to clinical trials enrollment: experience of a single institution. Cancers 2023;15:5261.
30. Delaye M, Rousseau A, Try M et al. Inclusion of patients with chronic kidney disease in randomized phase 3 clinical trials in patients with prostate, breast, lung, and colorectal cancer. Cancer Med 2022;12:3172-5.
31. He J, Morales DR, Guthrie B. Exclusion rates in randomized controlled trials of treatments for physical conditions: a systematic review. Trials 2020;21:228.
32. National Institute for Health and Care Excellence. Preventing relapse. Depression in adults: treatment and management. London: National Institute for Health and Care Excellence, 2022.
33. Department of Veteran Affairs, Department of Defense. The management of major depressive disorder, 4th ed. Washington: U.S. Government Printing Office, 2022.
34. Ministerio de Sanidad. Guía de práctica clínica sobre el manejo de la depresión en el adulto. Madrid: Ministerio de Sanidad, 2023.
35. Lam RW, Kennedy SH, Adams C et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2023 update on clinical guidelines for management of major depressive disorder in adults. Can J Psychiatry 2024;69:641-87.
36. Fiest KM, Currie SR, Williams JVA et al. Chronic conditions and major depression in community-dwelling older adults. J Affect Disord 2011;131:172-8.
37. Dong M, Zeng LN, Lu L et al. Prevalence of suicide attempt in individuals with major depressive disorder: a meta-analysis of observational surveys. Psychol Med 2018;49:1691-704.
38. Cai H, Xie XM, Zhang Q et al. Prevalence of suicidality in major depressive disorder: a systematic review and meta-analysis of comparative studies. Front Psychiatry 2021;12:690130.
39. Sokero TP, Melartin T, Rytsälä H et al. Suicidal ideation and attempts among psychiatric patients with major depressive disorder. J Clin Psychiatry 2003;64:1094-100.
40. Cai H, Jin Y, Liu S et al. Prevalence of suicidal ideation and planning in patients with major depressive disorder: a meta-analysis of observation studies. J Affect Disord 2021;293:148-58.
41. Tang VM, Yu D, Weissman CR et al. Treatment outcomes in major depressive disorder in patients with comorbid alcohol use disorder: a STAR*D analysis. J Affect Disord 2023;339:691-7.
42. Krishnan KRR. Comorbidity and depression treatment. Biol Psychiatry 2003;53:701-6.
43. Davis LL, Wisniewski SR, Howland RH et al. Does comorbid substance use disorder impair recovery from major depression with SSRI treatment? An analysis of the STAR*D level one treatment outcomes. Drug Alcohol Depend 2010;107:161-70.
44. Iosifescu DV, Bankier B, Fava M. Impact of medical comorbid disease on antidepressant treatment of major depressive disorder. Curr Psychiatry Rep 2004;6:193-201.
45. Chan JKN, Solmi M, Correll CU. All-cause and cause-specific mortality in people with depression: large-scale systematic review and meta-analysis of relative risk and aggravating or attenuating factors, including antidepressant treatment. World Psychiatry 2025;24:404-21.
46. Taipale H, Tiihonen J. Registry-based studies: what they can tell us, and what they cannot. Eur Neuropsychopharmacol 2021;45:35-7.
47. Nordon C, Karcher H, Groenwold RHH et al. The "efficacy-effectiveness gap": historical background and current conceptualization. Value Health 2016;19:75-81.
48. Borentain S, Nash AI, Dayal R et al. Patient-reported outcomes in major depressive disorder with suicidal ideation: a real-world data analysis using PatientsLikeMe platform. BMC Psychiatry 2020;20:384.
49. Haller H, Anheyer D, Cramer H et al. Complementary therapies for clinical depression: an overview of systematic reviews. BMJ Open 2019;9:e028527.

DOI:10.1002/wps.70013

All-cause and cause-specific mortality risk in individuals with eating disorders: systematic review and meta-analysis of relative risk and aggravating or attenuating factors

Seana N. Semchishen[1], Mikkel Højlund[2-4], Danielle Lemaire[1], Ishika Obeegadoo[1], Nicole G. Hammond[1], Brianna Frangione[1], Hanna Ogawa[5], Rebecca Sunderland[6], Aditya Singh[7], Gamal Wafy[1], Mattia Campana[8], James Sakeah[1], Karine Brousseau[1], Christoph U. Correll[9-14], Elias Wagner[15,16], Ian Colman[1], Marco Solmi[9,17-19]

[1]School of Epidemiology and Public Health, University of Ottawa, Ottawa, ON, Canada; [2]Department of Psychiatry Aabenraa, Mental Health Services in the Region of Southern Denmark, Aabenraa, Denmark; [3]Clinical Pharmacology, Pharmacy, and Environmental Medicine, Department of Public Health, University of Southern Denmark, Odense, Denmark; [4]Child and Adolescent Mental Health Centre, Mental Health Services Capital Region of Denmark, Copenhagen, Denmark; [5]Department of Psychology, Simon Fraser University, Burnaby, BC, Canada; [6]School of Psychology, University of Ottawa, Ottawa, ON, Canada; [7]Faculty of Science, University of Ottawa, Ottawa, ON, Canada; [8]Department of General Psychiatry 2, LVR Hospital, H. Heine University, Düsseldorf, Germany; [9]Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin Berlin, Berlin, Germany; [10]German Center for Mental Health (DZPG), partner site Berlin, Berlin, Germany; [11]German Center for Child and Adolescent Health (DZKJ), partner site Berlin, Berlin, Germany; [12]Department of Psychiatry, Zucker Hillside Hospital, Northwell Health, Glen Oaks, NY, USA; [13]Department of Psychiatry and Molecular Medicine, Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA; [14]Center for Psychiatric Neuroscience, Feinstein Institute for Medical Research, Northwell Health, New Hyde Park, NY, USA; [15]Evidence-based Psychiatry and Psychotherapy, Faculty of Medicine, University of Augsburg, Augsburg, Germany; [16]Department of Psychiatry, Psychotherapy and Psychosomatics, Medical Faculty, University of Augsburg, Augsburg, Germany; [17]SCIENCES lab, Department of Psychiatry, University of Ottawa, Ottawa, ON, Canada; [18]Regional Centre for Treatment of Eating Disorders and On Track: Champlain First Episode Psychosis Program, Department of Mental Health, Ottawa Hospital, Ottawa, ON, Canada; [19]Ottawa Hospital Research Institute, Ottawa, ON, Canada

Previous meta-analyses estimating mortality risk in eating disorders (EDs) were restricted to specific disorders or causes of death, and were published before the release of the DSM-5, which introduced significant changes in ED classification. We conducted a PRISMA 2020-compliant systematic review and random-effects meta-analysis assessing all-cause (primary outcome) and cause-specific mortality risk ratio (RR) in cohort/case-control studies of individuals with EDs versus the general population or groups matched by physical and/or psychiatric comorbidities. Meta-regression/subgroup analyses assessed risk aggravating or attenuating factors. Study quality was evaluated using design-specific US National Institutes of Health tools. Altogether, 83 studies were meta-analyzed (patients with EDs: N=307,710, general population controls: N=15,719,076; mean follow-up: 11.96 years, females: 94.35%, mean age: 25.52 years). The quality was rated as "good" in 65.0%, "fair" in 21.7%, and "poor" in 13.3% of the studies. Any ED was associated with higher all-cause mortality vs. the general population (RR=4.92, 95% CI: 4.03-6.00, ranging from RR=5.52, 95% CI: 4.47-6.82 in anorexia nervosa (AN) to non-significant difference in binge eating disorder), as well as with higher suicide-related mortality (RR=8.45, 95% CI: 5.73-12.47, ranging from RR=9.86, 95% CI: 5.63-17.27 in AN to RR=6.15, 95% CI: 2.52-15.04 in bulimia nervosa). Mortality risk from both natural and non-natural causes was also increased in individuals with EDs vs. the general population (RR=3.47, 95% CI: 2.29-5.25, and RR=6.46, 95% CI: 4.62-9.04, respectively). All-cause mortality increased with lower body mass index and shorter follow-ups. Male sex, any psychiatric comorbidity, and comorbid substance use, alcohol use, mood or personality disorders were significantly associated with higher all-cause mortality risk in any ED. These data confirm that EDs are associated with a high all-cause, suicide-related and other cause-specific mortality risk, and indicate that monitoring of physical and psychiatric complications and suicide risk early after diagnosis, particularly in AN, males and individuals with low body mass index, is absolutely needed. Further research is warranted to identify actionable factors that can reduce ED-associated mortality risk.

Key words: Eating disorders, all-cause mortality, cause-specific mortality, suicide, mental health comorbidities, body mass index

(World Psychiatry 2026;25:125–140)

Eating disorders (EDs) are a group of conditions characterized by dysfunctional eating behaviors, which can result in significant adverse physical and psychological consequences. According to the DSM-5, they include anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED), avoidant/restrictive food intake disorder (ARFID), and other specified feeding and eating disorders (OSFED)[1].

EDs are known to be associated with high mortality rates[2]. In particular, AN has one of the highest mortality risks among all psychiatric disorders[3], with 16.64 (95% CI: 7.45-25.82) years of potential life lost[4]. Many physical and psychological factors can contribute to mortality risk, including malnutrition, impaired kidney function [5], bowel obstruction[6], electrolyte abnormalities[7], and adverse cardiovascular disease events[8], as well as psychiatric comorbidities, particularly mood and anxiety disorders[9].

Virtually no body system is spared from the impact of EDs[10], and classic risk factors and monitoring approaches for physical health do not always apply to people with EDs. Acute as well as chronic kidney disease can originate from hypothalamic changes, chronic dehydration or laxative misuse[11,12], and is difficult to monitor, due to the low clinical utility of creatinine levels in an underweight and sarcopenic population. Bowel obstruction can be the result of electrolyte abnormalities, atrophic smooth muscle, chronic restriction resulting in hypomotility, and chronic laxative misuse[13]. Cardiovascular and cerebrovascular diseases can originate from chronic malnourishment and acute hypoglycemia (or, on the contrary, metabolic syndrome in those with BED), with risk of superior mesenteric artery syndrome, myocardial infarction, and stroke[14,15]. Cardiac arrhythmias can be caused by electrolyte abnormalities and demand long-term monitoring[16]. The burden of comorbid mental disorders can contribute to an increased risk of non-suicidal self-harm and suicide attempts[17,18].

Physical health complications, which can be risk factors for premature mortality, have been historically studied among AN and BN populations[19], but are less known in people with BED and other EDs[20]. This scarcity of information is concerning, since the lifetime prevalence of eating disorders not otherwise specified (EDNOS) and OSFED (3.8-11.5%) is higher than that of AN and BN (<2%)[21], and diagnostic migration from AN or BN to OSFED is relatively common[22]. Moreover, many epidemiological studies of individuals with EDs have been conducted in Western countries[23], and data are lacking from Eastern and global South regions.

Several systematic reviews and meta-analyses have investigated mortality in individuals with EDs. However, they were based on female-only or largely female samples[24] and were published prior to the release of the DSM-5, which introduced significant changes in ED classification[25]. Moreover, no previous systematic review has summarized evidence on all-cause and cause-specific mortality risk ratio (RR), and none has adopted a transdiagnostic approach measuring the risk of premature death across all EDs.

The primary aim of this systematic review and meta-analysis was to evaluate the all-cause mortality risk in individuals presenting with an ED. The secondary objectives were to determine cause-specific mortality risk, including both natural and non-natural causes, and to identify attenuating or aggravating factors associated with mortality in individuals with EDs.

METHODS

We conducted a PRISMA 2020-compliant systematic review[26]. The study protocol was pre-published on the Open Science Framework (https://osf.io/7mh2e).

Eligibility

To be included in the systematic review and meta-analysis, studies had to be: a) cohort or case-control observational studies, b) recruiting individuals diagnosed with AN, BN, BED, EDNOS, OSFED and/or ARFID, according to DSM or ICD criteria/requirements, validated scales with cut-offs, electronic health and/or clinical records, c) reporting on the RR (or other metric that could be converted to RR) of all-cause mortality, suicide-related mortality, natural cause mortality, or other cause-specific mortality, d) comparing mortality risk with the general population or with a control group matched by comorbid physical or mental health condition, and e) published in a peer-reviewed journal in any language.

We excluded: a) cross-sectional studies, randomized controlled trials, interventional studies, editorials, study protocols, book chapters, thesis dissertations, and reviews, b) animal/non-human studies, and c) studies of patients with ED symptoms but without an ED diagnosis.

Search and study selection process

We searched EMBASE and Medline up to October 23, 2024. Screening was conducted by two independent reviewers using Covidence. Disagreements were resolved via consensus, or with a third reviewer.

We kept multiple studies reporting on the same population and outcome only if the study dates or samples overlapped for less than 50%. In case of larger overlap, we prioritized the largest sample size. If one study reported an unadjusted (but larger) outcome and another an adjusted outcome, both studies were kept (the larger in the main analyses and the adjusted one in the subgroup analyses) without double-counting.

Data extraction

Raw numbers or effect sizes – RR, standardized mortality ratio (SMR), hazard ratio (HR), or odds ratio (OR) – were extracted by two independent reviewers for the following outcomes: all-cause mortality, suicide-related mortality, natural cause mortality, and specific causes of mortality. The longest follow-up outcome was considered.

We extracted data regarding study design, country, sample size, type of comparison, follow-up time, median year of data collection, study setting, ED diagnosis and subtypes, representativeness of the study population, type/extensiveness of the adjustment of the analyses, diagnostic classification (ICD, DSM, other), body mass index, and mean age. We recorded sex/gender, race and ethnicity, as well as mental health and somatic comorbidities. We also extracted information regarding socio-demographic index (SDI) of the country/countries where the studies were conducted[27].

Risk of bias

The US National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies and the NIH Quality Assessment of Case-Control Studies[28] were used, as appropriate, by two independent reviewers to assess the risk of bias in individual studies.

Analyses

Random-effects meta-analyses were conducted to calculate pooled RR for mortality among individuals with EDs compared to control groups. Ratio measures were used or calculated from raw numbers. In case of zero events in one group, we added a constant of 0.5 to allow RR calculation. If a study had zero events in both groups, it was excluded from the calculations. Between-study variance was estimated using the restricted maximum-likelihood estimator. Confidence intervals (CIs) were calculated using Hartung and Knapp method with ad hoc variance correction[29].

To explore potential causes of heterogeneity, we conducted subgroup analyses either by pooling individual patient-level results from within-study subgroup analyses (i.e., males vs. females) or by pooling across-study results (e.g., representative vs. non-representative studies). We also conducted mixed-effects meta-regression analyses to explore the associations between mortality in any ED and various individual or study characteristics. I^2 was used to assess heterogeneity[30]. Publication bias was evaluated using Egger's test with a level of significance of $p<0.1$[31], when ≥10 studies were reported for the respective outcome.

All data management and analyses were conducted using R 4.3.2 and the metafor/meta-package[32].

RESULTS

Literature search

After removal of duplicates, the search identified 6,857 publications, of which 6,387 were excluded at the title/abstract level. Altogether, 470 full-text records were screened, and 83 studies[2,7,9,33-112] were included with populations not substantially overlapping based on the above criteria (see Figure 1).

Of these 83 studies (N=307,710 individuals with EDs, N=15,719,076 general population controls, females: 94.35%, mean age: 25.52±10.25 years, representative cohorts: 59%, mean follow-up: 11.96±6.69 years), 46 focused on AN only (N=75,782 patients, N=2,079,367 general population controls), three on BN (N=2,461 patients, N=7,020 general population controls), and the remaining 34 studies examined more than one ED type (N=229,467 patients, N=13,632,689 general population controls). The quality was good in 65.0%, fair in 21.7%, and poor in 13.3% of the studies.

Studies were conducted in 17 countries, including Canada, Denmark, Finland, France, Germany, Hong Kong, Iceland, Israel, Italy, Japan, New Zealand, South Korea, Spain, Sweden, Taiwan, the UK and the US. One study was conducted in multiple countries. There were 20 prospective and 50 retrospective cohort studies, plus 13 case-control studies. The study periods ranged from 1935 to 2020 (see Table 1).

There were 66 studies that compared subjects with an ED versus the general population. Six studies compared subjects with an ED versus a control group matched for a physical (e.g., cancer, stroke) or mental health (e.g., personality disorder, substance use disorder) comorbidity. Three studies compared subjects with ED versus other mental disorders. Twenty-two studies investigated the association between present/absent risk/protective factors and mortality within two groups of subjects with ED (e.g., ED

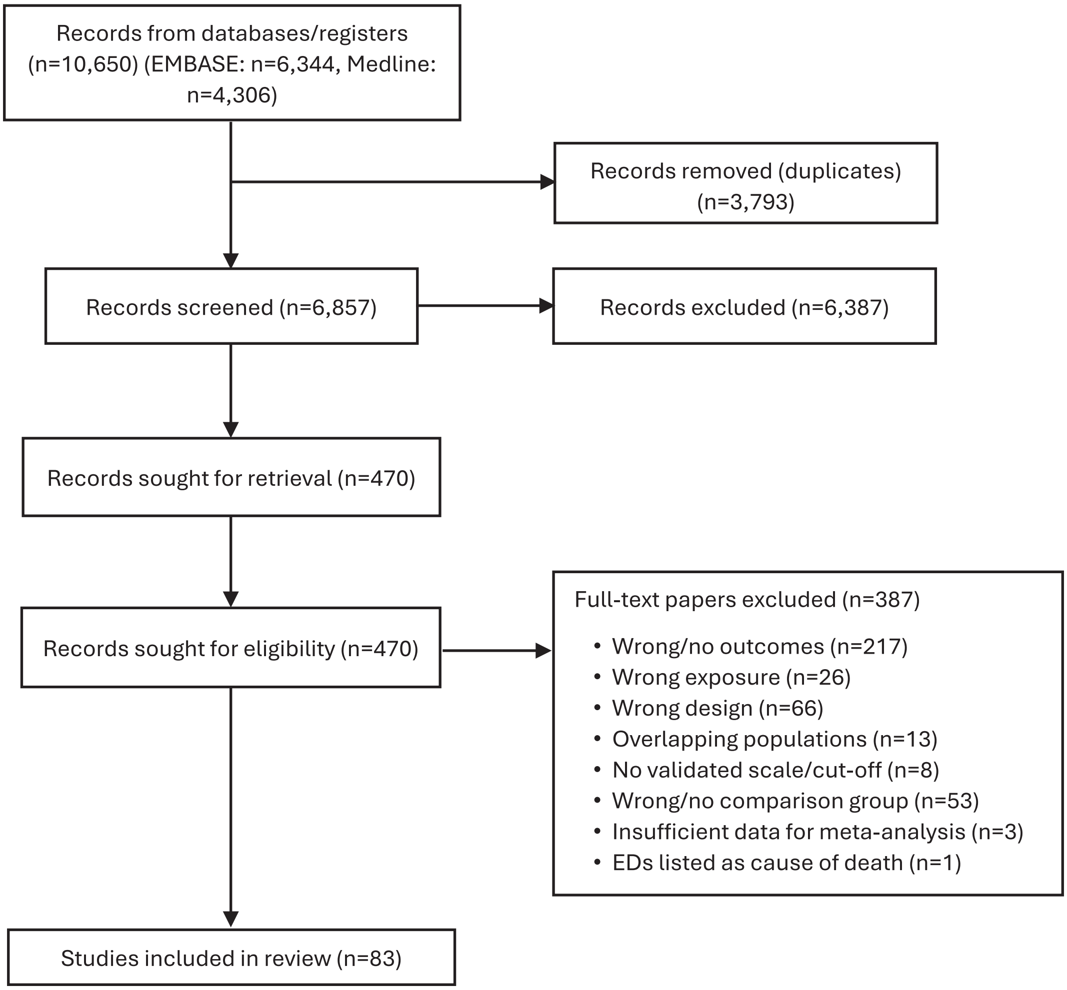


Figure 1 Study selection flow. EDs – eating disorders

Table 1 Characteristics of studies reporting mortality risk in persons suffering from an eating disorder (ED)

	Country	Design	Comparison	N patients	N controls	Observation period	Setting	Diagnoses	NIH rating
Abry et al[33]	France	CC	ED ± risk factor	48	NA	2011-2020	Inpatient	AN	Poor
Ajetunmobi et al[34]	UK	RC	ED vs. general population	851	SMR	1986-2010	National patient registry	Mixed EDs	Good
Amemiya et al[35]	Japan	PC	ED vs. general population	67	SMR	2006-2007	Inpatient	AN, AN-R, AN-BP	Good
Auger et al[36]	Canada	RC	ED vs. general population	5,169	1,293,721	1989-2018	National patient registry	AN	Fair
Bens et al[37]	Sweden, Denmark, Finland	RC	ED vs. no ED (matched for breast cancer)	76	1,462	1968-2010	National registries	AN	Fair
Birmingham et al[38]	Canada	RC	ED vs. general population; ED ± risk factor	954	SMR	1981-2000	Inpatient	AN, BN, EDNOS	Good
Bulik et al[39]	Sweden	PC	ED vs. no ED (twin pairs)	191	16,206	1972-2002	National patient registry	AN	Good
Button et al[40]	UK	CC	ED vs. general population	295	SMR	1992-2004	Hospital	AN, BN, EDNOS	Good
Castellini et al[9]	Italy	PC	ED vs. general population	1,277	SMR	1994-2018	Clinic	AN, AN-R, AN-BP, BN, BED	Fair
Cooke et al[41]	UK	CC	ED vs. general population	42	28	1990-1992	Inpatient	AN, BN	Poor
Coren et al[42]	US	RC	ED vs. general population	571	1,713	1986-1990	National registry	AN	Good
Crisp et al[43]	UK	RC	ED vs. general population	935	SMR	1960-1995	National patient registry	AN	Fair
Crow et al[44]	US	RC	ED vs. general population	1,885	SMR	1979-1997	Outpatient	AN, BN, EDNOS	Good
Demmler et al[45]	UK	CC	ED vs. general population	15,558	62,219	1990-2017	Clinic and hospital	AN, BN, Other ED	Good
Deter & Herzog[46]	Germany	PC	ED vs. general population	84	SMR	1971-1980	Medical clinic	AN	Poor
Duriez et al[47]	France	RC	ED vs. general population	5,452	14,967	2013/2014-2016/2017	Hospital	AN, BN	Good
Eckert et al[48]	US	RC	ED vs. general population	76	SMR	NR	Inpatient	AN	Good
Edakubo & Fushimi[49]	Japan	RC	ED ± risk factor	361	6937	2010-2016	Administrative inpatient database	AN, AN-BP	Good
Emborg[50]	Denmark	RC	ED vs. general population	2,763	SMR	1970-1993	Inpatient	AN, EDNOS	Fair
Erdur et al[51]	Germany	RC	ED ± risk factor	169	NA	2010-2011	Inpatient	AN, AN-R, AN-BP	Good
Fichter et al[52]	Germany	CC	ED ± risk factor	5,484	NA	2012	Inpatient	AN, BN, EDNOS	Fair
Fichter et al[53]	Germany	PC	ED vs. general population	103	202	NR	Inpatient	AN, AN-R, AN-BP	Fair
Fichter et al[54]	Germany	PC	ED vs. general population	264	SMR	NR	Inpatient	BN, BN-P, BED	Fair
Franko et al[55]	US	PC	ED vs. general population	246	SMR	1987-2010	Hospital	AN, AN-R, AN-BP, BN	Good

Table 1 Characteristics of studies reporting mortality risk in persons suffering from an eating disorder (ED) *(continued)*

	Country	Design	Comparison	N patients	N controls	Observation period	Setting	Diagnoses	NIH rating
Frederiksen et al[56]	Denmark	CC	ED vs. general population	702	7,020	1997-2017	Hospital (cases) and community (controls)	Atypical BN	Fair
Frederiksen et al[57]	Denmark	CC	ED vs. general population	560	5,600	1997-2017	Hospital (cases) and community (controls)	AN	Fair
Gibbings et al[58]	Canada	CC	ED vs. no ED (matched for diabetes mellitus)	168	1,680	2014-2020	Hospital	AN, BN, EDNOS	Good
Godart et al[59]	France	RC	ED vs. general population	105	258	NR	Hospital	AN	Fair
Goldberg et al[60]	Israel	RC	ED vs. general population; ED vs. ED (moderate/severe vs. mild)	1,356	577,399	NR	Hospital and community	All EDs in DSM-5	Fair
Gueguen et al[61]	France	PC	ED vs. general population	1,009	SMR	1988-2004	Inpatient	AN, AN-R, AN-BP	Poor
Guinhut et al[62]	France	RC	ED vs. general population	384	SMR	1997-2014	Inpatient	AN, AN-R, AN-BP	Good
Herzog et al[63]	US	PC	ED vs. general population	136	SMR	1987/1990-2000	Hospital	AN	Good
Hewitt et al[64]	US	RC	ED ± risk factor	724	NA	1986-1990	National registry	AN	Poor
Himmerich et al[65]	UK	RC	ED vs. general population, ED ± risk factor	1,501	SMR	2007-2016	National patient registry	BN	Good
Himmerich et al[66]	UK	RC	ED vs. general population	1,970	SMR	2007-2016	National patient registry	AN	Good
Hjern et al[67]	Sweden	RC	ED vs. general population	748	528,621	1987-2002	Inpatient	AN	Good
Hoang et al[68]	UK	RC	ED vs. general population	19,572	SMR	2001-2009	National patient registry	AN, BN, EDNOS	Good
Huas et al[69]	France	PC	ED vs. general population	601	SMR	1988-2008	Inpatient	AN, AN-R	Good
Huas et al[70]	France	PC	ED vs. general population	258	SMR	1988-2008	Inpatient	BN, BN-P	Good
Iwajomo et al[71]	Canada	RC	ED vs. general population	19,041	SMR	1990-2013	Hospital	AN, BN, EDNOS	Good
James et al[72]	UK	RC	ED vs. general population	3,028	SMR	1998-2004	Hospital	All EDs	Good
Joergensen[73]	Denmark	RC	ED vs. general population	87	SMR	1977-1986	Hospital	AN	Poor
John et al[74]	UK	RC	ED vs. general population	7,462	SMR	2003-2016	National patient registry	All EDs	Good
Karamanis et al[75]	Sweden	RC	ED vs. general population	6,009	SMR	1973-2003	Inpatient	AN	Good
Kask et al[76]	Sweden	RC	ED vs. general population, ED ± risk factor	8,069	76,995	1973-2010	National patient registry	AN	Good

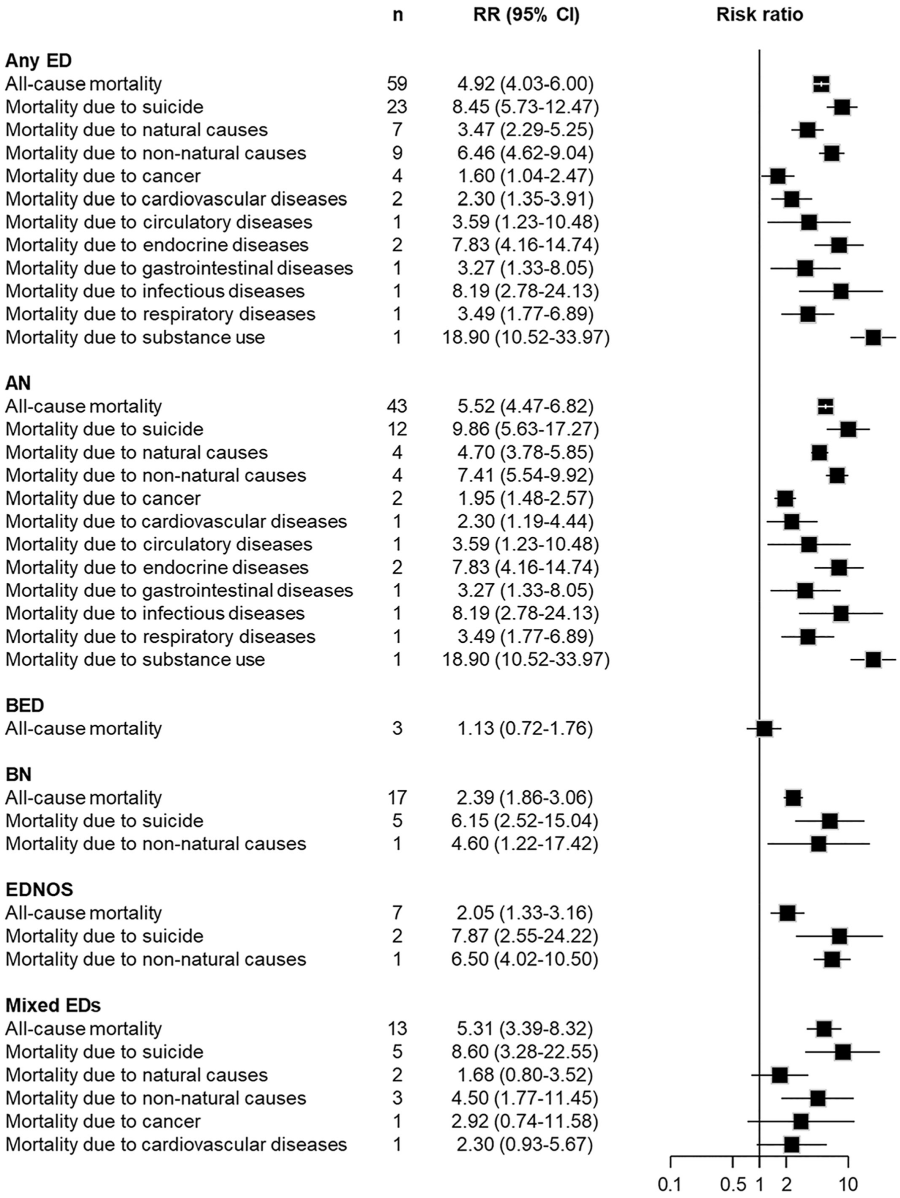
Table 1 Characteristics of studies reporting mortality risk in persons suffering from an eating disorder (ED) *(continued)*

	Country	Design	Comparison	N patients	N controls	Observation period	Setting	Diagnoses	NIH rating
Kask et al[77]	Sweden	CC	ED vs. general population, ED ± risk factor	609	6,025	1973-2010	National patient registry (patients) and administrative database (controls)	AN	Good
Keel et al[78]	US	PC	ED vs. general population	246	SMR	1987-2000	Outpatient	AN, AN-R, AN-BP, BN	Good
Korndorfer et al[79]	US	RC	ED vs. general population	208	SMR	1935-1989	National patient registry	AN	Good
Landi et al[80]	Italy	PC	ED vs. no ED (matched for admittance to same medical facility)	744	2,043	1998-2000	Outpatient	AN	Good
Larsen et al[81]	Denmark	RC	ED vs. general population	17,098	1,650,279	1981-2009	National patient registry	AN, BN, EDNOS	Good
Lee et al[82]	Hong Kong	RC	ED vs. general population	88	SMR	1984-2000	Inpatient	AN, AN-R, AN-BP	Fair
Löwe et al[83]	Germany	PC	ED vs. general population	84	SMR	1971-1998	Inpatient	AN, AN-R, AN-BP	Good
Mellentin et al[2]	Denmark	RC	ED vs. general population	20,759	83,036	1994-2015	National patient registry	AN, BN, EDNOS	Good
Millar et al[84]	UK	RC	ED vs. general population	524	SMR	1965-1999	National registry and administrative databases	AN	Good
Momen et al[85]	Denmark	RC	ED ± risk factor	11,489	NA	1977-2010	National patient registry	AN	Good
Momen et al[86]	Denmark	RC	ED vs. general population; ED vs. no ED (matched for physical or mental comorbidity); ED ± risk factor	23,570	5,923,230	2000-2017	Hospital	AN	Good
Mortier et al[87]	Spain	RC	ED vs. other mental disorders	1,627	42,640	2014-2019	National patient registry	ED	Good
Nielsen et al[88]	Denmark	RC	ED vs. general population, ED ± risk factor	658	510	1970-1987	National registry	AN	Fair
Nielsen et al[89]	Denmark	CC	ED vs. general population	22,633	90,486	1970-2014	National registry	AN, BN, psychogenic overeating, other ED, ED unspecified	Good
Norring & Sohlberg[90]	Sweden	PC	ED vs. general population	30	SMR	1984-1990	Hospital	AN, BN, EDNOS restricter, EDNOS bulimic	Poor
Pagsberg & Wang[91]	Denmark	RC	ED vs. general population	42	SMR	1970-1989	Primary care + hospital	AN	Poor
Papadopoulos et al[92]	Sweden	RC	ED vs. general population	6,009	SMR	1973-2003	National patient registry	AN	Good

Table 1 Characteristics of studies reporting mortality risk in persons suffering from an eating disorder (ED) *(continued)*

	Country	Design	Comparison	N patients	N controls	Observation period	Setting	Diagnoses	NIH rating
Papadopoulos et al[93]	Sweden	RC	ED ± risk factor	5,251	NA	1973-2003	National patient registry	AN	Good
Patton[94]	UK	RC	ED vs. general population	481	SMR	1985-1986	Hospital	AN, BN, other ED	Good
Rosling et al[95]	Sweden	RC	ED vs. general population	201	SMR	1974-2001	Inpatient	AN, BN, other EDs	Good
Signorini et al[96]	Italy	RC	ED vs. general population	138	SMR	1994-2003	Inpatient	AN, AN-R	Fair
Sigurdardottir et al[97]	Iceland	RC	ED vs. general population	84	SMR	1983-2008	Hospital	AN	Good
Singhal et al[98]	UK	RC	ED vs. general population	18,917	NR	1999-2011	National patient registry	All EDs according to ICD-9/10	Fair
Soeby et al[99]	Denmark	RC	ED vs. general population, ED ± risk factor	14,774	SHR	1977-2018	National patient registry	AN, AN with psychiatric comorbidities	Good
Solmi et al[7]	Canada	RC	ED ± risk factor	1,987	4,176	2008-2019	Ontario patient registry	AN, BN, EDNOS	Good
Song et al[100]	Republic of Korea	CC	ED vs. matched controls	529	319,966	2009-2013	National patient registry	ES	Good
Stheneur et al[101]	France	PC	ED vs. general population	29	166	1996-2008	Inpatient	AN	Poor
Sullivan et al[102]	New Zealand	CC	ED vs. general population	70	98	1981-1993	Community and hospital	AN	Fair
Suokas et al[103]	Finland	CC	ED vs. general population	2,450	9,676	1995-2010	Hospital	AN, atypical AN, BN, atypical BN, BED, other EDs	Good
Suzuki et al[104]	Japan	PC	ED vs. no ED (matched for AUD); ED ± risk factor	86	31	1990-1998	Inpatient	AN, BN, EDNOS	Good
Tolstrup et al[105]	Denmark	PC	ED vs. general population	151	SMR	1960-1976	Inpatient	AN	Fair
Tseng et al[106]	Taiwan	RC	ED vs. no ED (propensity-score matched)	15,733	314,660	2002-2017	National patient registry	AN, BN	Good
Tuohisto-Kokko et al[107]	Finland	RC	ED vs. general population	1,081	16,031	1980-2010	Inpatient	AN, BN, unspecified ED	Good
Vignaud et al[108]	France	RC	ED ± risk factor	68	NA	2006-2008	Inpatient	AN	Poor
Ward et al[109]	UK	PC	ED vs. general population	155	SMR	1965-1999	National patient registry	AN	Good
Winkler et al[110]	Denmark	RC	ED vs. general population	998	SMR	1994-2004	Inpatient	AN, BN, EDNOS	Good
Yao et al[111]	Sweden	RC	ED vs. general population	11,543	2,257,243	1979-2009	National registry	AN, BN	Good
Zipfel et al[112]	Germany	PC	ED vs. general population	77	SMR	NR	Inpatient	AN	Poor

AN – anorexia nervosa, AN-R – anorexia nervosa, restricting subtype, AN-BP – anorexia nervosa, binge-eating/purging subtype, BN – bulimia nervosa, BED – binge eating disorder, EDNOS – eating disorder not otherwise specified, AUD – alcohol use disorder, CC – case-control study, PC – prospective cohort study, RC – retrospective cohort study, SMR – standardized mortality ratio (no sample size of control group was reported), SHR – Fine and Gray sub-distribution hazard ratio, NIH – US National Institutes of Health, NA – not applicable, NR – not reported



	n	RR (95% CI)
Any ED		
All-cause mortality	59	4.92 (4.03-6.00)
Mortality due to suicide	23	8.45 (5.73-12.47)
Mortality due to natural causes	7	3.47 (2.29-5.25)
Mortality due to non-natural causes	9	6.46 (4.62-9.04)
Mortality due to cancer	4	1.60 (1.04-2.47)
Mortality due to cardiovascular diseases	2	2.30 (1.35-3.91)
Mortality due to circulatory diseases	1	3.59 (1.23-10.48)
Mortality due to endocrine diseases	2	7.83 (4.16-14.74)
Mortality due to gastrointestinal diseases	1	3.27 (1.33-8.05)
Mortality due to infectious diseases	1	8.19 (2.78-24.13)
Mortality due to respiratory diseases	1	3.49 (1.77-6.89)
Mortality due to substance use	1	18.90 (10.52-33.97)
AN		
All-cause mortality	43	5.52 (4.47-6.82)
Mortality due to suicide	12	9.86 (5.63-17.27)
Mortality due to natural causes	4	4.70 (3.78-5.85)
Mortality due to non-natural causes	4	7.41 (5.54-9.92)
Mortality due to cancer	2	1.95 (1.48-2.57)
Mortality due to cardiovascular diseases	1	2.30 (1.19-4.44)
Mortality due to circulatory diseases	1	3.59 (1.23-10.48)
Mortality due to endocrine diseases	2	7.83 (4.16-14.74)
Mortality due to gastrointestinal diseases	1	3.27 (1.33-8.05)
Mortality due to infectious diseases	1	8.19 (2.78-24.13)
Mortality due to respiratory diseases	1	3.49 (1.77-6.89)
Mortality due to substance use	1	18.90 (10.52-33.97)
BED		
All-cause mortality	3	1.13 (0.72-1.76)
BN		
All-cause mortality	17	2.39 (1.86-3.06)
Mortality due to suicide	5	6.15 (2.52-15.04)
Mortality due to non-natural causes	1	4.60 (1.22-17.42)
EDNOS		
All-cause mortality	7	2.05 (1.33-3.16)
Mortality due to suicide	2	7.87 (2.55-24.22)
Mortality due to non-natural causes	1	6.50 (4.02-10.50)
Mixed EDs		
All-cause mortality	13	5.31 (3.39-8.32)
Mortality due to suicide	5	8.60 (3.28-22.55)
Mortality due to natural causes	2	1.68 (0.80-3.52)
Mortality due to non-natural causes	3	4.50 (1.77-11.45)
Mortality due to cancer	1	2.92 (0.74-11.58)
Mortality due to cardiovascular diseases	1	2.30 (0.93-5.67)

Figure 2 All-cause and cause-specific relative mortality risk in individuals with vs. without an eating disorder (ED). RR – risk ratio, AN – anorexia nervosa, BED – binge eating disorder, BN – bulimia nervosa, EDNOS – eating disorders not otherwise specified.

males vs. ED females).

EDs were grouped into AN, BN, BED, EDNOS, and mixed eating disorders. There was no information available to conduct syntheses specifically on OSFED and ARFID.

Primary outcome

There was significantly higher all-cause mortality in individuals with any ED versus the general population (n=59, RR= 4.92, 95% CI: 4.03-6.00, I^2=94%, p<0.001). Of the specific EDs investigated, AN had the highest mortality risk (n=43, RR=5.52, 95% CI: 4.47-6.82, I^2=90%, p<0.001), followed by mixed EDs (n=13, RR=5.31, 95% CI: 3.39-8.32, I^2=98%, p<0.001), EDNOS (n=7, RR=2.05, 95% CI: 1.33-3.16, I^2=90%, p<0.001), and BN (n=17, RR=2.39, 95% CI: 1.86-3.06, I^2=55%, p<0.001). BED missed statistical significance (n=3, p=0.60) (see Figure 2). There was no evidence of publication bias in any of the analyzed primary outcome comparisons (see also supplementary information).

People with any ED had a higher all-cause mortality risk compared with individuals without ED matched by underlying physical or mental comorbidities (n=5, RR=2.84, 95% CI: 1.76-4.56, I^2= 95%, p<0.001) (see Figure 3). The all-cause mortality risk was also significantly elevated for individuals with AN compared to those

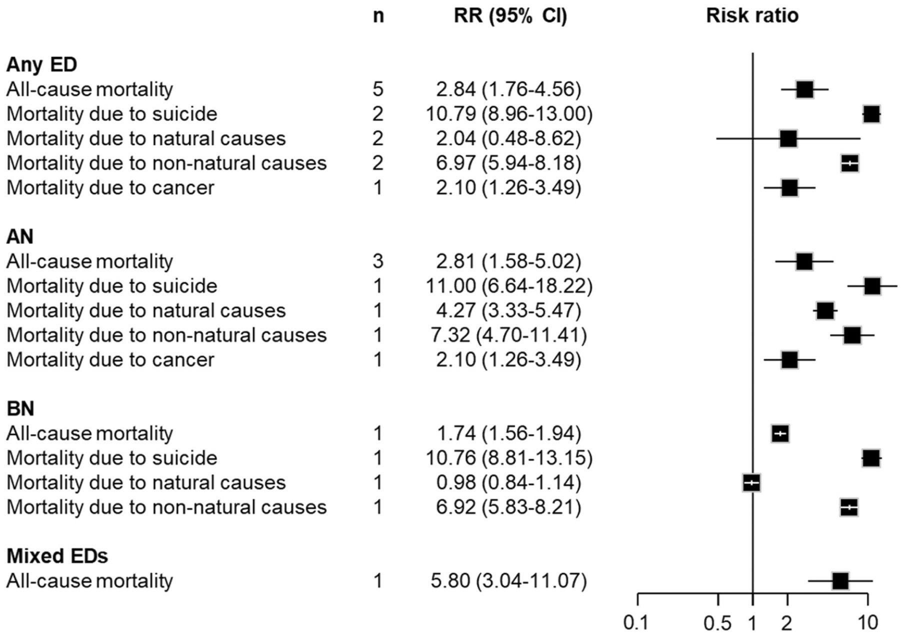


Figure 3 Mortality risk in individuals with vs. without an eating disorder (ED) matched by comorbid conditions. RR – risk ratio, AN – anorexia nervosa, BN – bulimia nervosa

without AN matched by underlying conditions (n=3, RR=2.81, 95% CI: 1.58-5.02, I^2=94%, p<0.001). The same was true for individuals with BN (n=1, RR=1.74, 95% CI: 1.56-1.94, p<0.001), and mixed EDs (n=1, RR=5.80, 95% CI: 3.04-11.07, p<0.001) (see Figure 3).

Secondary outcomes

The risk of suicide-related mortality was markedly increased in individuals with any ED versus the general population (n=23, RR=8.45, 95% CI: 5.73-12.47, I^2=93%, p<0.001) (see Figure 2), and versus individuals without ED matched by underlying physical or mental comorbidities (n=2, RR=10.79, 95% CI: 8.96-13.00, I^2=0%, p<0.001) (see Figure 3).

The risk of suicide-related mortality was consistently the highest contributor to the increased mortality risk in all ED subgroups, except when mortality due to substance use was reported, which was only the case for AN (n=1, RR=18.90, 95% CI: 10.52-33.97, p<0.001) (see Figure 2).

The risk of mortality from natural causes was higher in individuals with EDs than in the general population (n=7, RR=3.47, 95% CI: 2.29-5.25, I^2=97%, p<0.001) (see Figure 2), but was not significantly increased compared to individuals without ED matched by underlying physical or mental comorbidities (n=2, p=0.33) (see Figure 3).

The mortality risk for non-natural causes was significantly greater in individuals with EDs versus the general population (n=9, RR=6.46, 95% CI: 4.62-9.04, I^2=83%, p<0.001) (see Figure 2) and compared with individuals without ED matched by underlying physical or mental comorbidities (n=2, RR=6.97, 95% CI: 5.94-8.18, I^2=0%, p<0.001) (see Figure 3).

There was no evidence of publication bias in any of the secondary outcome comparisons (see also supplementary information).

Any ED was not significantly associated with a higher all-cause (p=0.22) or suicide-related (p=0.37) mortality risk compared to other mental disorders. However, it was associated with a higher mortality risk due to natural causes (n=1, RR=5.22, 95% CI: 2.35-11.62, p<0.001) (see also supplementary information).

Subgroup and meta-regression analyses

In study-wide subgroup analyses, higher all-cause mortality was significantly associated with poor study quality (p=0.006), while higher suicide-related mortality was significantly associated with non-representative studies (p=0.008) (see Table 2).

In meta-regression analyses, higher all-cause mortality was significantly associated with lower mean body mass index (n=16, beta=–0.144, 95% CI: –0.218 to –0.070, p<0.001) and shorter mean follow-up time (n=49, beta=–0.052, 95% CI: –0.083 to –0.022, p<0.001). There was no significant association with the median year of study data collection (n=45, p=0.78), proportion of males (n=53, p=0.60), or mean age (n=27, p=0.67) (see Table 3).

Suicide-related mortality was not significantly associated with any of the investigated factors. Lower mortality from natural causes was significantly associated with a more recent median year of data collection (n=7, beta=–0.069, 95% CI: –0.093 to –0.046, p<0.001), longer mean follow-up period (n=4, beta=–0.112, 95% CI: –0.184 to –0.040, p=0.002), larger sample size (n=6, beta=–0.001, 95% CI: –0.001 to 0.000, p<0.001), and higher country SDI (n=7, beta=25.552, 95% CI: 2.574-48.530, p=0.029) (see Table 3).

Table 2 Subgroup analyses of moderators of relative mortality risk in individuals suffering from an eating disorder (ED)

	n	RR (95% CI)	I^2	p
All-cause mortality				
Diagnosis system				
DSM/ICD	53	1.64 (1.43-1.86)	94	0.73
Other	6	1.23 (0.83-1.63)	96	
Quality rating				
Good	39	1.53 (1.29-1.77)	95	0.0058
Fair	13	1.50 (1.02-1.97)	89	
Poor	7	2.18 (1.84-2.52)	23	
Representativeness				
Representative	25	1.46 (1.20-1.72)	96	0.23
Non-representative	34	1.70 (1.41-1.99)	91	
Adjusted estimates				
Yes	36	1.68 (1.44-1.92)	95	0.29
No	23	1.45 (1.10-1.80)	92	
Mortality from suicide				
Diagnosis system				
DSM/ICD	20	2.17 (1.72-2.61)	93	0.75
Other	3	2.03 (1.34-2.72)	84	
Quality rating				
Good	20	2.16 (1.71-2.61)	94	0.72
Fair	3	2.05 (1.64-2.45)	0	
Representativeness				
Representative	16	1.83 (1.45-2.21)	95	0.0076
Non-representative	7	2.99 (2.23-3.76)	82	
Adjusted estimates				
Yes	13	2.19 (1.64-2.74)	90	0.77
No	10	2.07 (1.50-2.65)	95	
Mortality from natural causes				
Diagnosis system				
DSM/ICD	6	1.22 (0.73-1.71)	97	0.52
Other	1	1.39 (1.25-1.52)	-	
Quality rating				
Good	7	1.24 (0.83-1.66)	97	NA
Representativeness				
Representative	7	1.24 (0.83-1.66)	97	NA
Adjusted estimates				
Yes	5	1.08 (0.58-1.59)	98	0.14
No	2	1.62 (1.13-2.11)	89	
Mortality from non-natural causes				
Diagnosis system				
DSM/ICD	8	1.82 (1.44-2.20)	83	0.13
Other	1	2.14 (1.99-2.29)	-	
Quality rating				
Good	9	1.87 (1.53-2.20)	83	NA
Representativeness				
Representative	9	1.87 (1.53-2.20)	83	NA
Adjusted estimates				
Yes	7	1.76 (1.33-2.19)	83	NA
No	2	2.16 (2.03-2.29)	0	

RR – risk ratio, NA – not available

Lower mortality from non-natural causes was significantly associated with a more recent median year of data collection (n=6, beta=–0.063, 95% CI: –0.117 to –0.010, p=0.021) and a larger sample size (n=8, beta=–0.001, 95% CI: –0.001 to 0.000, p<0.001) (see Table 3).

Risk factors identified in individual studies

Altogether, 13 studies contributed quantitative data on the impact of specific risk factors on mortality risk in any ED[2,7,33,49,51,65,76,86,88,93,99,104,108], including 171 factors for all-cause, nine for natural cause, and 14 for non-natural cause mortality (see Figure 4 and supplementary information). Among these, 112 factors were significantly associated with all-cause, four with natural cause, and 12 with non-natural cause mortality. Only two factors – comorbid autism spectrum disorder (all-cause mortality), and giving birth to a child (all-cause and non-natural cause mortality) – were associated with lower mortality risk, with evidence from single studies.

Among risk factors pooled in ≥3 studies, any psychiatric comorbidity (n=4, RR=2.69, 95% CI: 1.83-3.94, I^2=75%, p<0.001), and comorbid substance use disorders (n=6, RR=3.28, 95% CI: 2.20-4.89, I^2=75%, p<0.001), alcohol use disorders (n=4, RR=2.38, 95% CI: 1.26-4.51, I^2=80%, p=0.008), mood disorders (n=4, RR=1.40, 95% CI: 1.01-1.94, I^2=62%, p=0.041) and personality disorders (n=4, RR=2.10, 95% CI: 1.25-3.53, I^2=90%, p=0.005) were significantly associated with increased all-cause mortality risk (see Figure 4).

Male sex was significantly associated with a higher all-cause mortality risk compared to female sex (n=6, RR=2.52, 95% CI: 1.86-3.41, I^2=90%, p<0.001). Refeeding syndrome was associated with a markedly increased risk for all-cause mortality (RR=21.79, 95% CI: 5.16-92.07, p<0001), although just in one study. Any somatic comorbidity also significantly increased all-cause mortality risk (RR=4.45, 95% CI: 1.19-16.66, p=0.027), although again only one study was available. Comorbid diabetes mellitus (n=3, p=0.067) or schizophrenia-spectrum disorders (n=3, p=0.085) did not significantly increase all-cause mortality in any ED (see Figure 4).

Any psychiatric comorbidity and comorbid alcohol use disorders were also associated with increased natural cause mortality

Table 3 Meta-regression analyses of moderators of relative mortality risk in individuals suffering from an eating disorder (ED)

	n	Coefficient (95% CI)	p
All-cause mortality (any ED)			
Mean age	27	0.020 (–0.070 to 0.109)	0.67
% male	53	–0.004 (–0.017 to 0.010)	0.60
Mean body mass index	16	–0.144 (–0.218 to –0.070)	0.00013
Median year of data collection	45	0.003 (–0.016 to 0.022)	0.78
Mean follow-up	49	–0.052 (–0.083 to –0.022)	0.00074
Sample size	57	0.000 (0.000 to 0.000)	0.53
Socio-demographic index	59	–0.896 (–7.591 to 5.799)	0.79
Mortality from suicide (any ED)			
Mean age	5	0.066 (–0.125 to 0.258)	0.50
% male	14	–0.006 (–0.028 to 0.016)	0.60
Median year of data collection	21	–0.046 (–0.098 to 0.006)	0.083
Mean follow-up	15	–0.054 (–0.132 to 0.024)	0.18
Sample size	22	0.000 (0.000 to 0.000)	0.37
Socio-demographic index	23	–4.119 (–24.903 to 16.664)	0.70
Mortality from natural causes (any ED)			
% male	5	–0.002 (–0.010 to 0.006)	0.65
Median year of data collection	7	–0.069 (–0.093 to –0.046)	<0.0001
Mean follow-up	4	–0.112 (–0.184 to –0.040)	0.0024
Sample size	6	–0.001 (–0.001 to 0.000)	<0.0001
Socio-demographic index	7	25.552 (2.574 to 48.530)	0.029
Mortality from non-natural causes (any ED)			
% male	7	–0.005 (–0.010 to 0.001)	0.083
Median year of data collection	6	–0.063 (–0.117 to –0.010)	0.021
Mean follow-up	6	–0.017 (–0.053 to 0.020)	0.37
Sample size	8	–0.001 (–0.001 to 0.000)	<0.0001
Socio-demographic index	9	2.511 (–20.519 to 25.541)	0.83

risk. Any psychiatric comorbidity, as well as comorbid substance use, alcohol use, personality and mood disorders were also associated with higher non-natural cause mortality risk (see Figure 4).

DISCUSSION

This systematic review and meta-analysis aimed to provide a comprehensive picture of the evidence concerning the all-cause and cause-specific mortality risk in individuals diagnosed with any ED. Individuals with an ED had an almost five-fold increased risk of all-cause mortality (RR=4.92) and a more than eight-fold increased risk of suicide-related mortality (RR=8.45) compared to the general population.

In meta-regression analyses, lower body mass index was associated with increased all-cause mortality risk, highlighting the need to consider it as a primary focus of treatment, especially early after ED onset[22]. Despite advances in treatments for EDs[113], there was no trend towards decreased all-cause mortality risk over time. Psychiatric and substance use comorbidities moderated larger mortality risk, emphasizing the need for personalized treatment of people with EDs, targeting and accounting for comorbid conditions[114].

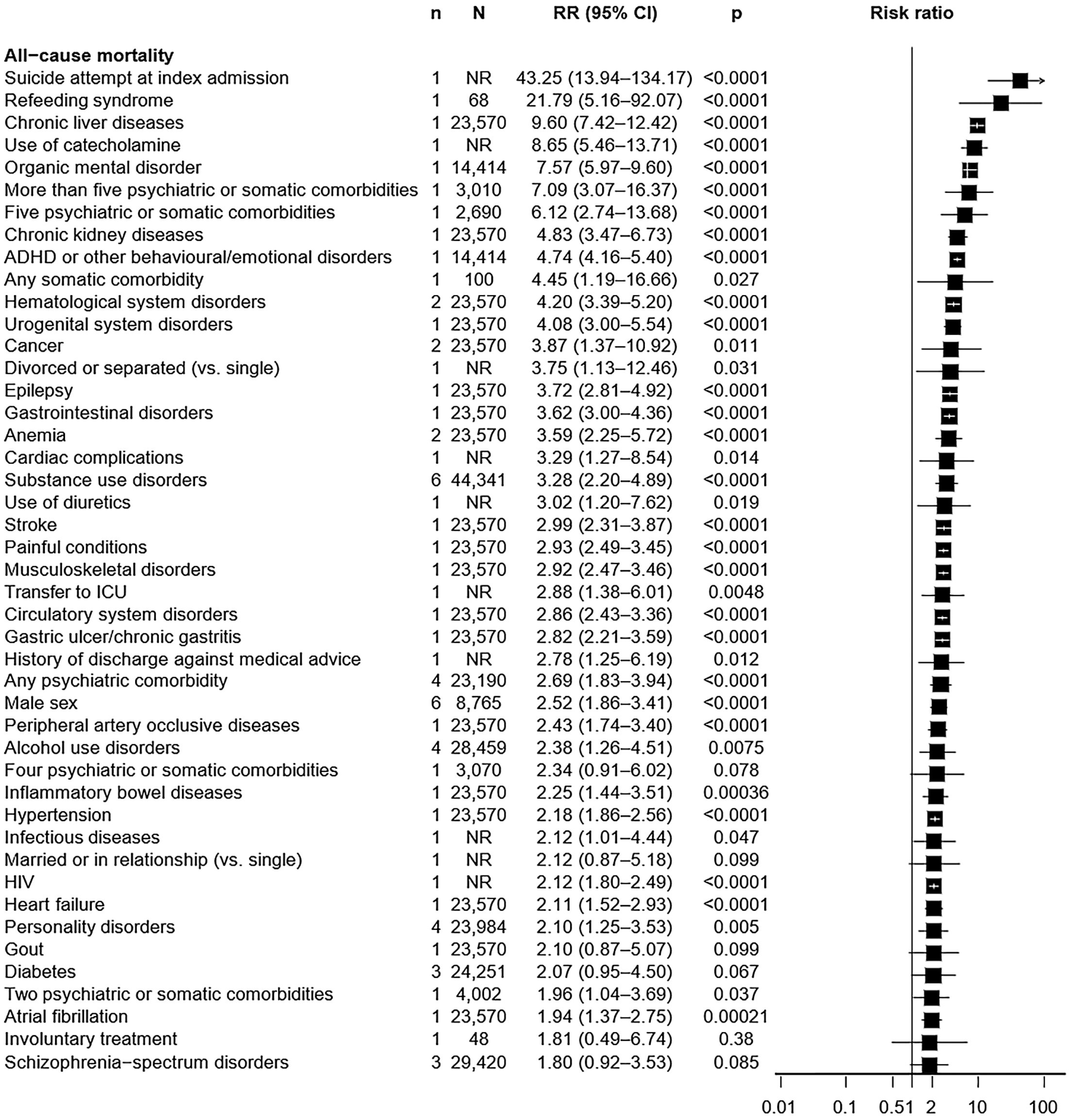
AN had the highest RR for all-cause and cause-specific mortality among EDs, likely due to more frequent and severe physical health complications and higher intent and lethality of suicide attempts[115,116], but also to substance use, that was the highest contributor to the increased mortality risk among individuals with AN in this meta-analysis (RR=18.90). Hence, weight restoration and attention to suicidality and substance use are paramount when treating individuals with AN. Concurrently, weight restoration should avoid refeeding syndrome[117], which is associated with markedly increased mortality.

Males with an ED were at higher risk of all-cause mortality compared to females (RR=2.52). Although men are generally at lower risk for EDs, they make more lethal suicide attempts[118], and die by suicide at a rate four times higher than women[119]. Depression and mortality are also more strongly associated in men than in women, although this difference has diminished over time[120].

Compared with the most comprehensive previous meta-analysis[24], we included 42 additional studies from population-based samples and large national registries, adding representativeness to the estimates. Overall, the RR was similar to previous findings, which highlights the need to conduct further studies focusing on modifiable factors that can mitigate the mortality risk in individuals with EDs[9]. Importantly, the above-mentioned previous meta-analysis included only two studies from non-Western countries, whereas we included six, making our review more globally representative. However, evidence from non-Western countries continues to be under-represented. This evidence gap is alarming, considering that, from 1990 to 2019, disability-adjusted life-years (DALYs) increased for EDs across all world regions, but particularly in South, East and Southeast Asia[121].

Comorbid autism spectrum disorder significantly decreased all-cause mortality risk, although with evidence from a single study. This finding may be related to greater dependence of people with that disorder on caregivers, who may provide effective supervision. The meta-analytic finding that giving birth to a child is associated with reduced mortality risk in AN stems from a Swedish registry study[93]. This association might be confounded by AN severity, with those suffering from a more severe condition possibly being less likely to become pregnant. However, caring for a child may also mitigate mortality-driving factors.

This meta-analysis has several strengths, in particular the large number of meta-analyzed studies (n=83), with 59% based on representative national or population-based cohorts, and the broad geographic representation, including six studies from non-Western countries. Additional strengths include the extended mean follow-up time, no restrictions in EDs and cause of death, and the analysis of specific risk factors and their associations with any mortality cause.



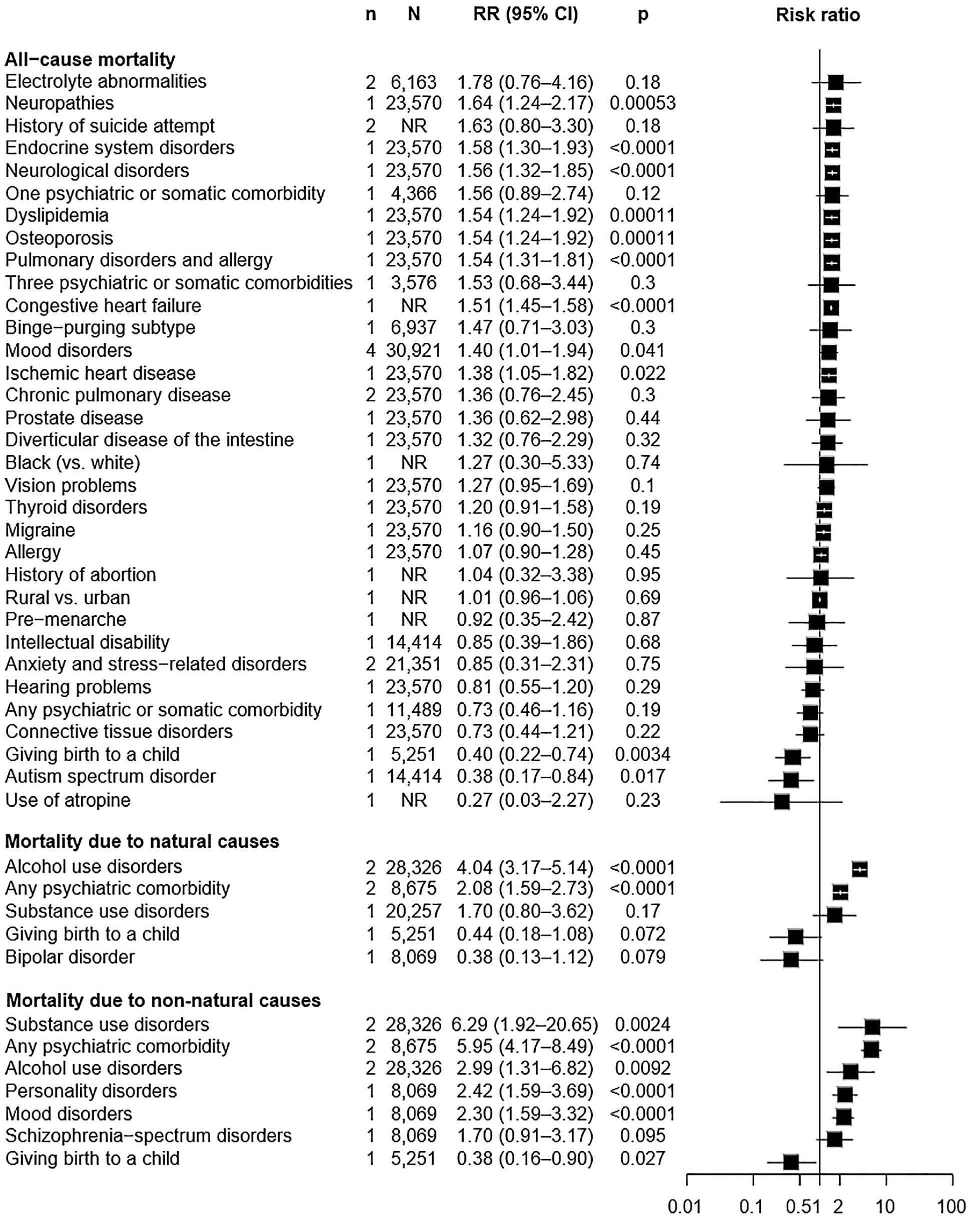
All−cause mortality	n	N	RR (95% CI)	p
Suicide attempt at index admission	1	NR	43.25 (13.94–134.17)	<0.0001
Refeeding syndrome	1	68	21.79 (5.16–92.07)	<0.0001
Chronic liver diseases	1	23,570	9.60 (7.42–12.42)	<0.0001
Use of catecholamine	1	NR	8.65 (5.46–13.71)	<0.0001
Organic mental disorder	1	14,414	7.57 (5.97–9.60)	<0.0001
More than five psychiatric or somatic comorbidities	1	3,010	7.09 (3.07–16.37)	<0.0001
Five psychiatric or somatic comorbidities	1	2,690	6.12 (2.74–13.68)	<0.0001
Chronic kidney diseases	1	23,570	4.83 (3.47–6.73)	<0.0001
ADHD or other behavioural/emotional disorders	1	14,414	4.74 (4.16–5.40)	<0.0001
Any somatic comorbidity	1	100	4.45 (1.19–16.66)	0.027
Hematological system disorders	2	23,570	4.20 (3.39–5.20)	<0.0001
Urogenital system disorders	1	23,570	4.08 (3.00–5.54)	<0.0001
Cancer	2	23,570	3.87 (1.37–10.92)	0.011
Divorced or separated (vs. single)	1	NR	3.75 (1.13–12.46)	0.031
Epilepsy	1	23,570	3.72 (2.81–4.92)	<0.0001
Gastrointestinal disorders	1	23,570	3.62 (3.00–4.36)	<0.0001
Anemia	2	23,570	3.59 (2.25–5.72)	<0.0001
Cardiac complications	1	NR	3.29 (1.27–8.54)	0.014
Substance use disorders	6	44,341	3.28 (2.20–4.89)	<0.0001
Use of diuretics	1	NR	3.02 (1.20–7.62)	0.019
Stroke	1	23,570	2.99 (2.31–3.87)	<0.0001
Painful conditions	1	23,570	2.93 (2.49–3.45)	<0.0001
Musculoskeletal disorders	1	23,570	2.92 (2.47–3.46)	<0.0001
Transfer to ICU	1	NR	2.88 (1.38–6.01)	0.0048
Circulatory system disorders	1	23,570	2.86 (2.43–3.36)	<0.0001
Gastric ulcer/chronic gastritis	1	23,570	2.82 (2.21–3.59)	<0.0001
History of discharge against medical advice	1	NR	2.78 (1.25–6.19)	0.012
Any psychiatric comorbidity	4	23,190	2.69 (1.83–3.94)	<0.0001
Male sex	6	8,765	2.52 (1.86–3.41)	<0.0001
Peripheral artery occlusive diseases	1	23,570	2.43 (1.74–3.40)	<0.0001
Alcohol use disorders	4	28,459	2.38 (1.26–4.51)	0.0075
Four psychiatric or somatic comorbidities	1	3,070	2.34 (0.91–6.02)	0.078
Inflammatory bowel diseases	1	23,570	2.25 (1.44–3.51)	0.00036
Hypertension	1	23,570	2.18 (1.86–2.56)	<0.0001
Infectious diseases	1	NR	2.12 (1.01–4.44)	0.047
Married or in relationship (vs. single)	1	NR	2.12 (0.87–5.18)	0.099
HIV	1	NR	2.12 (1.80–2.49)	<0.0001
Heart failure	1	23,570	2.11 (1.52–2.93)	<0.0001
Personality disorders	4	23,984	2.10 (1.25–3.53)	0.005
Gout	1	23,570	2.10 (0.87–5.07)	0.099
Diabetes	3	24,251	2.07 (0.95–4.50)	0.067
Two psychiatric or somatic comorbidities	1	4,002	1.96 (1.04–3.69)	0.037
Atrial fibrillation	1	23,570	1.94 (1.37–2.75)	0.00021
Involuntary treatment	1	48	1.81 (0.49–6.74)	0.38
Schizophrenia−spectrum disorders	3	29,420	1.80 (0.92–3.53)	0.085

Figure 4 Impact of specific risk factors on mortality risk in individuals suffering from any eating disorder (ED). RR – risk ratio, HIV – human immunodeficiency virus, ICU – intensive care unit, ADHD – attention-deficit/hyperactivity disorder, NR – not reported.

The meta-analysis also has limitations. First, insufficient data were available on cause-specific mortality for BED, BD and ED-NOS. Second, substance use-related mortality, that by far carried the highest relative mortality risk, was only reported for AN. Data on substance use-related mortality in other EDs should be collected and reported. Third, we did not find any studies investigating ARFID or OSFED that met our eligibility criteria, indicating a critical gap in the literature. These diagnostic categories are new in the DSM-5, and have fallen into the mixed ED group. The prevalence of ARFID in non-clinical populations may range from 0.3 to 15%[122]. More data are clearly needed for these EDs.

Fourth, there were insufficient data on race and ethnicity, and on several population subgroups (e.g., sex, physical or psychiatric comorbidities) for outcomes related to specific types of mortality. Fifth, there was limited information on overweight/obese individuals, and only ten studies reported a mean body mass index higher than 18.5 in the study sample. Sixth, there was no information on gender and sexual orientation. If studies did mention the word "gender", it was in fact referring to biological sex. Issues relating to transgender and nonbinary individuals likely impact health, well-being and mortality risk. Specifically, compared to heterosexual people, sexual minority groups have a higher risk of EDs[123]. Seventh, the studies included had an observational design, which does not allow for causal inferences. Finally, only one study[82] originated from a low SDI country. Since body ideals and food type and availability seem to impact ED risk, more data from such countries and regions are needed.

In conclusion, EDs are associated with increased all-cause and



	n	N	RR (95% CI)	p
All−cause mortality				
Electrolyte abnormalities	2	6,163	1.78 (0.76–4.16)	0.18
Neuropathies	1	23,570	1.64 (1.24–2.17)	0.00053
History of suicide attempt	2	NR	1.63 (0.80–3.30)	0.18
Endocrine system disorders	1	23,570	1.58 (1.30–1.93)	<0.0001
Neurological disorders	1	23,570	1.56 (1.32–1.85)	<0.0001
One psychiatric or somatic comorbidity	1	4,366	1.56 (0.89–2.74)	0.12
Dyslipidemia	1	23,570	1.54 (1.24–1.92)	0.00011
Osteoporosis	1	23,570	1.54 (1.24–1.92)	0.00011
Pulmonary disorders and allergy	1	23,570	1.54 (1.31–1.81)	<0.0001
Three psychiatric or somatic comorbidities	1	3,576	1.53 (0.68–3.44)	0.3
Congestive heart failure	1	NR	1.51 (1.45–1.58)	<0.0001
Binge−purging subtype	1	6,937	1.47 (0.71–3.03)	0.3
Mood disorders	4	30,921	1.40 (1.01–1.94)	0.041
Ischemic heart disease	1	23,570	1.38 (1.05–1.82)	0.022
Chronic pulmonary disease	2	23,570	1.36 (0.76–2.45)	0.3
Prostate disease	1	23,570	1.36 (0.62–2.98)	0.44
Diverticular disease of the intestine	1	23,570	1.32 (0.76–2.29)	0.32
Black (vs. white)	1	NR	1.27 (0.30–5.33)	0.74
Vision problems	1	23,570	1.27 (0.95–1.69)	0.1
Thyroid disorders	1	23,570	1.20 (0.91–1.58)	0.19
Migraine	1	23,570	1.16 (0.90–1.50)	0.25
Allergy	1	23,570	1.07 (0.90–1.28)	0.45
History of abortion	1	NR	1.04 (0.32–3.38)	0.95
Rural vs. urban	1	NR	1.01 (0.96–1.06)	0.69
Pre−menarche	1	NR	0.92 (0.35–2.42)	0.87
Intellectual disability	1	14,414	0.85 (0.39–1.86)	0.68
Anxiety and stress−related disorders	2	21,351	0.85 (0.31–2.31)	0.75
Hearing problems	1	23,570	0.81 (0.55–1.20)	0.29
Any psychiatric or somatic comorbidity	1	11,489	0.73 (0.46–1.16)	0.19
Connective tissue disorders	1	23,570	0.73 (0.44–1.21)	0.22
Giving birth to a child	1	5,251	0.40 (0.22–0.74)	0.0034
Autism spectrum disorder	1	14,414	0.38 (0.17–0.84)	0.017
Use of atropine	1	NR	0.27 (0.03–2.27)	0.23
Mortality due to natural causes				
Alcohol use disorders	2	28,326	4.04 (3.17–5.14)	<0.0001
Any psychiatric comorbidity	2	8,675	2.08 (1.59–2.73)	<0.0001
Substance use disorders	1	20,257	1.70 (0.80–3.62)	0.17
Giving birth to a child	1	5,251	0.44 (0.18–1.08)	0.072
Bipolar disorder	1	8,069	0.38 (0.13–1.12)	0.079
Mortality due to non-natural causes				
Substance use disorders	2	28,326	6.29 (1.92–20.65)	0.0024
Any psychiatric comorbidity	2	8,675	5.95 (4.17–8.49)	<0.0001
Alcohol use disorders	2	28,326	2.99 (1.31–6.82)	0.0092
Personality disorders	1	8,069	2.42 (1.59–3.69)	<0.0001
Mood disorders	1	8,069	2.30 (1.59–3.32)	<0.0001
Schizophrenia−spectrum disorders	1	8,069	1.70 (0.91–3.17)	0.095
Giving birth to a child	1	5,251	0.38 (0.16–0.90)	0.027

Figure 4 Impact of specific risk factors on mortality risk in individuals suffering from any eating disorder (ED). RR – risk ratio, HIV – human immunodeficiency virus, ICU – intensive care unit, ADHD – attention-deficit/hyperactivity disorder, NR – not reported. *(continued)*

cause-specific mortality, particularly in AN, in males, and in the early stages of illness. Substance use, mental and physical disorder comorbidities, and refeeding syndrome are all associated with increased mortality risk. ED treatment should include a holistic approach accounting for overall physical and mental health. Further research is needed to quantify the mortality gap across the globe, and to identify and address risk and protective factors.

ACKNOWLEDGEMENTS

E. Wagner, I. Colman and M. Solmi contributed equally to this paper. Supplementary information on this study is available at https://osf.io/s2xj9.

REFERENCES

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed, text revision. Washington: American Psychiatric Association, 2022.
2. Mellentin AI, Mejldal A, Guala MM et al. The impact of alcohol and other substance use disorders on mortality in patients with eating disorders: a nationwide register-based retrospective cohort study. Am J Psychiatry 2022;179:46-57.
3. Chesney E, Goodwin GM, Fazel S. Risks of all-cause and suicide mortality in mental disorders: a meta-review. World Psychiatry 2014;13:153-60.
4. Chan JKN, Correll CU, Wong CSM et al. Life expectancy and years of potential life lost in people with mental disorders: a systematic review and meta-analysis. EClinicalMedicine 2023;65:102294.
5. Gurevich E, Steiling S, Landau D. Incidence of impaired kidney function among adolescent patients hospitalized with anorexia nervosa. JAMA Netw Open 2021;4:e2134908.

6. Norris ML, Harrison ME, Isserlin L et al. Gastrointestinal complications associated with anorexia nervosa: a systematic review. Int J Eat Disord 2016;49:216-37.
7. Solmi M, Fabiano N, Clarke AE et al. Adverse outcomes and mortality in individuals with eating disorder-related electrolyte abnormalities in Ontario, Canada: a population-based cohort study. Lancet Psychiatry 2024;11:818-27.
8. Sachs KV, Harnke B, Mehler PS et al. Cardiovascular complications of anorexia nervosa: a systematic review. Int J Eat Disord 2016;49:238-48.
9. Castellini G, Caini S, Cassioli E et al. Mortality and care of eating disorders. Acta Psychiatr Scand 2023;147:122-33.
10. Westmoreland P, Krantz MJ, Mehler PS. Medical complications of anorexia nervosa and bulimia. Am J Med 2016;129:30-7.
11. Stheneur C, Bergeron S, Lapeyraque AL. Renal complications in anorexia nervosa. Eat Weight Disord 2014;19:455-60.
12. Bouquegneau A, Dubois BE, Krzesinski JM et al. Anorexia nervosa and the kidney. Am J Kidney Dis 2012;60:299-307.
13. Ikegaya H, Nakajima M, Shintani-Ishida K et al. Death due to duodenal obstruction in a patient with an eating disorder: a case report. Int J Eat Disord 2006;39:350-2.
14. Lin CY, Tseng MM, Chiou KR et al. Bulimia nervosa and risk of cardiovascular outcomes: a longitudinal matched cohort study in Taiwan. Int J Eat Disord 2025;58:1523-34.
15. Park CS, Choi EK, Han KD et al. Increased cardiovascular events in young patients with mental disorders: a nationwide cohort study. Eur J Prev Cardiol 2023;30:1582-92.
16. Farasat M, Watters A, Bendelow T et al. Long-term cardiac arrhythmia and chronotropic evaluation in patients with severe anorexia nervosa (LACE-AN): a pilot study. J Cardiovasc Electrophysiol 2020;31:432-9.
17. Arnold S, Wiese A, Zaid S et al. Lifetime prevalence and clinical correlates of nonsuicidal self-injury in youth inpatients with eating disorders: a retrospective chart review. Child Adolesc Psychiatry Ment Health 2022;16:17.
18. Arnold S, Correll CU, Jaite C. Frequency and correlates of lifetime suicidal ideation and suicide attempts among consecutively hospitalized youth with anorexia nervosa and bulimia nervosa: results from a retrospective chart review. Borderline Personal Disord Emot Dysregul 2023;10:10.
19. Bhattacharya A, DeFilipp L, Timko CA. Feeding and eating disorders. Handb Clin Neurol 2020;175:387-403.
20. Fichter MM, Quadflieg N. Mortality in eating disorders – results of a large prospective clinical longitudinal study. Int J Eat Disord 2016;49:391-401.
21. Hay P, Aouad P, Le A et al. Epidemiology of eating disorders: population, prevalence, disease burden and quality of life informing public policy in Australia – a rapid review. J Eat Disord 2023;11:23.
22. Solmi M, Monaco F, Højlund M et al. Outcomes in people with eating disorders: a transdiagnostic and disorder-specific systematic review, meta-analysis and multivariable meta-regression analysis. World Psychiatry 2024;23:124-38.
23. van Eeden AE, van Hoeken D, Hoek HW. Incidence, prevalence and mortality of anorexia nervosa and bulimia nervosa. Curr Opin Psychiatry 2021;34:515-24.
24. Arcelus J, Mitchell AJ, Wales J et al. Mortality rates in patients with anorexia nervosa and other eating disorders. A meta-analysis of 36 studies. Arch Gen Psychiatry 2011;68:724-31.
25. Smink FR, van Hoeken D, Hoek HW. Epidemiology of eating disorders: incidence, prevalence and mortality rates. Curr Psychiatry Rep 2012;14:406-14.
26. Page MJ, McKenzie JE, Bossuyt PM et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
27. Solmi M, Song M, Yon DK et al. Incidence, prevalence, and global burden of autism spectrum disorder from 1990 to 2019 across 204 countries. Mol Psychiatry 2022;27:4172-80.
28. US National Institutes of Health. Study quality assessment tools. www.nhlbi.nih.gov.
29. Knapp G, Hartung J. Improved tests for a random effects meta-regression with a single covariate. Stat Med 2003;22:2693-710.
30. von Hippel PT. The heterogeneity statistic I(2) can be biased in small meta-analyses. BMC Med Res Methodol 2015;15:35.
31. Egger M, Davey Smith G, Schneider M et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.
32. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Health 2019;22:153-60.
33. Abry F, Gorwood P, Hanachi M et al. Longitudinal investigation of patients receiving involuntary treatment for extremely severe anorexia nervosa. Eur Eat Disord Rev 2024;32:179-87.
34. Ajetunmobi O, Taylor M, Stockton D et al. Early death in those previously hospitalised for mental healthcare in Scotland: a nationwide cohort study, 1986-2010. BMJ Open 2013;3:e002768.
35. Amemiya N, Takii M, Hata T et al. The outcome of Japanese anorexia nervosa patients treated with an inpatient therapy in an internal medicine unit. Eat Weight Disord 2012;17:e1-8.
36. Auger N, Potter BJ, Ukah UV et al. Anorexia nervosa and the long-term risk of mortality in women. World Psychiatry 2021;20:448-9.
37. Bens A, Papadopoulos FC, Pukkala E et al. Worse survival after breast cancer in women with anorexia nervosa. Breast Cancer Res Treat 2018;168:495-500.
38. Birmingham CL, Su J, Hlynsky JA et al. The mortality rate from anorexia nervosa. Int J Eat Disord 2005;38:143-6.
39. Bulik CM, Sullivan PF, Tozzi F et al. Prevalence, heritability, and prospective risk factors for anorexia nervosa. Arch Gen Psychiatry 2006;63:305-12.
40. Button EJ, Chadalavada B, Palmer RL. Mortality and predictors of death in a cohort of patients presenting to an eating disorders service. Int J Eat Disord 2010;43:387-92.
41. Cooke RA, Chambers JB, Singh R et al. QT interval in anorexia nervosa. Br Heart J 1994;72:69-73.
42. Coren S, Hewitt PL. Is anorexia nervosa associated with elevated rates of suicide? Am J Public Health 1998;88:1206-7.
43. Crisp A, Gowers S, Joughin N et al. Death, survival and recovery in anorexia nervosa: a thirty five year study. Eur Eat Disord Rev 2006;14:168-75.
44. Crow SJ, Peterson CB, Swanson SA et al. Increased mortality in bulimia nervosa and other eating disorders. Am J Psychiatry 2009;166:1342-6.
45. Demmler JC, Brophy ST, Marchant A et al. Shining the light on eating disorders, incidence, prognosis and profiling of patients in primary and secondary care: national data linkage study. Br J Psychiatry 2020;216:105-12.
46. Deter HC, Herzog W. Anorexia nervosa in a long-term perspective: results of the Heidelberg-Mannheim Study. Psychosom Med 1994;56:20-7.
47. Duriez P, Goueslard K, Treasure J et al. Risk of non-fatal self-harm and premature mortality in the three years following hospitalization in adolescents and young adults with an eating disorder: a nationwide population-based study. Int J Eat Disord 2023;56:1534-43.
48. Eckert ED, Halmi KA, Marchi P et al. Ten-year follow-up of anorexia nervosa: clinical course and outcome. Psychol Med 1995;25:143-56.
49. Edakubo S, Fushimi K. Mortality and risk assessment for anorexia nervosa in acute-care hospitals: a nationwide administrative database analysis. BMC Psychiatry 2020;20:19.
50. Emborg C. Mortality and causes of death in eating disorders in Denmark 1970-1993: a case register study. Int J Eat Disord 1999;25:243-51.
51. Erdur L, Kallenbach-Dermutz B, Lehmann V et al. Somatic comorbidity in anorexia nervosa: first results of a 21-year follow-up study on female inpatients. Biopsychosoc Med 2012;6:4.
52. Fichter MM, Naab S, Voderholzer U et al. Mortality in males as compared to females treated for an eating disorder: a large prospective controlled study. Eat Weight Disord 2021;26:1627-37.
53. Fichter MM, Quadflieg N, Hedlund S. Twelve-year course and outcome predictors of anorexia nervosa. Int J Eat Disord 2006;39:87-100.
54. Fichter MM, Quadflieg N, Hedlund S. Long-term course of binge eating disorder and bulimia nervosa: relevance for nosology and diagnostic criteria. Int J Eat Disord 2008;41:577-86.
55. Franko DL, Keshaviah A, Eddy KT et al. A longitudinal investigation of mortality in anorexia nervosa and bulimia nervosa. Am J Psychiatry 2013;170:917-25.
56. Frederiksen TC, Christiansen MK, Ostergaard PC et al. The QTc interval and risk of cardiac events in bulimia nervosa: a long-term follow-up study. Int J Eat Disord 2018;51:1331-8.
57. Frederiksen TC, Krogh Christiansen M, Charmoth Ostergaard P et al. QTc interval and risk of cardiac events in adults with anorexia nervosa: a long-term follow-up study. Circ Arrhythm Electrophysiol 2018;11:e005995.
58. Gibbings NK, Kurdyak PA, Colton PA et al. Diabetic ketoacidosis and mortality in people with type 1 diabetes and eating disorders. Diabetes Care 2021; 44:1783-7.
59. Godart N, Duclos J, Hubert T et al. Hospitalisation pour anorexie mentale à l'adolescence: quel devenir 10 ans plus tard pour ces jeunes femmes? Neuropsychiatr Enfance Adolesc 2014;62:263-70.
60. Goldberg S, Werbeloff N, Shelef L et al. Risk of suicide among female adolescents with eating disorders: a longitudinal population-based study. Eat Weight Disord 2015;20:295-300.
61. Gueguen J, Godart N, Chambry J et al. Severe anorexia nervosa in men: comparison with severe AN in women and analysis of mortality. Int J Eat Disord 2012;45:537-45.
62. Guinhut M, Godart N, Benadjaoud M-A et al. Five-year mortality of severely malnourished patients with chronic anorexia nervosa admitted to a medical unit. Acta Psychiatr Scand 2021;143:130-40.
63. Herzog DB, Greenwood DN, Dorer DJ et al. Mortality in eating disorders: a de-

scriptive study. Int J Eat Disord 2000;28:20-6.

64. Hewitt PL, Coren S, Steel GD. Death from anorexia nervosa: age span and sex differences. Aging Ment Health 2001;5:41-6.
65. Himmerich H, Hotopf M, Shetty H et al. Psychiatric comorbidity as a risk factor for the mortality of people with bulimia nervosa. Social Psychiatry Psychiatr Epidemiol 2019;54:813-21.
66. Himmerich H, Hotopf M, Shetty H et al. Psychiatric comorbidity as a risk factor for mortality in people with anorexia nervosa. Eur Arch Psychiatry Clin Neurosci 2019;269:351-9.
67. Hjern A, Lindberg L, Lindblad F. Outcome and prognostic factors for adolescent female in-patients with anorexia nervosa: 9- to 14-year follow-up. Br J Psychiatry 2006;189:428-32.
68. Hoang U, Goldacre M, James A. Mortality following hospital discharge with a diagnosis of eating disorder: national record linkage study, England, 2001-2009. Int J Eat Disord 2014;47:507-15.
69. Huas C, Caille A, Godart N et al. Factors predictive of ten-year mortality in severe anorexia nervosa patients. Acta Psychiatr Scand 2011;123:62-70.
70. Huas C, Godart N, Caille A et al. Mortality and its predictors in severe bulimia nervosa patients. Eur Eat Disord Rev 2013;21:15-9.
71. Iwajomo T, Bondy SJ, de Oliveira C et al. Excess mortality associated with eating disorders: population-based cohort study. Br J Psychiatry 2021;219:487-93.
72. James A, Clacey J, Seagroatt V et al. Adolescent inpatient psychiatric admission rates and subsequent one-year mortality in England: 1998-2004. J Child Psychol Psychiatry 2010;51:1395-404.
73. Joergensen J. The epidemiology of eating disorders in Fyn County, Denmark, 1977-1986. Acta Psychiatr Scand 1992;85:30-4.
74. John A, Marchant A, Demmler J et al. Clinical management and mortality risk in those with eating disorders and self-harm: e-cohort study using the SAIL databank. BJPsych Open 2021;7:e67.
75. Karamanis G, Skalkidou A, Tsakonas G et al. Cancer incidence and mortality patterns in women with anorexia nervosa. Int J Cancer 2014;134:1751-7.
76. Kask J, Ekselius L, Brandt L et al. Mortality in women with anorexia nervosa: the role of comorbid psychiatric disorders. Psychosom Med 2016;78:910-9.
77. Kask J, Ramklint M, Kolia N et al. Anorexia nervosa in males: excess mortality and psychiatric co-morbidity in 609 Swedish in-patients. Psychol Med 2017;47:1489-99.
78. Keel PK, Dorer DJ, Eddy KT et al. Predictors of mortality in eating disorders. Arch Gen Psychiatry 2003;60:179-83.
79. Korndorfer SR, Lucas AR, Suman VJ et al. Long-term survival of patients with anorexia nervosa: a population-based study in Rochester, Minn. Mayo Clin Proc 2003;78:278-84.
80. Landi F, Liperoti R, Lattanzio F et al. Effects of anorexia on mortality among older adults receiving home care: an observational study. J Nutr Health Aging 2012;16:79-83.
81. Larsen JT, Yilmaz Z, Bulik CM et al. Diagnosed eating disorders in Danish registers – incidence, prevalence, mortality, and polygenic risk. Psychiatry Res 2024;337:115927.
82. Lee S, Chan YYL, Hsu LKG. The intermediate-term outcome of Chinese patients with anorexia nervosa in Hong Kong. Am J Psychiatry 2003;160:967-72.
83. Lowe B, Zipfel S, Buchholz C et al. Long-term outcome of anorexia nervosa in a prospective 21-year follow-up study. Psychol Med 2001;31:881-90.
84. Millar HR, Wardell F, Vyvyan JP et al. Anorexia nervosa mortality in Northeast Scotland, 1965-1999. Am J Psychiatry 2005;162:753-7.
85. Momen NC, Petersen JD, Yilmaz Z et al. Inpatient admissions and mortality of anorexia nervosa patients according to their preceding psychiatric and somatic diagnoses. Acta Psychiatr Scand 2024;149:404-14.
86. Momen NC, Plana-Ripoll O, Agerbo E et al. Mortality associated with mental disorders and comorbid general medical conditions. JAMA Psychiatry 2022;79:444-53.
87. Mortier P, Conde S, Alayo I et al. Premature death, suicide, and nonlethal intentional self-harm after psychiatric discharge. JAMA Netw Open 2024;7:e2417131.
88. Nielsen S, Emborg C, Molbak AG. Mortality in concurrent type 1 diabetes and anorexia nervosa. Diabetes Care 2002;25:309-12.
89. Nielsen S, Vilmar JW. What can we learn about eating disorder mortality from eating disorder diagnoses at initial assessment? A Danish nationwide register follow-up study using record linkage, encompassing 45 years (1970-2014). Psychiatry Res 2021;303:114091.
90. Norring CE, Sohlberg SS. Outcome, recovery, relapse and mortality across six years in patients with clinical eating disorders. Acta Psychiatr Scand 1993;87:437-44.
91. Pagsberg AK, Wang AR. Epidemiology of anorexia nervosa and bulimia nervosa in Bornholm County, Denmark, 1970-1989. Acta Psychiatr Scand 1994;90:259-65.
92. Papadopoulos FC, Ekbom A, Brandt L et al. Excess mortality, causes of death and prognostic factors in anorexia nervosa. Br J Psychiatry 2009;194:10-7.
93. Papadopoulos FC, Karamanis G, Brandt L et al. Childbearing and mortality among women with anorexia nervosa. Int J Eat Disord 2013;46:164-70.
94. Patton GC. Mortality in eating disorders. Psychol Med 1988;18:947-51.
95. Rosling AM, Sparen P, Norring C et al. Mortality of eating disorders: a follow-up study of treatment in a specialist unit 1974-2000. Int J Eat Disord 2011;44:304-10.
96. Signorini A, De Filippo E, Panico S et al. Long-term mortality in anorexia nervosa: a report after an 8-year follow-up and a review of the most recent literature. Eur J Clin Nutr 2007;61:119-22.
97. Sigurdardottir A, Palsson SP, Thorsteinsdottir G. Anorexia nervosa in psychiatric units in Iceland 1983-2008, incidence of admissions, psychiatric comorbidities and mortality. Laeknabladid 2010;96:747-53.
98. Singhal A, Ross J, Seminog O et al. Risk of self-harm and suicide in people with specific psychiatric and physical disorders: comparisons between disorders using English national record linkage. J R Soc Med 2014;107:194-204.
99. Soeby M, Gribsholt SB, Clausen L et al. Overall and cause-specific mortality in anorexia nervosa; impact of psychiatric comorbidity and sex in a 40-year follow-up study. Int J Eat Disord 2024;57:1842-53.
100. Song A, Koh EJ, Lee WY et al. Suicide risk of chronic diseases and comorbidities: A Korean case-control study. J Affect Disord 2024;349:431-7.
101. Stheneur C, Ali A, Tric L et al. Impact of somatic severity on long-term mortality in anorexia nervosa. Eat Weight Disord 2017;22:285-9.
102. Sullivan PF, Bulik CM, Fear JL et al. Outcome of anorexia nervosa: a case-control study. Am J Psychiatry 1998;155:939-46.
103. Suokas JT, Suvisaari JM, Gissler M et al. Mortality in eating disorders: a follow-up study of adult eating disorder patients treated in tertiary care, 1995-2010. Psychiatry Res 2013;210:1101-6.
104. Suzuki K, Takeda A, Yoshino A. Mortality 6 years after inpatient treatment of female Japanese patients with eating disorders associated with alcoholism. Psychiatry Clin Neurosci 2011;65:326-32.
105. Tolstrup K, Brinch M, Isager T et al. Long-term outcome of 151 cases of anorexia nervosa. The Copenhagen Anorexia Nervosa Follow-Up Study. Acta Psychiatr Scand 1985;71:380-7.
106. Tseng MM, Chien LN, Tu CY et al. Mortality in anorexia nervosa and bulimia nervosa: a population-based cohort study in Taiwan, 2002-2017. Int J Eat Disord 2023;56:1135-44.
107. Tuohisto-Kokko S, Holttinen T, Kaltiala R. Morbidity and mortality after adolescent eating disorders requiring inpatient care. Nord J Psychiatry 2023;77:566-73.
108. Vignaud M, Constantin J-M, Ruivard M et al. Refeeding syndrome influences outcome of anorexia nervosa patients in intensive care unit: an observational study. Crit Care 2010;14:R172.
109. Ward A, Ramsay R, Russell G et al. Follow-up mortality study of compulsorily treated patients with anorexia nervosa. Int J Eat Disord 2015;48:860-5.
110. Winkler LA-D, Bilenberg N, Horder K et al. Does specialization of treatment influence mortality in eating disorders? – A comparison of two retrospective cohorts. Psychiatry Res 2015;230:165-71.
111. Yao S, Kuja-Halkola R, Thornton LM et al. Familial liability for eating disorders and suicide attempts: evidence from a population registry in Sweden. JAMA Psychiatry 2016;73:284-91.
112. Zipfel S, Lowe B, Reas DL et al. Long-term prognosis in anorexia nervosa: lessons from a 21-year follow-up study. Lancet 2000;355:721-2.
113. Monteleone AM, Pellegrino F, Croatto G et al. Treatment of eating disorders: a systematic meta-review of meta-analyses and network meta-analyses. Neurosci Biobehav Rev 2022;142:104857.
114. Schmidt UH, Claudino A, Fernández-Aranda F et al. The current clinical approach to feeding and eating disorders aimed to increase personalization of management. World Psychiatry 2025;24:4-31.
115. Smith AR, Zuromski KL, Dodd DR. Eating disorders and suicidality: what we know, what we don't know, and suggestions for future research. Curr Opin Psychol 2018;22:63-7.
116. Guillaume S, Jaussent I, Olié E et al. Characteristics of suicide attempts in anorexia and bulimia nervosa: a case-control study. PLoS One 2011;6:e23578.
117. Haas V, Kohn M, Körner T et al. Practice-based evidence and clinical guidance to support accelerated re-nutrition of patients with anorexia nervosa. J Am Acad Child Adolesc Psychiatry 2021;60:555-61.
118. Dombrovski AY, Szanto K, Duberstein P et al. Sex differences in correlates of suicide attempt lethality in late life. Am J Geriatr Psychiatry 2008;16:905-13.
119. Chatmon BN. Males and mental health stigma. Am J Mens Health 2020;14:1557988320949322.
120. Gilman SE, Sucha E, Kingsbury M et al. Depression and mortality in a longitudinal study: 1952-2011. CMAJ 2017;189:E1304-10.

121. Piao J, Huang Y, Han C et al. Alarming changes in the global burden of mental disorders in children and adolescents from 1990 to 2019: a systematic analysis for the Global Burden of Disease study. Eur Child Adolesc Psychiatry 2022;31:1827-45.
122. Sanchez-Cerezo J, Nagularaj L, Gledhill J et al. What do we know about the epidemiology of avoidant/restrictive food intake disorder in children and adolescents? A systematic review of the literature. Eur Eat Disord Rev 2023;31:226-46.
123. Barakat S, McLean SA, Bryant E et al. Risk factors for eating disorders: findings from a rapid review. J Eat Disord 2023;11:8.

DOI:10.1002/wps.70014

The art of prescribing psychotropic medications

Clinical experience and research suggest that patients respond best to pharmacotherapy when they feel understood by their prescriber, like their prescriber, and feel that the prescriber likes them. This "therapeutic alliance" is a partnership characterized by a warm, open and caring prescriber sharing responsibility for the medication treatment with a patient who agrees to take the medication as prescribed and accurately report about its efficacy and side effects. For the patient, there is assurance that the prescriber will be available for consultation as the treatment progresses. For the prescriber, there is assurance of a cooperative patient who can be trusted to make contact if any issue related to the treatment arises. Research has shown that medication adherence and treatment outcome are improved in the setting of a valid therapeutic alliance[1].

Why is a therapeutic alliance necessary? The sensible prescriber understands that patients may have many pre-conceived negative thoughts about psychotropic medications. For example, some patients believe that taking a medication means "I must be crazy"[2] or be out of behavioral control. They may think or ask themselves: Do I really need medication? Do I like (trust) this prescriber? Does medication mean that I am weak, emotionally inadequate, a failure in life? Will medications change my personality or my ability to function? Will I lose my creativity, my physical prowess, my emotional sensitivity? For some individuals, taking psychotropic medications may be a sign of characterological weakness, or a failure of religious faith, or disobedience with family (and group) rules, practices and beliefs.

The sensible prescriber understands that, for some people, being prescribed a psychotropic medication is evidence that they are too sick to benefit from psychotherapy or another mental health approach. For some paranoid patients, medication may represent a specific threat to their autonomy. A hopeless depressed person may refuse medication as useless: how will a drug change a hopeless condition? Patients with schizophrenia are sometimes unaware that they are ill and cannot understand the reason for medication. The sensible prescriber recognizes, therefore, that offering medication may be more complicated than simply picking the right drug and dosage. Sensitivity to the patient's background and beliefs can help develop the alliance that will facilitate effective prescribing.

The therapeutic alliance and sensible prescribing can be recognized as examples of transference and countertransference. In many societies, prescribers ("medicine men") are perceived as powerful and authoritarian. Whether a patient can trust and respect a prescriber of psychotropic medications may be influenced by past experiences with prior figures of authority. The sensible prescriber understands that hopelessness, depressed mood and suicidal ideation are not only part of a mood disorder, but may also communicate a long-standing low self-esteem that can be therapeutically explored in a gentle discussion. Some patients are embarrassed by their symptoms and lack of personal control over their behavior, and feel that prescription of a psychotropic medication signals personal failure.

Adult patients, when sick, especially with disturbing or crippling symptoms, may become regressed and needy[3,4], and even act in a child-like manner. In order to not feel helpless, others may behave in an arrogant, insulting, disrespectful way in the consultation. Still others who value rigid control may ridicule the importance of the prescriber and his/her medication. Some individuals believe that only psychotherapy can truly help emotional suffering. In these cases, the patient may demean the prescriber of psychotropic medications as only a "mechanic" who has little appreciation for the complexity of his/her experience. Sometimes these patients may make the prescriber feel uncomfortable or irritated. Some patients may remind the prescriber of someone (such as a parent) who may have been arrogant or insulting, thereby triggering countertransference feelings that might interfere with forming a therapeutic alliance.

There are also individuals whose emotional suffering paradoxically solves some problem in their lives that has resisted solution. This can also be seen in families who praise and support the prescriber, but then manage to interfere with the patient taking the medication. It is not unusual that an individual's psychiatric symptoms may serve to stabilize an otherwise unfixable individual or family problem. The sensible prescriber will understand these dynamics and not insist on treatment with medication until a more stable therapeutic alliance has been created.

One guideline to sensible prescribing and building a therapeutic alliance is for the prescriber of psychotropic medications to recall his/her own emotional responses to illness that required medication treatment. How did you feel when sick, frightened or even disabled in encountering a prescriber for the first time? Was it reassuring, or was it more frightening? Did the prescriber seem to care, show concern, ask useful questions? Did the prescriber look at you or just type into a computer? Did the prescriber become distracted during the interview, seem to rush, look at his/her watch frequently? Did you like the prescriber and did you feel that the prescriber liked you? Would you return for a second consultation?

"Empathic transactions do not occur in a vacuum: a reciprocal relationship exists between the patient and his or her treater"[5]. Prescribing clinicians should fully use their diagnostic and interviewing skills when evaluating an individual for medications. Medication prescription that is associated with sensitive inquiry into the circumstances of the patient's current (and past) psychological difficulties results in an improved therapeutic alliance and better treatment outcome[6]. Prescribing is an art as well as a science. Within the therapeutic alliance, therefore, the prescriber listens to the background and context of the overt symptoms rather than just listening to a recitation of the symptoms[7].

Appreciation of how the patient feels about him/herself can provide a starting point for a valid alliance that may enhance the therapeutic benefits of the prescribed psychotropic medications. For some patients and prescribers, the formation of a therapeutic alliance early in treatment leads to years of therapeutic interaction for chronic and recurrent disorders. Sometimes this alliance focused on medication also becomes the basis for ongoing psychotherapy[8].

The rapidly growing knowledge of the neurobiological underpinnings of some psychiatric disorders is providing an increasingly scientific basis for their drug treatment. However, it is unfortunate that, as prescribers learn more about neurobiology, they appear to be paying less attention to the empathic component of prescribing. It would be helpful to many patients seeking psychotropic drug treatment, as well as to their prescribers, if psychopharmacology training programs included discussions of sensible prescribing and therapeutic alliance in their curricula, in conjunction with the science of psychotropic drug treatments[9].

Carl Salzman
Department of Psychiatry, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA

1. Frank AF, Gunderson JG. Arch Gen Psychiatry 1990;47:226-36.
2. Kahn MW. Rev Psychiatry 1990;47:226-36.
3. Balint M. The doctor, the patient and his illness, 2nd ed. Amsterdam: Churchill Livingstone, 2000.
4. Busch FN, Sandberg LS. Psychotherapy and medication. The challenge of integration. New York: Routledge, 2007.
5. Bennett MJ. The empathic healer: an endangered species? San Diego: Academic Press, 2001.
6. Mintz D. Psychodynamic psychopharmacology. Washington: American Psychiatric Association Publishing, 2022.
7. Chodorow N. The psychoanalytic ear and the sociological eye. New York: Routledge, 2020.
8. Gutheil TG. Bull Menninger Clin 1982;46:321-30.
9. Salzman C. J Nerv Ment Dis 2018;206:380-2.

DOI:10.1002/wps.70034

Off-label use of medications in psychiatry: the need and the caveats

Psychiatric diagnosis is important to guide the formulation of a reasonable therapeutic plan and prognosis. In other areas of medicine, the need for a diagnosis is not a matter of debate, but in psychiatry, due to the variety of theoretical orientations and to social stigma, diagnosis is often seen as an expression of reductionism or as a potentially detrimental label. However, diagnosis provides the foundation for treatment indications, which are strictly regulated for the sake of our patients' safety, especially as far as pharmacotherapy is concerned. Regulators play a central role in the advancement of science and health care, and indications are important because they ensure that an approved drug has a solid scientific evidence for its use in clinical practice.

Drug approval is a long and often bumpy process aimed at ensuring that any new medication is safe and efficacious enough to be placed in the market. Reimbursement policies vary from country to country. Devices are regulated through a different process, while psychotherapies – which are presumed to be free of side effects (wrong assumption[1]) – are often not regulated at all, but are expected to be based on scientific evidence.

Once a new medication has been granted marketing authorization, there is a period of time in which the patent owner has the privilege of exclusivity. After that period, generic versions are allowed and the investments on seeking further indications for the medication rapidly decrease. Unless public funding is placed for this purpose, the lack of financial incentives is likely to discourage the identification of other conditions for which that drug may be indicated.

In psychiatry, the borders between diagnostic categories are often blurred, and there may be overlaps between different categories; this is a major source of so-called "comorbidity". The limited clinical utility of biomarkers in our field leads to the use of "soft" outcomes such as symptom severity scales, and this makes our treatments a bit unspecific. We learnt more from the mechanism of action of drugs discovered by "serendipity" and repurposing than from direct attempts to ascertain the pathophysiology of mental disorders. Moreover, placebo is not easy to beat in the context of a clinical trial[2]. Given this background, there is obviously plenty of room for off-label use of drugs in psychiatry.

Off-label prescription consists of implementing a treatment out of the strict guidance of the approval by the regulatory agencies. Deviations can regard indications (diagnosis), but also doses, treatment duration, adjunctive vs. monotherapy use, age range, and several other aspects. In psychiatry, off-label prescription is extremely common. It is obvious that clinical trials have limited generalizability (for example, a recent report calculated that only 20% of patients with schizophrenia would qualify to be enrolled in a registration trial[3]), and clinicians have to deal with complex patients that are quite different from those who provided the evidence base for drug approval.

It would probably be impossible to practice psychiatry with good results if all prescriptions were in-label. However, drug indications and rules are important, and there is no excuse to ignore them as if they did not exist. The science and art of practicing medicine consists of making the best use of knowledge, tradition, experience and innovation. This often means slightly drifting from the strict statements contained in the summary of product characteristics and the medication package insert.

Off-label prescription is, hence, not ideal but often necessary. Given that psychiatric drugs treat symptoms, not disorders, it is fair to use them in situations where there is no approved alternative, always looking at the specific patient's needs and taking ethical aspects into account. Conditions such as anorexia nervosa, autism, personality disorders, and many more could not be treated pharmacologically otherwise. These and other conditions may benefit from psychosocial approaches, but some symptomatic relief is often necessary, and drugs may help in this regard. Even within approved indications, outliers such as poor or rapid metabolizers may need doses out of the approved range. The whole field of child psychiatry is full of off-label prescriptions[4], due to the limited available research evidence and the substantial unmet needs. The problem of being "too permissive" about off-label drug use mainly concerns the overutilization of drugs such as antipsychotics in vulnerable populations such as children or the elderly, given their safety profile[5].

An open question is to what extent drug regulations and current market access barriers might contribute to the expansion of off-label prescription. For example, in many countries, if a drug is granted a second indication, its price is lowered, resulting in a disincentive to seeking secondary indications for patent owners. So, the same prescription can be, for example, in-label in the US and off-label in the UK.

Treatment guidelines are important to cover the treatment gaps, but some of them rely so heavily on evidence from clinical trials that they fail to provide sensible advice on what to do beyond the approved indications for the available drug armamentarium. Anyway, safety is the priority concern, especially in children and the elderly, and it is necessary to look carefully into the tolerability profile of drugs and to exercise caution[6].

I recommend, before implementing off-label prescription, to look first for suitable in-label options. If these are not available, my advice is to consider guidelines, observational studies, case reports, and ultimately expert opinion supporting a reasonable choice. Make sure that you discuss the pros and cons of your prescription with the patient and, when appropriate, with his/her significant others. Write down in the clinical record the rationale of your decision and the fact that the prescription was based on an agreement with the patient. Finally, follow up the patient and monitor the safety, tolerability and effectiveness of your prescription.

In the future, we may be able to predict treatment response based on genetic, imaging or other biomarkers, which may be the best guidance for safe and efficient prescription. This will be the era of precision psychiatry, which in my view has already started[7,8]. Meanwhile, off-label prescription is still necessary in some cases, and the art of practicing medicine includes assessing the benefit-risk balance for each individual, and deciding when, how and for whom this prescription is appropriate.

Eduard Vieta
Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain

1. O'Neil A, Rossell SL, Berk M. World Psychiatry 2025;24:194-5.
2. Similon MVM, Paasche C, Krol F et al. Eur Neuropsychopharmacol 2022;60:91-9.
3. Taipale H, Schneider-Thoma J, Pinzón-Espinosa J et al. JAMA Psychiatry 2022;79:210-8.
4. Feka A, Di Paolo ER, Pauchard JY et al. Swiss Med Wkly 2022;152:w30124.
5. Hoekstra PJ, Dietrich A. Eur Child Adolesc Psychiatry 2022;31:1-3.
6. Solmi M, Fornaro M, Ostinelli EG et al. World Psychiatry 2020;19:214-32.
7. Vieta E. Rev Psiquiatr Salud Ment 2015;8:117-8.
8. Salagre E, Vieta E. Eur Neuropsychopharmacol 2021;52:94-5.

DOI:10.1002/wps.70035

Euthanasia for mental suffering in young people: a critical global perspective

Medical assistance in dying (MAID) on psychiatric grounds remains deeply controversial, particularly when applied to young adults. In the Netherlands, an increasing number of such requests are made by young women under 30 years, often with complex trauma histories or neurodevelopmental disorders (e.g., autism, attention-deficit/hyperactivity disorder) and intersecting vulnerabilities[1].

The growing prevalence of such cases among young people with complex psychiatric profiles raises fundamental questions about autonomy, irremediability, and the moral authority of medicine. This ethical complexity intensifies when one considers the widespread shortage of accessible mental health care for psychiatric patients. In the Netherlands, over 100,000 patients are on a waiting list for mental health care on an annual basis. At least 20,000 vacancies are expected to open up in the Dutch mental health care sector in the near future. This sector has the highest absenteeism rate, at over 8%, and many professionals are retiring, discouraged by the administrative burden.

In the Netherlands, no legal, ethical or clinical distinction is made – with respect to MAID – between somatic and mental suffering, or between a physical terminal illness, unavoidably leading to death, and chronic mental suffering. Yet, phenomenologically, they are worlds apart[2]. Physical illnesses often have a measurable trajectory; mental suffering is dynamic, relational, existentially driven and context-dependent.

A further ambiguity lies in the question of definitional authority. Who decides what constitutes "unbearable suffering"? Whose judgment counts in establishing that suffering is "irremediable"? Psychiatric assessments of irremediability rely heavily on subjective interpretation, with little empirical consensus or prognostic accuracy. For conditions such as treatment-resistant depression, clinicians cannot reliably predict long-term outcomes, making the irremediability criterion epistemologically unstable.

This uncertainty is compounded when considering young adults. It is questionable whether individuals under the age of 25 can consistently meet the threshold of decisional capacity required for MAID[1]. Especially in cases of persistent low mood and a narrow focus on the underlying death wish, young individuals often lack the experiential perspective needed to imagine recovery or alternative futures, undermining the reflective balance required for informed consent.

Mental suffering is often due to a complex interplay of trauma, meaning, social marginalization, and emotional pain. For young women with histories of complex trauma, requests for euthanasia may reflect not only mental illness but also structural neglect, relational isolation, or a cry for recognition. Some euthanasia requests are the endpoint of unconscious self-destructiveness rather than lucid end-of-life planning[3]. In such cases, the clinical response should be containment and understanding, not terminal intervention.

A common rationale for euthanasia in psychiatric settings is the claim that it prevents violent or traumatic suicides. Yet this argument does not withstand scrutiny. Suicidality is a common and chronic symptom in psychiatric populations, not an isolated end-stage event. There is broad consensus that the clinical approach includes managing risk and treating the underlying cause, not providing euthanasia. There is no evidence that availability of MAID reduces overall suicide rates[4], which is perhaps unsurprising given that completed suicides occur predominantly among men, while euthanasia requests for mental suffering are primarily submitted by women. In fact, the presence of MAID as a socially sanctioned death route may deepen suicidal fixation in vulnerable individuals. The ecological and psychological risks of offering death as an exit strategy are rarely acknowledged in policy frameworks.

Despite the moral gravity of euthanasia decisions, MAID in psychiatric patients is often overseen by physicians operating without multidisciplinary oversight or psychodynamic training. A growing number of cases are handled by older or retired doctors, sometimes without active psychiatric supervision. Physicians, who face important barriers in trauma-informed care, may unconsciously act out countertransference in such situations, colluding with self-destruction instead of offering containment[3].

The Dutch Psychiatric Association has developed detailed guidelines facilitating euthanasia for mental suffering, emphasizing clinical autonomy and individual judgment. However, this position sharply contrasts with those taken by sister organizations in countries such as the UK and Canada, which have expressed strong reservations or outright opposition to psychiatric MAID.

The UK Royal College of Psychiatrists[5] has stated unequivocally that it cannot support the Terminally Ill Adults (End of Life) Bill in its current form, citing insufficient safeguards and lack of meaningful psychiatric oversight. This position reflects a broader ethical stance that mental suffering cannot be equated with terminal illness and requires distinct and robust assessment pathways.

Similarly, the Canadian Psychiatric Association[6] has consistently urged caution. In response to proposed legislation expanding MAID eligibility to individuals with mental illness as the sole condition, the Association highlighted the absence of clinical consensus on irremediability, risks of misinterpreting suicidal ideation, and the need for enhanced training and ethical oversight. These concerns were influential in prompting the Canadian federal government to delay MAID expansion for psychiatric conditions until at least 2027.

Though legally allowed, the Belgian Society for Psychiatrists decided not to support MAID for mentally suffering patients younger than 28, for the same reasons mentioned above – that is, the risk of not being able to judge objectively the death wish, suffering and treatment refractoriness.

The Dutch model thus represents an international outlier, a system where psychiatric MAID is operationalized without a formal distinction between mental and physical suffering and with limited interdisciplinary input. Such disciplinary closure stifles debate, sidelines alternative narratives, and undermines democratic oversight. When dissenting voices are ignored, a small group of activists may exercise disproportional great influence[1]. The appropriation of the sole right to decide on ethical frameworks for euthanasia by Dutch medical interest groups not only demonstrates a failure to recognize the complexity and scope of this ethical issue, but also excludes other scientific disciplines and public opinion on the basis of misplaced medical authority.

Internationally, the practice of psychiatric MAID in the Netherlands has raised concerns. The United Nations (UN) Committee on the Rights of Persons with Disabilities warned that euthanasia for people with psychosocial disabilities violates their right to life and reinforces structural ableism[7]. The International Society for Psychological and Social Approaches to Psychosis[8] similarly warned that normalizing death as an outcome for mental illness undermines therapeutic hope and violates professional ethics.

The Dutch model of psychiatric euthanasia exposes a painful tension at the heart of medicine: on what grounds is medical expertise solely responsible for existential mental suffering? The current practice raises more questions than it answers. At the very least, it demands serious international scrutiny, robust ethical debate, and cross-disciplinary regulation.

Euthanasia may be ethically defensible, but its use in the context of youth, trauma and emotional distress must never become routine. In navigating this terrain, we must hold fast to the principle articulated by C. Saunders[9]: “There is so much more to be done, even when nothing can be done”.

Jim van Os[1], Damiaan Denys[2]
[1]Department of Psychiatry, Utrecht University Medical Centre, Utrecht, The Netherlands; [2]Department of Psychiatry, Faculty of Medicine, University of Amsterdam, Amsterdam, The Netherlands

1. Kiverstein J, Dings R, Denys D. Am J Bioeth 2025;25:59-61.
2. Braun E, Scholten M, Vollmann J. Bioethics 2024;38:61-8.
3. Najjarkakhaki A, Frederickson J, Bloothoofd G. Psychodyn Psychiatry 2025;53:45-60.
4. Doherty AM, Axe CJ, Jones DA. BJPsych Open 2022;8:e108.
5. Royal College of Psychiatrists. The RCPsych cannot support the Terminally Ill Adults (End of Life) Bill for England and Wales in its current form. https://www.rcpsych.ac.uk.
6. Canadian Psychiatric Association. CPA position statement on medical assistance in dying. https://www.cpa-apc.org.
7. United Nations Committee on the Rights of Persons with Disabilities. Concluding observations on the initial report of the Kingdom of the Netherlands. https://undocs.org/en/CRPD/C/NLD/CO/1.
8. International Society for Psychological and Social Approaches to Psychosis. Release of statement on euthanasia. https://isps-us.org.
9. Saunders C. GKT Gazette 1966;80:136-42.

DOI:10.1002/wps.70036

Psychiatric advance directives: challenges emerging from implementation and possible steps forward

A psychiatric advance directive (PAD) is a legal document stating a person's treatment choices, usually combined with the appointment of a proxy decision-maker, for use when the person is going to lack capacity and become unable to faithfully communicate or make treatment decisions.

PADs have been available in the US for more than three decades, although not robustly implemented in practice[1], and have been adopted in some form in a number of other countries, including Australia, Belgium, Canada, Germany, Ireland, India, the Netherlands and the UK, although their legal and clinical context varies considerably across these countries.

PADs can be viewed as an extremely useful device to communicate treatment preferences between the person with mental illness, a health care proxy, and health care providers. Many adults with serious mental illnesses are indeed able, based on previous experiences, to anticipate and competently plan ahead for a future mental health crisis. By giving advance consent to a needed hospital admission, the choice of effective treatment, and the appointment of a trusted person to serve as a health care proxy, the person may avoid the potentially traumatic loss of control that often comes with forced mental health treatment and confinement.

Research has shown that adults with serious mental illnesses, when given assistance, can complete legally valid PADs, and that these documents help them obtain effective crisis treatment[2]. Clinicians and family members of persons with serious mental illness largely endorse PADs in concept[3]. According to a study of over 1,000 psychiatric outpatients in five US cities, there is still a large latent demand for PADs among persons with mental illness[4]. However, a Cochrane review of PADs failed to find strong evidence for effects on hospital admissions, treatment compliance, self-harm or number of arrests[5], although the review included only two randomized controlled trials and failed to evaluate other types of interventional or observational studies.

Challenges to PAD implementation identified by research include difficulty of completing PAD documents without assistance, inadequate infrastructure for timely retrieval of PAD information, clinicians' lack of knowledge of PADs, tendency of clinicians to override lack of consent with involuntary commitment, and health systems' lack of buy-in to implement PADs[6]. Further challenges include clinicians' fear of legal liability from complying with PADs, fear that patients will use PADs to refuse appropriate treatment, fear that PADs will interfere with other clinical aspects of care, and issues with enforceability and revocability of PADs[7].

There is indeed considerable controversy about revocability, and particularly how binding the PAD should be when a patient, in the present, disagrees with the previously stated preferences. In jurisdictions where PADs are intended to be "self-binding", they are deemed irrevocable when the patient is incapacitated, and thus they are effectively "Ulysses contracts" – referencing the Greek mythology wherein Ulysses commanded his crew to bind him to the mast of his ship and ignore the call of the sirens, even if he subsequently wished to follow the sirens. Ethical scholars have long debated the notion of overriding the current preferences of a patient in favor of previous stated preferences and, as a result, some PADs are designed not to be self-binding. Advocates for supported decision-making often disagree with the notion of overriding a patient's current treatment preferences, even if he/she is incapacitated, in favor of assisting the patient in making his/her own decisions, even with difficulty[8].

PADs are essentially a mechanism for communication among key actors in psychiatric crisis treatment. They have been shown to work well in controlled clinical research settings, but often tend to fail in ordinary community-based services and crisis care. Several operational barriers must be addressed to enhance both the "transmitter" and "receiver" features of PADs.

On the "transmitter" side, PADs require enough awareness of the illness to allow the patient to construct a future plan of care. The person must be able to decode a statutory form with often-dense legal language, complete witnessing and notarization, and file the PAD in an appropriate health care record. The completed PAD itself must be informative, coherent and succinct, in order to be helpful in often busy crisis settings. Trust serves a critical role in the PAD process: the person must be able to trust the legal authority of PADs, and trust the health care proxy to serve as an effective advocate during a crisis. Unfortunately, many health care proxies are not adequately prepared for their role, especially because this requires them to navigate an often confusing crisis care in order to effectively represent the preferences of the person in crisis.

These "transmitter" features of PADs may be formidable barriers for people with serious mental illnesses. Fortunately, studies have shown that assistance with PAD completion can overcome these barriers. Research staff, clinicians, peer support specialists and family members can effectively assist in PAD completion[9]. Such support is also being developed via computer assistance, but this is yet untested. Unfortunately, models of training for health care proxies on maximizing the effectiveness of their role are sorely lacking, although critical to assuring PAD implementation.

On the "receiver" side, free-standing websites for storage of advance care planning documents have been increasingly replaced by storage in electronic health records, although they are often not retrieved there, because there are relatively few PADs in the record and due to lack of clinicians' familiarity with PADs. In the US, health care systems are legally required to comply with PADs, otherwise risking the loss of federal insurance reimbursement. However, lapses in compliance are typically investigated only following patient complaints, and systematic enforcement is lacking. Unlike the growing influence of public campaigns in the US to encourage attention to advance care planning in general health care, there are no analogous campaigns encouraging PAD creation or their general awareness.

Legal activation of a PAD occurs when a physician or other authorized clinician documents the patient's lack of capacity to make treatment decisions in the clinical record. Declaring a patient incapable, which puts into motion the PAD's decision making authority, is often an informal clinical process, distinct from a legal adjudication of incompetency. Training is needed for clinicians on their crucial role in implementing PADs in times of crisis, and the potential benefit of incorporating PADs in clinical care.

PADs have the promise of preserving a sense of autonomy and significantly improving crisis care for psychiatric patients. Although this is largely untested, they could also improve outcomes for persons with serious mental illnesses by optimizing their care, avoiding involuntary treatment, and even reducing the risk of criminal justice involvement. Increasing public awareness, advocacy by patients' rights constituencies and regulatory leverage have brought end-of-life advance directives into routine use in several countries. Dissemination of PADs lags far behind, but use of the same levers could allow them to realize their promise.

Marvin S. Swartz, Jeffrey W. Swanson
Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine, and Wilson Center for Science and Justice at Duke University School of Law, Durham, NC, USA

1. Substance Abuse and Mental Health Services Administration. A practical guide to psychiatric advance directives. Rockville: Substance Abuse and Mental Health Services Administration, 2019.
2. Lenagh-Glue J, Potiki J, O'Brien A et al. Psychiatr Serv 2021;72:216-8.
3. Swanson JW, Swartz MS, Ferron J et al. J Am Acad Psychiatry Law 2006;34:43-57.
4. Swanson JW, Swartz MS, Hannon MJ et al. Int J Forensic Mental Health 2003; 2:73-86.
5. Campbell L, Kisely S. Cochrane Database Syst Rev 2009;1:CD005963.
6. Swartz MS, Swanson JW, Easter MM et al. Psychiatr Serv 2021;72:219-21.
7. Shields LS, Pathare S, van der Ham AJ et al. Adm Policy Ment Health 2014;41:753-66.
8. Knight F, Kokanovic R, Ridge D et al. Qual Health Res 2018;28:1002-15.
9. Easter MM, Swanson JW, Robertson AG et al. Psychiatr Serv 2017;68:717-23.

DOI:10.1002/wps.70037

New WHO guidance on mental health and well-being across government sectors

Mental health and well-being are foundational to both individual and societal health and overall development. No society can truly prosper without them, as mental health is central to all areas of life and essential for communities to thrive.

The unprecedented convergence of multiple global crises and shocks, including climate change, conflict and epidemics/pandemics, is having profound and direct effects on mental health and well-being worldwide, while also exacerbating and compounding social and structural determinants that undermine mental health and well-being[1-3].

Because mental health is deeply interconnected with all sectors, addressing these challenges cannot be the responsibility of the health sector alone. Action across all sectors is essential – not only to improve mental health and societal well-being, but also to foster overall development, promoting social inclusion, equity, universal health care, human rights, and sustainable economic progress. Yet, in most countries, policies, strategies and plans across government sectors – including but not limited to health – do not adequately reflect or address the determinants of mental health and well-being.

To support governments in this effort, the World Health Organization (WHO) has developed a new Collection of resources titled "Mental health and well-being across government sectors", a practical package designed to help countries embed mental health and well-being into policies across all government sectors.

The Collection has two main parts:

- The overarching document, *Guidance on policy and strategic actions to protect and promote mental health and well-being across government sectors*[4]. This provides the full framework and roadmap for governments and partners seeking to integrate mental health across all areas of public policy, while also helping sectoral stakeholders understand how their mandates connect with and reinforce other sectors.
- Twelve companion documents, including one focused on cross-sectoral policy directives and strategic actions, and eleven sector-specific guides (e.g., education, justice, employment, environment, social protection). These reproduce relevant sections of the overarching Guidance, so that sector-specific stakeholders can easily access what applies to them, enhancing dissemination and uptake.

The overarching Guidance in the Collection supports governments to identify how sector mandates, policies and plans influence mental health, and provides practical steps to embed mental health and well-being into the development, implementation and evaluation of sectoral strategies. It emphasizes the role of structural and social determinants in shaping mental health and provides concrete actions through which sectors can contribute to advancing mental health and well-being.

The Guidance highlights the close and mutually reinforcing links between mental health and the United Nations' Sustainable Development Goals (SDGs), showing that mental health intersects with nearly all of the Goals[5]. Promoting mental health supports progress on education, employment, justice, equality, climate action, and peace-building, among other areas. At the same time, protecting mental health reinforces the realization of international human rights commitments, including the right to the highest attainable standard of mental health.

Given these interconnections, a whole-of-government and whole-of-society approach is essential. This requires integrating mental health considerations into policies and investments across all government sectors, from national to municipal levels. Key sectors include: culture, arts and sport; defence and veterans; education; employment; environment, conservation and climate protection; health; interior; justice; social protection; and urban and rural development.

The Guidance begins by outlining the rationale for cross-sectoral action, the development imperatives tied to the SDGs, and the core principles that must underpin any whole-of-government approach. These include a human rights-based lens, life-course perspective, attention to structural and social determinants, meaningful participation of people with lived experience, elimination of stigma and discrimination, and use of evidence-based strategies.

It proposes eight flexible, adaptable, interlinked process steps to integrate mental health into sectoral policies and plans. These steps can be implemented, adapted and tailored to different country contexts, sectors, and institutional structures. They include:

- Initiate high-level policy dialogue to build commitment and engage senior leadership on the benefits of addressing mental health.
- Raise awareness and shift mindsets to integrate mental health into sector-specific policy, strategies and plans.
- Review existing policies and strategies to assess how well they support mental health, using the Guidance as a reference.
- Form an inclusive drafting team with broad representation from government sectors, affected communities, and people with lived experience.
- Revise or develop policy content based on gaps identified in the review and a situational analysis.
- Consult stakeholders and the public to gather feedback, address concerns, and refine the draft.
- Implement the policy and plan through updated procedures, training, and clear targets, timelines, budgets and indicators.
- Monitor and evaluate progress continuously to ensure effectiveness, responsiveness and accountability.

At the core of this overarching Guidance are two key components. First, it presents a set of government-led cross-sectoral policy directives and strategic actions, focused on whole-of-government leadership, political prioritization, accountability and financing. These are designed to support national leadership in advancing mental health and well-being across all sectors and areas of public administration.

Second, it offers detailed, sector-specific guidance for the key government sectors noted above. Each sectoral chapter includes an overview and a menu of policy directives and associated strategic actions, along with illustrative indicators to guide adaptation, implementation and monitoring.

The Guidance reaffirms that integrating mental health into sectoral policies and plans requires strong political will, inclusive stakeholder engagement, adequate financial resources, and clear accountability mechanisms. It emphasizes that many relevant actions already fall within the core mandates of government sectors and can be enhanced through deliberate alignment with mental health objectives.

This WHO Guidance provides a practical and flexible roadmap for embedding mental health and well-being into all areas of public policy. It helps governments identify shared priorities, coordinate action, and ensure that mental health is protected and promoted as a public good.

Importantly, this new Collection builds on earlier WHO work. It should be used in conjunction with the Guidance on mental health policy and strategic action plans[6,7], launched in March 2025. While that document focused specifically on strengthening leadership, governance, service delivery, and workforce capacity within the mental health sector, the new Collection expands the focus to all government sectors.

We urge governments and sector leaders to apply this Guidance in developing and implementing strategies that prioritize mental health and well-being across all government sectors, and to ensure that this work is grounded in human rights, social inclusion, and sustainable development.

Michelle Funk, Natalie Drew, Celline Cole, Maria Francesca Moro
Department of Mental Health, Brain Health and Substance Use, World Health Organization, Geneva, Switzerland

1. World Health Organization. Social determinants of mental health. Geneva: World Health Organization, 2014.
2. Kirkbride JB, Anglin DM, Colman I et al. World Psychiatry 2024;23:58-90.
3. Campion J, Javed A, Lund C et al. Lancet Psychiatry 2022;9:169-82.
4. World Health Organization. Guidance on policy and strategic actions to protect and promote mental health and well-being across government sectors. Geneva: World Health Organization, 2025.
5. United Nations. The 17 Sustainable Development Goals. https://sdgs.un.org/goals.
6. World Health Organization. Guidance on mental health policy and strategic action plans. Module 2: key reform areas, directives, strategies, and actions for mental health policy and strategic action plans. https://www.who.int/publications/i/item/9789240106819.
7. Funk M, Drew N, Cole C et al. A new WHO roadmap for mental health policy reform. World Psychiatry 2025;24:441-2.

DOI:10.1002/wps.70016

Artificial intelligence and psychiatric diagnosis: a warning to the mental health community

Artificial intelligence (AI) will soon be better than humans at almost everything, and psychiatric diagnosis is likely to be no exception. The pace of the AI revolution is astounding; its reach ubiquitous; its development unregulated; its potential impact both wonderful and terrible; its implications largely undiscussed.

Most psychiatrists are uninformed about AI's exponentially expanding power and/or in denial about the profound impact that it is going to have on our patients and profession. Complacency is a common response: the assumption that psychiatry is so personal and human that it could not possibly be practiced by a machine. This is demonstrably false. AI psychotherapy bots are already in widespread use and very popular among patients[1].

My goal here is to explore three topics: ways in which AI may be superior to humans in psychiatric diagnosis; dangers posed by AI; and the potential for psychiatry to develop a collaborative relationship with AI.

The most obvious potential advantage of AI in psychiatric diagnosis is the vast and varied data base that it can tap. A human clinician may diagnose a few thousand patients over an entire career; AI will have experience with millions. AI diagnosis may also be more systematic, thorough, accurate, data driven, and reproducible; as well as less subjective, impressionistic and idiosyncratic. AI can scan the entire scientific literature pertinent to each patient and apply it in a personalized way.

Most important, AI is far superior to humans in pattern recognition. Thus, it may discover new patterns of psychopathology previously not identified by human nosologists, relating onsets, symptom presentations, history, medical problems, medications, substance use, course, family history, genetics, biological test results, social risk factors, and many other variables that have never occurred to us.

Moreover, AI is going to beat human diagnosticians in cost, convenience and accessibility. Most of the world has a shortage of mental health practitioners, and those who are available are often geographically inaccessible, expensive and/or too busy. AI will soon be available everywhere, at little cost, on call 24/7. In addition, human clinicians are prone to over-diagnosing people who differ in race, language, socioeconomic status, religion, or cultural background. Once AI develops a diverse data set, it will most likely be fluent, knowledgeable, and diagnostically accurate across cultures.

The most fundamental AI advantage is its fantastic ability to crunch numbers and calculate probabilities, allowing it to perform sophisticated dimensional diagnosis. Humans are great at naming things, but awful at describing them with numbers. This explains why we are stuck using inaccurate categorical diagnostic systems such as the DSM and ICD. Mental disorders occur on a continuum with each other and with normality. Assuming that they are completely present or completely absent brings about the loss of a great deal of information and a distortion of clinical reality. AI is masterful at instantaneously manipulating the vast complexity of numbers needed to describe clinical reality.

On the other hand, because AI responses are based on calculating so many probabilities, mistakes will be inevitable. It is a statistical certainty that a small percentage of responses will be outliers that make no clinical sense. Unfortunately, AI does not like to be caught in mistakes, and will sometimes stubbornly lie to cover them up. AI scientists admit that they have difficulty detecting errors and usually cannot explain how and why they occurred.

Worst of all, humanity is rushing headlong into the AI revolution without the safety data necessary to ensure that benefits will exceed harms. Fiercely competitive AI companies focus on profit, not safety. Techies with no clinical experience have been let loose with no regulation. AI algorithms have as their primary goals maximizing engagement and collecting data that can be monetized. New apps are offered without the systematic research necessary to compare their accuracy with clinical diagnosis and with each other. There is no reason to believe that different AI systems will agree with one another, and no way to judge which is most accurate, valid, robust, useful and safe.

AI is being used as a screening tool to identify people with unrecognized psychiatric disorders and to predict those likely to develop them in the future. The potential is appealing, but risks are enormous. Screening tests always have a high false positive rate, that can result in overdiagnosis, overtreatment and stigma. AI companies will be tempted to set low thresholds for diagnosing pathology in order to increase numbers of users.

The widespread use of AI will lead to massive data collection on psychiatric patients, risking massive invasions of privacy. Data are never safe from misuse, and risks escalate as data systems get larger, more concentrated, and more widely disseminated. AI-generated diagnostic data might easily be subject to breaches, unauthorized use, ransomware, cyber hacking, identity theft, Internet bullying or exploitation, discrimination in hiring or licensing, insurance denials, and so on. And we cannot assume that centralized data collection will always be in benign hands. Let's not forget that Nazi extermination of psychiatric patients was facilitated by IBM machines used in identifying them.

AI creators are themselves in the dark about how it works, its potential emergent properties, and how to ensure that its incentives remain aligned with ours. Fierce competition among powerful companies and across countries drives a frenetic pace of development. In this atmosphere, regulation has been, and may always be, impossible.

The spread of AI diagnosis is inevitable and unstoppable. The only question is whether AI will be a tool used by human psychiatrists or whether it will replace us.

Radiology provides an attractive model for psychiatry. Because AI is far better than any human at reading images, it seemed inevitable that radiology would be the first medical profession to be replaced. Instead, radiology is still thriving, because radiologists have adapted to a team approach, using AI as a powerful diagnostic tool, but carving out the tasks that humans do best: clinical coordination and communication. Human clinicians and AI working together are better than either working alone[2].

We must similarly find ways to work cooperatively with AI, rather than ignoring or competing with it. Human clinicians are much better in dealing with emergencies and novel presentations that are outside AI's database. We are needed for quality control to detect and correct mistakes. We are able to spot important human psychological and social contexts lost in the numbers. We will be useful in coordinating psychiatric and medical treatments. And there are times when only the human touch will do, and some patients will insist on human clinicians.

There is a real danger that mental health workers may gradually be deskilled by AI, and become excessively dependent on it. This would grease the slippery slope toward our being replaced by AI. If psychiatrists are to remain relevant, we must become better and better psychiatrists.

Mental health associations have been up to now passive and powerless in addressing the grave risks that AI presents to our patients and professions. They do worry about the lack of AI safety research, regulation, and public education, and do lobby for government protections against AI products that deceptively pretend to be human. But none of this has had any impact up to now. The only (perhaps forlorn) hope is that mental health advocacy groups around the world come together with one strong voice articulating AI dangers. This could be coordinated by the World Health Organization and/or the World Psychiatric Association. The stakes are high: the safety of our patients, the viability of our profession, and perhaps even the survival of humanity.

Allen Frances
Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine, Duke University, Durham, NC, USA

1. Zao-Sanders M. How people are really using generative AI now. Harvard Business Review, April 9, 2025.
2. Twenter P. Mayo Clinic radiology leads in AI use. Becker's Hospital Review, May 14, 2025.

DOI:10.1002/wps.70015

Do generative AI chatbots increase psychosis risk?

A growing body of clinical trials and meta-analyses shows that generative artificial intelligence (AI) chatbots can reduce psychiatric symptoms, confirming their therapeutic potential. The vast majority of this research is case based, with low quality evidence. More clinically focused research has demonstrated reductions in anxiety and depression scores, but only against a waitlist control group. Yet, the rapid progress in AI, especially with the newest generation of large language models (LLMs), suggests that progress may be rapid and we should expect widespread use for mental health in the near future[1].

What this will mean for those with serious mental illness or at risk for psychosis remains unknown. There are increasing concerns that chatbots often fail to recognize serious mental health problems, including suicidality, and to provide appropriate responses such as referral to a support service. Moreover, open-ended systems such as ChatGPT shape replies to the user's private cognitive world, blurring the line between external conversation and internal thought. This is what might make individuals at risk for psychosis particularly vulnerable.

Early warning signs are already visible. The Rolling Stone magazine published an article in May 2025 on users who reported in different online forums worsening psychosis symptoms after ChatGPT confirmed their delusions[2]. Shortly after, the company rolled back the update, explaining that it was "overly flattering or agreeable". A recent Wall Street Journal article reported that ChatGPT "admitted" to ignoring signs of psychological distress to a young man who appeared to have developed psychosis symptoms in relation to the chatbot use[3]. Not only these anecdotal reports allude to novel risks, but the fact that they are appearing in the popular press media instead of medical journals highlights how far behind the psychiatric field already is.

There is increasing concern that LLMs may "generate delusions" by supplying elaborate, convincing-but-false narratives that slot seamlessly into pre-existing psychotic frameworks[4]. Popular mental health outlets are now documenting users who withdraw socially, converse compulsively with the chatbot, and begin to hallucinate textual voices when the device is off. Why might generative AI increase psychosis risk in vulnerable individuals? Several mechanisms may be involved.

First, *social substitution*: the continuous, on-demand dialogue available in generative AI chatbots satisfies the affiliation needs of individuals at risk for psychosis who are already often socially isolated. By serving as a virtual, pseudo-social, seemingly compassionate and accommodating companion, the device can lead to further withdrawal from a society that may be judgmental and stigmatizing. Use of the widely accessible AI platforms may also induce at-risk individuals not to utilize potentially corrective interpersonal feedback.

Second, *confirmatory bias*: generative AI may reinforce users' existing beliefs by preferentially generating "sycophantic" responses[5] that are in alignment with users' way of thinking, rather than presenting a balanced perspective or challenging them. These responses can be highly impactful on patients with psychosis, known to have a bias against dis-confirmatory evidence[6]. Delusion-prone individuals also tend to have a need for closure, and may therefore choose to jump to hasty conclusions with limited evidence. This may occur when they are presented with explanations from generative AI that may appear convincing[7].

Third, "*hallucinations*" can occur with LLMs when they generate text that sounds plausible but is false, misleading, or unsupported by data. If the LLM model has little or no data on a topic, it may "fill in the blanks" with made-up information that fits linguistically but is not real. Users with psychosis or those at-risk struggle to distinguish between imagined and real contents.

Fourth, *assignment of external agency*: generative AI content and features, including speech and video generation, which believably resemble those of humans, may blur reality testing and make vulnerable individuals attribute agency, sentience and intelligence to them. The tendency of users to accept advice from AI may be related to such attribution[8]. Since the model "learns" about the user, it can appear to know information beyond what was fed to it. This algorithmic prediction can be construed as some credible omniscient intelligent agent, which could result in the user having high trust in the AI, that may turn delusions which started as epistemically innocent into a more persistently harmful version.

Finally, individuals at risk for psychosis are thought to have an *aberrant salience* which, in the absence of appropriate contextual validation, may maladaptively update the representation of the world with irrelevant information[8].

Thus, several aspects of AI may likely interact with the psychological predisposition to psychosis. Together, all the above factors might conspire to facilitate maladaptive updating of external sensory inputs, thus increasing the risk of AI-associated psychosis-related symptoms.

Regulatory and professional bodies have begun to respond to this situation. The World Health Organization's 2024 guidance on large multimodal models urges governments to require human oversight, transparency of training data, and real-time risk monitoring before deployment in health contexts[9]. Related efforts by the UK Medicines and Healthcare Products Regulatory Agency, the US Food and Drug Administration, the Australian Therapeutic Goods Administration, and the European Medicines Agency highlight the global awareness of a need for oversight.

Yet, while these efforts are welcome, most are not yet codified into enforceable standards. More research is clearly needed to understand the relationship between generative AI use and risk for psychosis and other psychiatric conditions. At the same time, there are competing pressures from governments and even the health care sector for AI to assume a larger role in care to help bridge unmet clinical needs. And AI will itself continue to evolve and change, introducing a brand new set of risks and benefits.

Thus, there is merit in a flexible framework approach. We propose three priorities: a) design guardrails such as mandatory psycholinguistic filters that monitor and detect prolonged circular dialogue, self-harm or persecutory content, and prompt referral to humans in the feedback loop, or forced "time-out" features; b) clear, user-facing, disclaimers that the system is not a human, combined with session-length caps and built-in digital hygiene nudges; and c) automatic hand-off pathways to licensed professionals when risk thresholds are met. Given the clinical concerns and the current limitations of governance, generative AI-based approaches should be best used as a supportive tool by the clinician working with patients in the context of a broader treatment plan.

In conclusion, while generative AI chatbots offer promising opportunities for mental health support, their use among individuals vulnerable to psychosis presents significant and underrecognized risks. The sycophantic and anthropomorphic nature of these systems may unintentionally amplify psychotic processes through mechanisms such as social substitution, confirmatory bias, and blurred reality testing.

As these technologies advance rapidly, clinical research, regulatory frameworks, and ethical oversight must evolve in parallel. Proactive integration of safety mechanisms, combined with a human-in-the-loop model, is essential to safeguard vulnerable users and to ensure that AI serves as a responsible adjunct – not a substitute – for human care.

Matcheri Keshavan, John Torous, Walid Yassin
Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA

The authors acknowledge Meghana Keshavan for her insights as a ChatGPT super-user.

1. Torous J, Linardon J, Goldberg SB et al. World Psychiatry 2025;24:156-74.
2. Klee M. People are losing loved ones to AI-fueled spiritual fantasies. Rolling Stone, May 4, 2025.
3. Jargon J. He had dangerous delusions. ChatGPT admitted it made them worse. Wall Street Journal, July 20, 2025.
4. Østergaard SD. Schizophr Bull 2023;49:1418-9.
5. Du Y. arXiv 2025;2504.09343.
6. McLean BF, Mattiske JK, Balzan RP. Schizophr Bull 2017;43:344-54.
7. Colombatto C, Birch J, Fleming SM. Commun Psychol 2025;3:84.
8. Corlett PR, Murray GK, Honey GD et al. Brain 2007;130:2387-400.
9. World Health Organization. Ethics and governance of artificial intelligence for health: guidance on large multi-modal models. www.who.int.

DOI:10.1002/wps.70017

Process-outcome effects in psychotherapy research: an umbrella systematic review and meta-analysis

Understanding how therapeutic processes are related to treatment outcome is one of the main challenges in psychotherapy research[1,2]. Although process-outcome research has grown exponentially in the last two decades, with several meta-analyses available, no prior study has synthesized these findings across the whole range of therapeutic processes associated with outcome. We performed an umbrella systematic review of process-outcome meta-analyses, classifying them into conceptual categories, and estimating aggregate outcome effects for each type of process.

A systematic search was conducted in PubMed and PsycINFO databases in February 2024, with an updated search in March 2025. We included meta-analyses focusing on the relationship between process/es and outcome, and reporting at least one correlational effect size. The first title and abstract screening was performed by two independent reviewers (agreement: 94%). On a second step, full manuscripts were checked for eligibility (agreement: 89%). Disagreements at each stage were addressed by consensus. In the included studies, reviewers coded information from both the meta-analyses and primary studies.

Processes of change were classified in the following categories[3]: relational processes, technical processes, patient processes, and therapist processes. Intersession processes focusing on the time between sessions (such as homework compliance) were not integrated into the systematic search.

We extracted all primary study correlational effect sizes (usually Pearson's correlations) that represented an association between a psychotherapy process and a post-treatment outcome (including primary and secondary outcomes). We conducted four-level meta-analyses estimating sample variance of the effect sizes (Level 1), between-effect size variance (Level 2), between-primary studies variance (Level 3), and between-meta-analyses variance (Level 4), using the R package metafor[4]. We first transformed correlational effect sizes into Fisher's z[5]. To enhance interpretability, the results were back-transformed into correlation coefficients (see also supplementary information).

There were 60 meta-analytic studies that examined 24 different processes of change meeting inclusion criteria for the systematic review. The working alliance was the most studied process of change, with 25 meta-analyses providing effect sizes for its association with outcome. The other most meta-analyzed processes were adherence/competence/fidelity/integrity in therapeutic interventions (four meta-analyses), and patient treatment expectations (three meta-analyses). The majority of the meta-analyses examined relational processes (n=39; 65.0%), followed by technical (n=7; 11.7%), therapist (n=9; 15.0%), and patient (n=6; 10.0%) processes. One meta-analysis explored both therapist and patient processes.

The category of relational processes was dominated by the working alliance[6]. It also included further processes related to the alliance, but also having conceptual specificity, such as real relationship, alliance rupture-resolution, goal consensus collaboration or congruence/genuineness, counter-transference experiences, group cohesion, patient-therapist mutuality or nonverbal synchrony.

The technical processes included therapist behaviors related to the adherence, competence, fidelity and integrity to/of theory-specific interventions or methods. Some of these techniques were evaluated generically (e.g., cognitive-behavioral or psychodynamic interventions), while in other cases meta-analyses explored the effect of specific theory-driven techniques, such as homework assignments and use of psychodynamic interpretations.

The therapist processes category included other, non-technical therapist behaviors, such as therapists' cultural/multicultural competences, cultural humility, positive regard, empathy, emotional expression or behaviors seeking patients' emotional expression.

The patient processes included patients' experiences within treatment that might be connected to psychotherapy outcome, such as emotional expression, cognitive restructuring, and treatment expectations and credibility.

Out of the 60 meta-analyses included, 48 reported primary studies information. From those meta-analyses, we extracted 1,981 effect sizes from 993 unique primary studies.

The four-level meta-analytic model suggested an average process-outcome effect of r=0.238, z=0.243, SE=0.012, 95% CI: 0.219-0.267, t_{1980}=19.94, p<0.001, with significant heterogeneity among the effect sizes (Q_{1980}=7388.1, p<0.001).

When including types of process as moderators, the aggregated process-outcome associations of all the categories were significant. Following process-specific rule of thumbs for effect sizes interpretation[7], the models showed small effects on outcome for technical processes (r=0.102, p<0.001), small-to-medium effects for patient processes (r=0.227, p<0.001), medium effects for relational processes (r=0.267, p<0.001), and medium-to-high effects for therapist processes (r=0.291, p<0.001).

In the comparison of the effect sizes across the different types of process, the association of technical processes with outcome was significantly lower compared to relational processes (z=0.172, SE=0.022, 95% CI: 0.058-0.146, t_{1977}=6.95, p<0.001), therapist processes (z=0.198, SE=0.037, 95% CI: 0.126-0.270, t_{1977}=5.42, p<0.001), and patient processes (z=0.129, SE=0.034, 95% CI: 0.062-0.197, t_{1977}=3.79, p<0.001).

There were no significant differences between the effect sizes of relational and therapist processes (z=0.026, SE=0.031, 95% CI: –0.035 to 0.087, t_{1977}=0.83, p=0.409), relational and patient processes (z=–0.043, SE=0.028, 95% CI: –0.099 to 0.013, t_{1977}=–1.50, p=0. 135), or therapist and patient processes (z=0.068, SE=0.039, 95% CI: –0.008 to 0.145, t_{1977}=1.75, p=0.081).

This is the first comprehensive systematic review of meta-analyses examining processes of change in psychotherapy, providing estimates of the effect size for each type of process. Our results indicate that all the processes explored have significant effects, ranging from small to medium-to-high sizes. These findings advance our understanding of how psychotherapies work, providing evidence that can be useful to support their enhancement.

Relational, therapist and patient processes were found to have significantly greater effect sizes than technical processes. These findings match empirical and theoretical developments in the field supporting the relevance of therapeutic processes outside the disorder- and orientation-specific framework of specific techniques[8,9]. However, it is important to note that the processes involved in psychotherapy change are not discretely separated, but operate together during treatment. This interaction should be the target of future specific studies.

Juan Martín Gómez Penedo[1-3], **Christoph Flückiger**[1]
[1]University of Kassel, Kassel, Germany; [2]Osnabrück University, Osnabrück, Germany; [3]Vrije Universiteit Brussel, Bruxelles, Belgium

Supplementary information on this study is available at https://osf.io/xn9y7.

1. Crits-Christoph P, Gibbons MBC. In: Barkham M, Lutz W, Castonguay LG (eds). Bergin and Garfield's handbook of psychotherapy and behavior change, 7th ed. Hoboken: Wiley, 2021:263-95.
2. Wampold BE, Imel ZE. The great psychotherapy debate: the evidence for what makes psychotherapy work, 2nd ed. New York: Routledge, 2015.
3. Orlinsky DE, Rønnestad MH, Willutzki U. In: Lambert MJ (ed). Bergin and Garfield's handbook of psychotherapy and behavior change, 5th ed. New York: Wiley, 2004:307-89.
4. Viechtbauer W. J Stat Softw 2010;36:1-48.
5. Borenstein M, Hedges LV, Higgins JPT et al. Introduction to meta-analysis. Chichester: Wiley, 2009.
6. Flückiger C, Del Re AC, Wampold BE et al. Psychotherapy 2018;55:316-40.
7. Gómez Penedo JM, Flückiger C. Psychother Res 2025; doi: 10.1080/10503307.2025.2494270.
8. Asay TP, Lambert MJ. In: Hubble MA, Duncan BL, Miller SD (eds). The heart and soul of change: what works in therapy. Washington: American Psychological Association, 1999:23-55.
9. Cuijpers P, Miguel C, Harrer M et al. World Psychiatry 2023;22:105-15.

DOI:10.1002/wps.70018

A data re-analysis confirms the value of symptom networks in predicting psychotherapy outcome

In a paper published in this journal[1], we reported that person-specific symptom associations were highly predictive of short- and long-term outcome of psychotherapy for patients with chronic depression. In that analysis, individual symptom associations and their change through treatment were indicated by person-specific symptom networks, estimated by a multilevel longitudinal network model. Subsequently, the estimated change in symptom associations was used to predict clinician-rated treatment outcome.

The network model that we used assumed that all change in symptom severity during psychotherapy was due to changing symptom associations. In contrast, traditionally used models in psychotherapy research consider that, in addition to the variables of interest (e.g., treatment group), an unknown number of unmeasured variables (e.g., developing therapeutic alliance) might impact change in symptom severity. Traditional models capture the collective effect of these unmeasured variables by a main effect of time[2]. By assuming that change in symptom severity is only due to changing symptom associations – i.e., not including the main effect of time – our network model did not consider these further potentially influencing factors.

Moreover, when predicting short- and long-term treatment outcome, only changes in symptom associations during treatment, but not changes in symptom severity, were included as predictors. In other terms, our study did not assess to what extent change in symptom associations show an improved prediction of (long-term) treatment outcome beyond change in symptom severity. Aligning the analysis with the more traditional framework of assessing treatment effects, i.e. changes in symptom severity, ensures that findings can be more directly compared and understood by clinical researchers and clinicians, alongside the broader psychotherapy literature. Additionally, it can clarify the incremental predictive value of symptom associations.

We therefore extended our analysis considerably, in order to allow a comparison with more traditional treatment effect models. The network model was extended by including a linear main effect of time and the interaction between time and treatment group. This extended network model considers that change in symptom severity might be due to changes in symptom associations and/or time (implicitly capturing the effect of unmeasured variables). We estimated this network model with the original data on self-rated depressive symptoms during psychotherapeutic treatment for chronic depression. We then re-ran the outcome prediction analysis to determine the predictive value of the updated symptom association change parameters for short- and long-term treatment outcome. Going beyond the original paper, in this further analysis, we also evaluated the predictive performance of symptom severity and symptom associations, and to what extent symptom associations predict beyond symptom severity.

In this re-analysis, the unique prediction with change in symptom associations (based on the updated network model) yielded results similar to the original findings[1], explaining 53% of the variance of depression severity at treatment end (adjusted R^2=0.53; 95% credibility interval, CI: 0.47-0.58). Change in symptom severity during treatment explained 47% of the variance (adjusted R^2=0.47, 95% CI: 0.40-0.53). The combined prediction with change in symptom severity and change in symptom associations increased the explained variance to 56% (adjusted R^2=0.56, 95% CI: 0.50-0.61).

For observer-rated depression severity one year after treatment, change in symptom associations (based on the updated network model) explained 51% of the variance (adjusted R^2=0.51, 95% CI: 0.45-0.56), similar to the original results. A third of the variance (32%) could be uniquely explained by change in symptom severity during therapy (adjusted R^2=0.32, 95% CI: 0.24-0.39). The combined prediction with change in symptom severity and change in symptom associations increased the explained variance to 54% (adjusted R^2=0.54, 95% CI: 0.48-0.58).

Two years after treatment, the predictive performance was 24% for change in symptom associations alone (adjusted R^2=0.24, 95% CI: 0.16-0.32), 22% for change in symptom severity alone (adjusted R^2=0.22, 95% CI: 0.13-0.29), and 25% for both variables (adjusted R^2=0.25, 95% CI: 0.17-0.33).

Thus, we found that, even when the network model accounted for the impact of unmeasured variables (by including the main effect of time), symptom associations remained highly predictive of short- and long-term treatment outcome. This suggests that the outcome prediction with symptom associations found in the original study was not impacted by the modeling choice made during the person-specific network estimation.

The fact that the variance explained by both symptom severity and symptom associations is similar to the variance explained by each of these predictors individually implies that they are highly related. In other terms, the unique and joint predictive value of change in symptom severity and change in symptom associations overlap to some extent, and parts of the variance in treatment outcome was explained by both. While this might be due to a statistical artefact, it could also indicate a serial dependence of these effects, according to which changes in symptom associations might cause change in symptom severity (as proposed by the network theory[3]) or vice versa.

Most importantly, we found substantial incremental predictive value for symptom associations beyond predictions with symptom severity (9% at the end of treatment, 22% one year later, and 3% after two years). The incremental value of symptom associations, especially one year after treatment, indicates that they provide additional information about the treatment effect that is not captured by changes in symptom severity change alone. These findings further support the notion that symptom networks might offer new opportunities for a better understanding of the effects of psychotherapeutic treatment.

Taken together, the findings of this re-analysis relate changes in symptom associations during psychotherapy to traditional models of change in symptom severity, and underscore the added value of the network approach for understanding treatment effects. From an empirical perspective, the substantial incremental predictive value of symptom network parameters can be considered promising. In addition to a possible empirical advantage over traditional models, network models offer another important benefit: a coherent theory of psychopathology and a novel theoretical approach for understanding treatment effects.

Investigating changes in symptom associations could offer new clues into understanding how treatment affects the problem-maintaining mechanisms of mutually reinforcing symptoms. Symptom networks can also indicate the stability of certain mental health states, i.e. whether a person is likely to change between high and low symptom severity[4,5]. The stability of high symptom severity at treatment start could provide crucial information on the readiness to change, and the stability of low symptom severity at treatment end might indicate vulnerability to relapse, thus being related to long-term treatment outcomes. Thus, changing symptom networks might reveal possible working mechanisms of mental health treatments, explain individual differences in treatment effects, and offer new avenues for improving current psychotherapeutic treatments.

Lea Schumacher[1], Levente Kriston[1], Omid V. Ebrahimi[2], Adam Finnemann[3], Jan Philipp Klein[4], Jonas M.B. Haslbeck[5]

[1]Department of Medical Psychology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [2]Department of Experimental Psychology, University of Oxford, Oxford, UK; Department of Psychiatry, University of Oxford, Oxford, UK; [3]Center for Urban Mental Health, Amsterdam University Medical Center, Amsterdam, The Netherlands; [4]Department of Psychiatry, Psychosomatics and Psychotherapy, University of Lübeck, Lübeck, Germany; [5]Department of Psychological Methods, University of Amsterdam, Amsterdam, The Netherlands

Supplementary information on this study is available at https://osf.io/n82zk/?

view_only=74556323721b4f7ba49acffbb3cb9ead.

1. Schumacher L, Klein JP, Hautzinger M et al. World Psychiatry 2024;23:411-20.
2. Falkenström F, Finkel S, Sandell R et al. J Consult Clin Psychol 2017;85:537-49.
3. Borsboom D. World Psychiatry 2017;16:5-13.
4. Lunansky G, Bonanno GA, Blanken TF et al. Psychol Rev 2025;132:1396-409.
5. van Bork R, Lunansky G, Borsboom D. Measurement 2024;232:114643.

DOI:10.1002/wps.70021

Sex modifies the relationship between depression and risk for dementia: implications for targeted prevention

Alzheimer's disease and related dementias (ADRD) are projected to affect 13.8 million Americans by 2060, with women comprising nearly two-thirds of those diagnosed[1]. Depression, a highly prevalent and modifiable risk factor, is nearly twice as common in women and has been independently linked to elevated ADRD risk[2-4]. Yet, the joint effect of sex and depression on cognitive decline remains under-explored in large-scale longitudinal studies.

We analyzed 75,069 visits from 11,091 participants aged 65 and older, using data from 42 Alzheimer's Disease research centers across the US. The final sample had a mean of 9.71 visits (SD=3.43; range: 2-19) over an average follow-up period of 3,679 days, equivalent to approximately 10 years (range: 5-18 years). We used Cox proportional hazards models to examine time to cognitive impairment, defined as a clinical diagnosis of mild cognitive impairment or dementia, in relation to Geriatric Depression Scale (GDS-15) score, sex, age, and apolipoprotein E ε4 (APOE ε4) genotype. For ease of interpretation, depression was coded as binary (depressed: GDS-15 score ≥5; not depressed: GDS-15 score <5).

Controlling for age and APOE ε4 genotype, depression increased the risk of cognitive impairment by 77% in men (hazard ratio, HR=1.77, 95% CI: 1.68-1.87, p<0.001) and by 119% in women (HR=2.19, 95% CI: 2.02-2.38, p<0.001). The interaction between depression and sex was statistically significant (HR=1.24, p<0.001). While women had lower baseline hazard of cognitive impairment (HR=0.62), they experienced a disproportionately greater increase in impairment risk when depressed.

We then used a time-varying covariate model, which accounts for changes in depression status across repeated observations, to test whether risk trajectories differed over time. In this model, at baseline, men with depression had a 165% higher risk of cognitive impairment (HR=2.65), while women had only a 19% increase (HR=1.19). The depression-sex interaction was HR=0.45. However, over time, men who became depressed were 23% less likely to develop cognitive impairment, while women who became depressed were 19% more likely to develop impairment at some point. Therefore, the depression-sex interaction at follow-up became HR=1.55 (95% CI: 1.12-2.15, p<0.01). This suggests that depression that emerges or persists later in life may have a more harmful effect on women's brain health than men's. Importantly, these effects remained consistent across older age groups, indicating that the depression-sex interaction is stable across the later life course.

In additional analyses, we modeled depression continuously and found that each additional point on the GDS-15 increased the risk of cognitive impairment by approximately 14.5% (HR=1.14, 95% CI: 1.139-1.150, p<0.001). We also categorized depression severity into three groups using GDS-15 scores: normal (0-4), mild (5-8), and moderate-to-severe (9-15). Our analyses showed a clear dose-response relationship between depression severity and risk of cognitive impairment. Mild depression was associated with a 69% increased risk (HR=1.69; 95% CI: 1.57-1.82), while moderate-to-severe depression increased risk by 80% (HR=1.80; 95% CI: 1.59-2.04). Importantly, time-varying effects indicated that the impact of moderate-to-severe depression slightly increased over time (p<0.001), suggesting cumulative risk, whereas the impact of mild depression remained stable. These results were adjusted for age, APOE ε4 genotype, and accounted for time effects, underscoring the importance of recognizing even mild depression as a significant and clinically actionable ADRD risk factor.

To assess the robustness of our findings, we conducted several sensitivity analyses. First, we examined attrition bias, and found that dropout rates were low and comparable between sexes (men: 1.6%, women: 1.5%, p=0.72). Next, we assessed baseline depression severity, finding that men had slightly higher mean GDS-15 scores than women (4.14 vs. 4.02; Wilcoxon W=110,604,030, p<0.001). We conducted an additional test to assess significant differences in depression severity by sex: for the 6,186 observations in the depressed group, there were none (W=4,475,864, p=0.07). Therefore, any sex differences in cognitive impairment predicted by depression are not driven by differences in depression severity between groups. Third, we accounted for center-level differences, by including ADRD research center-level frailty terms in all models. Finally, we expanded the sample to include participants under age 65, and found that the depression-by-sex interaction remained significant (HR=1.22, p<0.001).

Together, these results indicate that sex modifies the relationship between depression and ADRD, and that this effect is not due to measurement or sampling bias, but likely reflects a biologically meaningful difference. Several mechanisms could account for women's heightened susceptibility to cognitive impairment. Compared to men, women with depression may exhibit greater neuroinflammatory responses[5], more rapid hippocampal atrophy[6], and heightened hypothalamic-pituitary-adrenal axis dysregulation[7], all of which may magnify the long-term neurodegenerative impact of depression.

Clinically, our findings support the prioritization of depression screening and treatment as a key strategy for ADRD prevention, especially for women. Despite global efforts[8,9], sex remains underutilized as a stratifying factor in both research and practice. Furthermore, depression is often treated as a static covariate in models of cognitive decline, despite being dynamic and potentially interactive.

We offer the following recommendations for future research and clinical care: a) routine screening and early intervention for depression, especially in mid- to late-life women; b) inclusion of sex-stratified and interaction models in ADRD risk prediction and observational research; c) clinical trials of depression treatment that examine cognitive outcomes by sex across the lifespan; d) mechanistic studies exploring sex-specific inflammatory, hormonal, and stress-related pathways linking depression and neurodegeneration.

In sum, our longitudinal analysis of over 75,000 visits across US Alzheimer's Disease research centers revealed that depression significantly increases ADRD risk for both sexes, but the trajectory and magnitude differ by sex. The interaction between sex and depression persists across time, analytic methods, and population subsets. Women with depression are at disproportionately higher risk for cognitive impairment as they age. These findings underscore the urgency of tailoring ADRD prevention strategies to account for sex-specific vulnerabilities.

Lauren A. Rutter[1], Lucas J. Hamilton[2], Skylar Wilson[1], Anne C. Krendl[1], Brea L. Perry[3]

[1]Department of Psychological and Brain Sciences, Indiana University, Bloomington, IN, USA; [2]Department of Psychology, Augustana University, Sioux Falls, SD, USA; [3]Department of Sociology, Indiana University, Bloomington, IN, USA

The US National Alzheimer's Coordinating Center (NACC) database is funded by the US National Institute on Aging/National Institutes of Health (NIA/NIH) (grant no. U24 AG072122). NACC data are contributed by the NIA-funded Alzheimer's Disease research centers. L.A. Rutter and B. Perry are supported by NIA grants (respectively, no. K01 AG086598 and no. R01 AG057739).

1. Alzheimer's Association. Alzheimers Dement 2023;19:1598-695.
2. Livingston G, Huntley J, Sommerlad A et al. Lancet 2020;396:413-46.
3. Ownby RL, Crocco E, Acevedo A et al. Arch Gen Psychiatry 2006;63:530-8.
4. Salk RH, Hyde JS, Abramson LY. Psychol Bull 2017;143:783-812.
5. Mac Giollabhui N, Ng TH, Ellman LM et al. Mol Psychiatry 2021;26:3302-14.
6. Diniz BS, Teixeira AL, Machado-Vieira R et al. J Gerontol B Psychol Sci Soc Sci 2014;69:845-51.
7. Maekawa K, Yamanaka K. Clin Exp Neuroimmunol 2023;14:100-9.
8. Mielke MM, Vemuri P, Rocca WA. Clin Epidemiol 2014;6:37-48.
9. Ferretti MT, Iulita MF, Cavedo E et al. Nat Rev Neurol 2018;14:457-69.

DOI:10.1002/wps.70022

Nutritional psychiatry on the move: the activities of the ECNP Nutrition Network to leverage nutrition for brain health

Brain health is a pressing global concern[1]. Neurodevelopmental and mental disorders are leading causes of disability. As the population continues to grow and age, the number of individuals affected by dementia worldwide is expected to rise significantly. While evidence-based interventions for mental disorders are available, challenges persist, particularly as not all patients respond to current pharmacological or psychological treatments.

Our limited understanding of psychiatric conditions and their treatment stems from major gaps in knowledge of the underlying neurobiological mechanisms. Emerging research suggests that the pathophysiological underpinnings of mental disorders can extend beyond the central nervous system. Compelling evidence indicates that disorders such as major depression should be viewed as whole-body conditions that entail both central processes, such as changes in neurotransmitter systems and reduced neuroplasticity, and peripheral factors resulting from the involvement of the immune and neuroendocrine systems. Immune activation interacts with metabolic and endocrine systems that control energy homeostasis, as shown by significant associations between inflammatory markers (C-reactive protein, interleukin-6) and higher body mass index, fat mass, triglycerides, as well as lower HDL cholesterol in large-scale studies. Thus, metabolic and immune dysregulation are intertwined, prompting research to explore biomarkers of this combined dysregulation[2].

We are beginning to recognize that nutrition might help close the prevention and treatment gap in mental disorders. Poor diet quality is a major environmental risk factor for brain disorders and one of the few that are modifiable[3]. While evidence continues to grow on the impact of nutrition across the life course, we are still far from fully harnessing its potential to improve mental health conditions.

The field of nutritional psychiatry has recently gained momentum, driven by a surge in observational and intervention studies supporting a role for diet in managing psychiatric symptoms[4]. At the same time, epidemiological research highlights unhealthy eating as a growing risk factor for metabolic and brain health. Additionally, data indicate that obesity and metabolic conditions deriving from the use of medications, such as antipsychotics, present challenges for clinicians, reinforcing the need for an approach to mental disorders that considers brain and body health as a unique integrated system.

Individual nutrient needs are shaped by physical and psychological health, habitual diet and lifestyle, and differ across the life course and in response to environmental factors. One of the main challenges that nutritional psychiatry currently faces is the lack of conclusive evidence that diet and nutrition impact mental health. Overall, randomized controlled trials (RCTs) investigating dietary change in treatment of mental disorders remain limited, although some report significant improvements in mood and reduced anxiety in adults[5]. Not all studies reproduced these findings, underscoring the need to replicate, refine and scale-up dietary intervention research for prevention and treatment.

The Nutrition Network of the European College of Neuropsychopharmacology (ECNP) was established with the main mission to better understand the bidirectional links between mental health and nutrition, including the mediating systems, to inform novel neuropsychological and neuropharmacological interventions[4,6]. The Network fosters interdisciplinary research and strengthens connections with relevant stakeholders across Europe, including health and food policy makers. Founded in 2016 by researchers at the intersection of nutrition and mental health, it brings together experts from academia and industry, mainly neuroscientists, nutritionists, psychiatrists, psychologists and geneticists.

The Network's key areas of expertise include gut-brain signalling (hormones, vagal afferents, gut microbiota, inflammatory signals), neuroendocrine regulation, metabolites/nutrients, and the relevant neural systems (revealed through genetics, epidemiology, functional brain imaging, behavioral models in rodents, and morphological, biochemical and molecular neuroscience tools).

The Network's main areas of action include: a) identifying new strategies (dietary, lifestyle, pharmacotherapy) to improve mental health in individuals with mood and other mental disorders; b) exploring neural substrates and pathways linking diet to psychological constructs such as mood and neurocognition (e.g. impulsivity, reward sensitivity); c) investigating afferent signaling systems (hormones, genes, immune modulators, gut microbiota) connecting diet to these psychological constructs; d) clarifying interactions between diet and pharmacotherapy (including side effects) for mental health and metabolic diseases, combining dietary advice with pharmacotherapy to enhance efficacy; e) providing evidence to support dietary policies and guidelines for mental health improvement and for treatment of eating disorders; f) establishing strong collaborations with health and food policy makers, patient advocacy groups, and pharmaceutical and food industry stakeholders.

One of the key achievements of the Network to date has been its participation, as the BRAINFOOD cluster, in the European Union-funded EBRA (European Brain Research Agenda) project. EBRA was established as a catalyst for brain research, bringing together stakeholders, researchers, clinicians, patients, governments, funders and public institutions to streamline and better coordinate brain research across Europe while fostering global initiatives. In 2021 and 2022, expert and policy meetings were held with relevant stakeholders, culminating in a position paper emphasizing the need for public investments to unlock the full potential of nutrition for brain health.

A core principle of EBRA is that all relevant stakeholders – clinicians, patient advocates, and public and private research institutions – must collaborate in a coordinated, non-fragmented manner to identify knowledge gaps and research strategies that will drive meaningful progress in improving brain health through nutrition.

Our Network has taken on the role of coordinating research and policy in nutrition and mental health, identifying the most urgent research priorities in this field. Although dietary interventions appear to influence mood through various mechanisms, including the gut microbiome, inflammatory modulation, oxidative stress reduction, and hypothalamic-pituitary-adrenal axis regulation[7,8], more extensive RCTs are necessary to establish clear causal relationships, and to address the current variation in how diet interventions are implemented.

Health care professionals and policy makers should prioritize food and nutrition education[9], since significant misunderstandings persist among both the general public and health professionals regarding the role of nutrition in brain health, exacerbated by misleading and exaggerated messages in popular media.

Given the vast potential of nutrition to support brain health, we advocate for greater research investment to strengthen the relevant evidence base, increasing awareness among health professionals and the public, so that this critical topic becomes a priority in policy agendas[4,9].

Francesca Cirulli[1,2], Suzanne L. Dickson[1,3]
[1]ECNP Nutrition Network; [2]Center for Behavioral Sciences and Mental Health, Istituto Superiore di Sanità, Rome, Italy; [3]Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden

The authors are grateful for the support of the ECNP Nutrition Network, which contributed to the development and dissemination of this work.

1. Vos T, Lim SS, Abbafati C et al. Lancet 2020;396:1204-22.
2. Penninx BWJH, Lamers F, Jansen R et al. Lancet Reg Health Eur 2024;48:101166.
3. Marx W, Lane M, Hockey M et al. Mol Psychiatry 2021;26:134-50.
4. Adan RAH, van der Beek EM, Buitelaar JK et al. Eur Neuropsychopharmacol 2019;29:1321-32.
5. Jacka FN, O'Neil A, Opie R et al. BMC Med 2017;15:23.
6. Adan RAH, Cirulli F, Dye L et al. Brain Behav Immun 2022;105:201-3.
7. Dinan TG, Stanton C, Long-Smith C et al. Clin Nutr 2019;38:1995-2001.
8. Samà M, Musillo C, Cirulli F. Neuroscience 2025;566:142-8.
9. Higgs S, Aarts K, Adan RAH et al. Nutr Rev 2025;83:586-92.

DOI:10.1002/wps.70020

Reframing psychiatry of intellectual developmental disorders: from margins to mainstream, from classification to care

Over the past decade, recognition of the mental health needs of individuals with intellectual developmental disorders (IDD) has advanced significantly. These advances have transformed our understanding of etiology, enriched psychiatric practice, and increased focus on global equity. In this context, the WPA Section on Psychiatry of Intellectual and Developmental Disorders and its affiliated Working Group have maintained a strong global presence, focusing on building capacity, improving training, and promoting inclusive, person-centred psychiatric services[1]. We see a light at the end of a tunnel, one historically marked by neglect and inequality, now illuminated by scientific progress, ethical responsibility, and collective dedication.

For too long, individuals with IDD have been pushed to society's margins – excluded from education and health care, subjected to lifelong institutionalization, eugenic policies, and even state-sponsored extermination. Psychiatry, at times complicit, distanced itself by placing IDD in Axis II of the DSM frameworks. Individuals with IDD were often left out of epidemiological studies, clinical trials, public policies, and scientific research. Even the Global Burden of Disease Study limited its analysis to IDD without known aetiology, excluding established genetic conditions such as Down syndrome, perinatal injuries, and other identified causes[2]. Concurrent IDD continues to be often categorized under autism in estimates of disability adjusted life years and related costs. As a result, diagnostic overshadowing and therapeutic nihilism persist within the scientific community.

Nonetheless, today, IDD plays an increasingly central role in our understanding of developmental neurobiology, behavioral phenotypes, genomics, precision medicine, and comparative clinical effectiveness research, alongside its integrated model of health, social, and other sectors in care delivery. Early intervention, lifelong care, interdisciplinary collaboration, and a renewed focus on dignity and inclusion now define the field. This shift is not just scientific and technical – it is moral. Psychiatry is returning to its roots as a healing profession, grounded in shared humanity.

The inclusion of IDD in the neurodevelopmental disorder group in DSM-5 and ICD-11, led by members of this Section, has been catalytic, leading to significant changes in its diagnostic criteria[3]. Notably, severity levels now rely on adaptive behaviors instead of IQ-centric thresholds, with a tripartite model of these behaviors better reflecting key skill areas (conceptual, social and practical), which indicate individual support needs. The increased adoption of the biopsychosocial model, rooted in developmental and lifespan perspectives, has also further driven the shift from deficit-based to strength-based, person-centred care[4,5].

In response to global challenges – particularly in low-resource settings – our Section and its affiliated Working Group have adopted a strategic, multifaceted approach aligned with the goals outlined in the WPA Action Plan 2023-2026[6-8]. The initiatives described below show our effort to strengthen global capacity and promote equitable care.

Edited by Section officers, the *Textbook of Psychiatry of Intellectual Disability and Autism Spectrum Disorder*[9] is a volume with 43 chapters written by 116 leading specialists. It is the most comprehensive single resource on psychiatric comorbidity in IDD and low-functioning autism spectrum disorder to date, offering detailed guidance across etiology, assessment, treatment (including behavioral, pharmacological and psychosocial approaches), and prognosis. It has helped shift the field toward an integrated and evidence-informed framework for psychiatric care in these conditions, signalling significant progress aligned with the objectives of the WPA and the World Health Organization (WHO).

The Section and the Working Group also developed the *Global E-Handbook on Intellectual Developmental Disorder Psychiatry*, an evolving, open-access publication now available on the WPA website, consolidating insights from individual countries across all WPA regions. Covering policy, training, service models and human rights, the handbook is a living document that fosters international collaboration and promotes knowledge equity. Active encouragement for further global contributions is especially emphasized from underrepresented regions.

To improve foundational knowledge globally, the Section and the Working Group created a free *IDD Introductory Podcast* available on the WPA website. Designed as a primer for clinicians and trainees, this resource provides a concise overview of IDD diagnosis, intervention principles, and ethical considerations.

A dedicated chapter in the Global E-Handbook comprises the WPA Human Rights Statement on Mental Health in Individuals with IDD, which affirms the WPA's stance, approved by the General Assembly, on the rights of individuals with IDD and co-occurring mental disorders, reinforcing obligations under the United Nations Convention on the Rights of Persons with Disabilities. The statement emphasizes person-centred care and equitable access to psychiatric services as professional responsibilities, rather than mere aspirations.

We have also established a continuing professional development resource on IDD psychiatry hosted on the WPA web platform, which includes a certification pathway suitable for both academic and clinical training. A significant revision of this resource is scheduled in the next two years to incorporate new evidence, case studies, and evolving standards of practice.

The Section and the Working Group have also actively contributed to the WHO Package of Interventions, as part of the Rehabilitation 2030 initiative. The inclusion of Module 5, which focuses on neurodevelopmental disorders, marks a milestone in integrating IDD and autism spectrum disorder into global health strategies and rehabilitation systems, particularly for resource-limited countries[10].

Under the WPA Specialist Corner on Advances in Science and Ethics of IDD Clinical Care, we have established educational content that links scientific advances to ethical practice in IDD psychiatry. Launched as part of the WPA Action Plan 2023-2026, this platform will highlight the importance of culturally informed care models, with a focus on vulnerability, rights, and regional diversity.

Despite these advances, significant challenges lie ahead. Diagnostic overshadowing, service fragmentation, and marginalization persist as everyday issues in psychiatry. The ongoing neglect of individuals with borderline intellectual functioning, characterized by disproportionately high mental health burden, further emphasizes the need for training and system reform in this domain. Looking ahead, we will continue to prioritize the global key areas[11]. Expanding contributions to the Global E-Handbook will serve as a dynamic platform for international collaboration.

By increasing contributions, especially from underserved regions, we aim to better represent diverse systems and contexts in IDD psychiatry. Advancing person-centred care remains a key priority. We seek to continue to define psychiatry's role in promoting autonomy, dignity, and social inclusion for people with IDD. High clinical standards must be balanced with flexibility, cultural sensitivity, and respect for personal choices, as well as culturally responsive practices. Embedding ethics and human rights-based perspectives must be integral rather than additive in mainstream psychiatric training. Specialized content needs to address evolving regional insights and highlight gaps in culturally adapted care.

The efforts of the Section and the Working Group have gained significant momentum but need to be sustained. The support of future WPA Action Plans[12] remains essential. As psychiatrists and mental health professionals, members of the WPA now possess the frameworks, tools and global insights to challenge the historic marginalization of people with IDD. Continued investment in infrastructure, education and visibility is crucial. Psychiatry's role in IDD care must transition from a fragmented, medicalized approach to a comprehensive, value-based commitment to inclusion within mainstream psychiatry. With a clear vision and shared purpose, we believe that we are not only approaching the light at the end of the tunnel, but are actively heading toward it, moving from the margins to the mainstream.

Kerim Munir[1], Ashok Roy[2], Marco Bertelli[3], Gregorio Katz[4], Luis Salvador-Carulla[5]

[1]Developmental Medicine Center, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA; [2]Brooklands Hospital, Coventry and Warwickshire Partnership NHS Trust, Coventry, UK; [3]CREA (Research and Clinical Centre), San Sebastiano Foundation, Florence, Italy; [4]National Autonomous University of Mexico, Mexico City, Mexico; [5]Center for Mental Health Research, University of Canberra, Canberra, NSW, Australia

1. Munir K, Roy A, Javed A. World Psychiatry 2022;21:327-8.
2. GBD 2019 Mental Disorders Collaborators. Lancet Psychiatry 2022; 9:137-50.
3. Salvador-Carulla L, Reed GM, Vaez-Azizi LM et al. World Psychiatry 2011;10:175-80.
4. Dosen A. J Intellect Disabil Res 2005;49:9-15.
5. Harris JC. Intellectual disability. New York: Oxford University Press, 2006.
6. Wasserman D. World Psychiatry 2024;23:165-6.
7. Wasserman D. World Psychiatry 2024;23:302-3.
8. Wasserman D. World Psychiatry 2025;24:284-5.
9. Bertelli MO, Deb S, Munir K et al (eds). Textbook of psychiatry for intellectual disability and autism spectrum disorder. Cham: Springer, 2022.
10. World Health Organization. Package of interventions for rehabilitation: neurodevelopmental disorders. Geneva: World Health Organization, 2023.
11. Roy A, Courtney K, Odiyoor M et al. BJPsych Int 2021;18:54-7.
12. Schulze TG. World Psychiatry 2024;23:303-4.

DOI:10.1002/wps.70023

Report from the WPA Section on Positive Psychiatry 2015-2025

Since ancient times, philosophers and physicians have emphasized a holistic, well-being-centered approach to health, highlighting wisdom, resilience, social connections, optimism, moderation and self-control. Modern research confirms that these positive psychosocial traits support mental and physical health, even in persons with mental illnesses. Yet, modern medicine, including psychiatry, remains focused on diagnosing and treating disorders, often overlooking prevention. This diagnosis-driven and treatment-first model shifts the focus away from general well-being and illness prevention, and contributes to the growing shortage of mental health services[1].

Global behavioral epidemics of loneliness, social isolation, suicides, and drug abuse point to an urgent priority for developing strategies at both individual and societal levels to improve the well-being of the general population. It is noteworthy that, while over a thousand articles and several books have been published on positive psychology during recent decades, not a single paper or book could be found on PubMed with "positive psychiatry" in its title until 2013, when we published two such papers[2,3], and 2015, when we published the first book[4].

The WPA Section on Positive Psychiatry was established in 2015, and WPA congresses now regularly include several sessions on this topic, which are well attended and draw active participation from engaged audiences. Here we present evidence-based perspectives on positive psychiatry, along with highlights of exciting new initiatives led by members of our Section in Latin America, Asia, Europe, Africa, and North America.

Social determinants of health refer to social and environmental factors that impact individuals' physical and mental health[5]. While the medical and psychiatric literature has focused on the negative health impact of adverse social factors, positive social factors are associated with greater mental health and well-being. These include wisdom, especially empathy and compassion, resilience, optimism, positive social connections, purpose in life, and spirituality[1,6].

Specific genes are associated with positive traits such as resilience and optimism. Brain imaging studies have reported that higher levels of empathy, compassion, and emotional regulation are associated with activation of the anterior cingulate cortex, ventromedial and dorsolateral prefrontal cortex, insula, ventral striatum, and amygdala. Resilient adults have greater hippocampal gray and white matter volumes, and stronger connectivity between the central executive network and limbic regions. Individuals with greater social support have lower levels of inflammatory markers. The gut microbiome mediates the bidirectional association between psychosocial characteristics and overall health[1,6].

Our WPA Section has ongoing collaborations with several scientific organizations. An example is the World Federation of Psychotherapy, an affiliate of the WPA, which promotes psychotherapy, including positive psychotherapy. This Federation has led efforts to educate health care professionals in major forms of psychotherapy with positive impact on mental health across a number of Asian countries, including Malaysia, Indonesia and Thailand.

Another scientific organization with which our WPA Section collaborates is the World Association of Positive and Transcultural Psychotherapy, which has helped promote the value and pragmatics of positive psychotherapy worldwide, with postgraduate programs in 25 countries[7]. This organization highlights the importance of the Psychotherapy of Hope, rooted in the principles of the legacy of Persuasion and Healing. It promotes culturally adapted approaches to strengthen resilience and social support in local communities. It leads workshops and public awareness campaigns, working with primary care clinicians and local health workers to integrate wellness activities, such as group resilience training and mindfulness practices, into routine mental health care.

Members of our Section are implementing several innovative programs in a range of geographic contexts. In Argentina, the Global Psy network for Spanish-speaking psychiatrists has created a collaborative platform spanning multiple countries. It organizes training and community programs that emphasize mental health promotion and emotional well-being, as well as suicide prevention through resilience-building. It has made steady progress in establishing the Chapter of Positive Psychiatry and Lifestyle Medicine within the Latin American Psychiatric Association, an official member of the WPA.

In Mexico, the Mexican Consortium of Neuropsychopharmacology has been established, which prioritizes providing opportunities for professionals from low- and middle-income countries to meet in person with world experts, maintaining close social interactions and a sense of belonging, with program-embedded self-care activities such as yoga and mindfulness. It seeks to teach the attendees the state-of-the-art science while implementing key elements of healthy and productive health care communities[8].

In Kenya, "mental wellness clubs" have been created, in collaboration with schools and youth groups, teaching positive coping skills and offering peer support to youth facing adversity[9]. They partner with non-governmental and faith-based organizations to develop community support circles for women and families with economic hardship or trauma, employing gratitude practice and meaning-making.

In Canada, the Fountain of Health Association has been established, a national non-profit organization that promotes brain health and well-being[10]. Over 2,000 clinicians have been trained to date on the use of structured paper and digital tools, including goal-setting worksheets and behavior-tracking forms, with over 800 clinicians now using them in practice.

In the US, examples of effective community-based initiatives include intergenerational programs, age-friendly communities, and digital tools to support social connections and well-being. An exciting frontier is integrating artificial intelligence (AI) with human wisdom. The goal is to develop "artificial wisdom" systems beyond super-intelligent algorithms to incorporate compassion, ethical reasoning, and emotional intelligence. Such AI tools could help clinicians personalize wellness interventions and teach patients evidence-based skills for resilience and emotional regulation.

Looking ahead, the WPA Section on Positive Psychiatry will continue working with organizations worldwide – including the World Health Organization, national health ministries, universities and community groups – to integrate positive psychiatry principles into mainstream mental health care. In addition to live meetings at the WPA and other conferences, our members foster collaboration through webinars, virtual workshops, and training programs. We also support publications that advance the field and promote knowledge exchange among mental health professionals and stakeholders. We aim to connect diverse professionals to share best practices and emerging research. Our efforts include facilitating research involving neuroscientists, expert clinicians, public health leaders, economists, and others, supporting a comprehensive approach to mental health care.

The WPA Section on Positive Psychiatry is advancing a global, comprehensive, strengths-based approach to mental health – one that promotes not only treatment, but also prevention, resilience, and human flourishing. Growing evidence supports the impact of positive psychosocial factors, their biological basis, and cross-cultural relevance. Our Section remains committed to promoting culturally sensitive, biopsychosocial approaches for people with and without mental illness, and to supporting interventions that foster wisdom, resilience, optimism, spirituality, meaning, and social connections worldwide.

Dilip V. Jeste[1], Karen Reimers[2,3], Bernardo Ng[4], Hernán Alessandria[5], César A. Alfonso[6], Alma Jimenez[7], Hamid Peseschkian[8], Manasi Kumar[9], Renato D. Alarcon[10], Kiran Rabheru[11]

[1]Social Determinants of Health Network, La Jolla, CA, USA; [2]University of Minnesota, Minneapolis, MN, USA; [3]University of Central Florida, Orlando, FL, USA; [4]Mexican Consortium of Neuropsychopharmacology; [5]Argentine Association of Psychiatry; [6]Columbia University Medical Center, New York, NY, USA; [7]University of the Philippines, Manila, Philippines; [8]Wiesbaden Academy of Psychotherapy, Wiesbaden, Germany; [9]New York University Grossman School of Medicine, New York, NY, USA; [10]Mayo Clinic College of Medicine, Rochester, MN, USA; [11]University of Ottawa, Ottawa, ON, Canada

1. Shin J, Halbreich U, Jeste DV. Acad Ment Health Well-being 2025;2:1.
2. Jeste DV. Am J Psychiatry 2013;170:1102-5.
3. Jeste DV, Palmer BW. Br J Psychiatry 2013;202:81-3.
4. Jeste DV, Palmer BW (eds). Positive psychiatry: a clinical handbook. Washington: American Psychiatric Publishing, 2015.
5. Jeste DV, Alexopoulos GS, Blazer DG et al. Annu Rev Clin Psychol 2025;21:33-59.
6. Kirkbride JB, Anglin DM, Colman I et al. World Psychiatry 2024;23:58-90.
7. Messias E, Peseschkian H (eds). Positive psychiatry, psychotherapy and psychology: clinical applications for positive mental health, 2nd ed. Cham: Springer Nature, 2025.
8. Ng B. Indian J Psychiatry 2020;62(Suppl. 3):S467-9.
9. Kumar M, van Rensburgb AJ, Petersen I. Lancet Glob Health 2023;11:e1005-6.
10. Rabheru K, Cassidy KL, Cassidy B et al. In: Rootman I, Edwards P, Levasseur M (eds). Promoting the health of older adults: the Canadian experience. Toronto: Canadian Scholars, 2021:372-89.

DOI:10.1002/wps.70025

Report from the WPA Section on Suicidology: recent advances and activities

Suicide remains a major global public health concern, claiming more than 700,000 lives annually. The interdisciplinary field of suicidology seeks to understand the multifactorial nature of suicidal behavior – considering its clinical, psychological, sociological and biological components – and to translate this knowledge into effective prevention strategies. The WPA Section on Suicidology has been actively engaged in advancing this multidimensional perspective, contributing through professional education, research and international collaboration since the early 2000s.

Recent years have witnessed significant advances across multiple domains of research and practice on suicide prevention, spanning from novel therapeutic interventions, through the uptake of system-level approaches, to digital innovations. Among these developments, pharmacological advances, particularly the development of rapid-acting agents such as ketamine and esketamine, have opened new avenues for acute intervention in suicide prevention. These treatments show promise in reducing suicidal ideation among individuals with major depression, and members of our Section have contributed to the growing evidence base. However, the lack of evidence on longer-term effects requires rigorous follow-up[1].

At the same time, digital innovation is reshaping the field, with mobile apps, telepsychiatry platforms, and online interventions expanding access to care. The Section contributed to a special issue of the *Journal of Technology in Behavioral Science*, which discussed both the opportunities and challenges of digital tools in suicide prevention[2]. Digital interventions have also been incorporated into the World Health Organization (WHO) Mental Health Gap Action Programme (mhGAP), aimed at scaling up services in low- and middle-income countries, where more than 70% of suicides occur. Our Section supported the development of the most recent mhGAP Intervention Guide, reviewing the evidence on digital interventions for the self-management of suicidality.

While digital solutions offer clear advantages, such as increasing accessibility, reducing barriers to care, and providing anonymity, they raise important concerns regarding data privacy, inclusivity and equity, given their dependence on infrastructure and digital literacy. They show promise in managing suicidal ideation; however, evidence remains insufficient to establish their effectiveness in reducing suicide attempts and deaths, or to confirm safety as standalone interventions, particularly in resource-limited settings.

In parallel, digitalization is shaping the lives of young people and is relevant to their mental health. Suicide is one of the leading causes of death among children and adolescents worldwide, and many spend a significant portion of their day in front of screens – a habit linked to developmental changes and psychological outcomes. Yet, the rigorous evaluation of online interventions for youth is lagging behind, compared to the established school-based awareness and skill training programs, or interventions delivered in clinical and community settings[3]. Suicide among youth and relevant interventions need our attention as, although rates vary across regions, several countries have reported recent increases, particularly among teenage girls and marginalized groups, such as lesbian, gay, bisexual, transgender or queer (LGBTQ+) youth.

The COVID-19 pandemic underscored the urgency of monitoring and adapting suicide preventive strategies globally, as many countries reported shifts in rates during and following this period of intensified mental health strain[4]. Sustained, systematic surveillance is essential not only for understanding the impact of global crises and preventive efforts, but also for identifying long-term patterns that affect diverse populations.

To advance this effort, a newly established international collaboration – with active involvement of members of our Section – is analyzing large-scale epidemiological data from organizations such as the WHO and the United Nations. By examining suicide trends globally over past decades, and considering factors such as the human development index[5], the project seeks to identify both shared and region-specific risk factors. This evidence base will be critical for guiding the development of targeted, data-driven prevention strategies worldwide.

A notable shift in recent years has been the reconsideration of suicide risk assessment. For decades, clinicians relied on relatively static risk factors and predictive models. To this aim, enthusiasm surrounded artificial intelligence and machine learning, with hopes that larger and more diverse datasets would improve prediction. Yet, prediction accuracy has barely improved over the last 50 years[6]. While challenges persist, assessment of suicidality remains central to prevention and clinical practice, and our Section is committed to summarizing the evidence and providing guidance for professionals, including through dedicated courses under the umbrella of multiple World Congresses of Psychiatry.

Closely related to this, system-level strategies have gained prominence. Structured care models such as Zero Suicide and brief contact interventions (BCIs) offer scalable solutions to improve care that do not depend on risk categorization. By reaching a broader share of the population, these approaches deliver low-intensity, low-cost and proactive support.

Members of our Section are involved in the piloting of BCIs, and such approaches were discussed extensively during the European Symposium on Suicide and Suicidal Behavior (Rome, 2024) and the Swedish Suicide Research Conference (Stockholm, 2025). Both conferences were organized with active involvement of Section members, who also curated plenary sessions and symposia that advanced international dialogue and set the agenda for future directions in suicide prevention.

On a similar note, the WPA's Brief Motivational Intervention and Long-term Regular Follow-up Contact Program (BIC) was developed in collaboration with Section members and launched in 2021. Rooted in the SUPRE-MISS initiative[7], this program integrates brief motivational sessions with sustained follow-up, and has shown effectiveness in reducing suicide rates. BIC is currently active in the US, Brazil, India and Sweden, and open for additional centers to join.

Beyond health care, multi-sectorial and national strategies remain important and are now supported by WHO's "LIVE LIFE" guidelines. These provide a framework for population-level suicide reduction through comprehensive measures such as means restriction, responsible media reporting, and enhanced access to mental health services[8].

In a broader context, our Section has emphasized the cultural embeddedness of suicidal behavior. In collaboration with the WPA Section on Cultural Psychiatry, we organized an inter-sectional symposium at the 23rd World Congress of Psychiatry (Vienna, 2023) and hybrid workshops under the umbrella of a new international network focused on "transcultural suicidology". These initiatives highlighted the need for culturally adapted interventions and the influence of sociocultural contexts on risk and resilience. They also strengthened the Section's advocacy for inclusive prevention strategies and the call for more research on suicide among marginalized populations. This is particularly urgent given the rising number of forcibly displaced people worldwide – over 123 million by the end of 2024 – among whom high-quality suicide research remains scarce.

The network has emphasized that, in the 21st century, people increasingly live across borders – whether by choice or by being displaced – and that monitoring, health care, and suicide prevention strategies must adapt accordingly. The commitment to "Mental Health for All" and suicide prevention are further reflected in the WPA Action Plan 2023-2026[9,10], led by WPA President D. Wasserman, who is herself an active member of our Section.

The WPA Section on Suicidology has recently hosted a section symposium, a state-of-the-art symposium and a course at the 25th World Congress of Psychiatry in Prague, focusing on suicide risk assessment, scalable interventions and cultural considerations. Through its integrated activities, the Section continues to influence the future of suicide prevention with evidence-based, interdisciplinary, and globally relevant approaches.

Vladimir Carli, Sara Sutori, Miriam Iosue
National Centre for Suicide Research and Prevention, Department of Learning, Informatics, Management and Ethics, Karolinska Institutet, Stockholm, Sweden

1. McIntyre RS, Rosenblat JD, Nemeroff CB et al. Am J Psychiatry 2021;178:383-99.
2. Sutori S, Hadlaczky G, Eliasson E et al. J Technol Behav Sci 2024;9:440-51.
3. Wasserman D, Carli V, Iosue M et al. Asia Pac Psychiatry 2021;13:e12452.
4. Wasserman D, Iosue M, Wuestefeld A et al. World Psychiatry 2020;19:294-306.
5. Vigna E, Balkom IV, Bresnahan M et al. Arch Womens Ment Health 2025;28:287-96.
6. Franklin JC, Ribeiro JD, Fox KR et al. Psychol Bull 2017;143:187-232.
7. Fleischmann A, Bertolote JM, Wasserman D et al. Bull World Health Organ 2008;86:703-9.
8. World Health Organization. LIVE LIFE: an implementation guide for suicide prevention in countries. Geneva: World Health Organization, 2021.
9. Wasserman D. World Psychiatry 2024;23:165-6.
10. Wasserman D, Iosue M, Petros NG et al. World Psychiatry 2025;24:284-5.

DOI:10.1002/wps.70038

The evolving role of WPA Collaborating Centres: new perspectives and future directions

The establishment of the WPA Collaborating Centres marked a decisive step in strengthening the global mission of the WPA. Conceived in 2014, the Centres were designed to bring together leading institutions from different world regions, pooling their academic, clinical and policy expertise to support the WPA Action Plan and to respond to emerging mental health challenges worldwide[1]. From their inception, the Centres have acted as bridges between local realities and global strategy, combining scientific excellence and authority with a commitment to education, capacity building and innovation.

Initially seven in number, the Centres have progressively expanded, and now include ten sites across diverse countries, among them the UK, Italy, India, Egypt, Hong Kong, South Africa, Kenya, Qatar and Switzerland. Their mission has remained constant: to support the WPA Action Plan and the presidential strategy, while retaining independence, agility and flexibility. They are self-funded and self-administered, with directors and their teams bringing considerable expertise and resources to the network. In this way, the Centres have added strength to WPA's global offer without imposing additional demands on central resources, while promoting awareness of WPA activities and priorities in their respective contexts[2,3].

Over the years, the WPA Collaborating Centres have played a crucial role in disseminating educational resources, running competitions for trainees and medical students, supporting scholarship and research funds, and influencing policy at national and global levels. They have contributed to the development and dissemination of the chapter on mental disorders of the ICD-11, addressed physical comorbidities in patients with severe mental illness, promoted community mental health, focused on youth mental health, and advanced human rights in psychiatry. During the COVID-19 pandemic, they offered timely guidance on psychosocial consequences and public mental health responses, ensuring that WPA was able to act as a trusted global voice[2]. In parallel, they strengthened ties with the WPA Scientific Sections and Working Groups, supporting unmet educational needs and providing opportunities for early career psychiatrists and trainees[3].

The WPA Collaborating Centres have become an integrated global network, acting in concert to advance the mission of the Association. Their collective identity as a single network of excellence, fully aligned with the WPA's strategy, gives greater authority to the Association's Action Plans and strengthens their visibility within the international scientific community. Together, the Centres now operate as multipliers of WPA's initiatives, amplifying the reach of its programmes across diverse regions and ensuring continuity of its mission across successive leaderships. The alignment with the WPA Action Plan 2023-2026[4-7] and subsequent strategic priorities [8-11] provides coherence and direction, reinforcing the role of the Centres as engines of implementation.

This integrated network is expanding into regions that remain underrepresented in international activities, particularly in low- and middle-income countries, where the burden of mental disorders is greatest and resources are scarce. New Centres, selected on the basis of established criteria of excellence and capacity to address unmet needs, bring fresh infrastructure and expertise to strengthen psychiatric education, research and practice in underserved areas. In this way, the network extends its global reach while remaining firmly anchored in local contexts.

Education and training are at the core of this endeavour. The Centres jointly promote postgraduate education, support early career psychiatrists, and create opportunities for medical students to engage with psychiatry during medical school training, and through competitions and scholarships, consolidating ongoing initiatives for greater global impact[12,13]. By harnessing digital platforms, they are widening access to high-quality educational materials, including training on ICD-11, comorbidities, and innovative models of care [2,3]. Close collaboration with the World Health Organization and other international entities ensures that educational resources remain relevant to emerging challenges, including the opportunities and risks of digital mental health[14].

The coherence of this expanding network is supported by evolving governance and sustainability mechanisms. We are developing executive structures at national level, clear succession planning, transparent fund raising, and renewable three-year mandates aligned with WPA presidential terms. This combination of agility and continuity ensures that the WPA Collaborating Centres are equipped to sustain their role as a global alliance for mental health, offering a model for international collaboration that is authoritative, inclusive and durable over time[15].

Another defining feature of the network is its capacity to generate interdisciplinary and cross-centre collaborations. By pooling expertise across regions, the Centres are delivering joint projects on suicide prevention, digital innovation, health inequalities, and adolescent mental health. These collaborations allow for the production of multi-country data, consensus statements, and policy documents that amplify the visibility of psychiatry within broader health and social agendas[3].

Beyond academic and clinical priorities, the Centres remain committed to social responsivity and community engagement. They promote human rights, lead anti-stigma campaigns, and work with service users and carers to ensure that psychiatry speaks directly to the needs of communities. These activities demonstrate that they are not only a scientific resource, but also a driving force for advocacy and societal change.

The WPA Collaborating Centres have therefore evolved into a dynamic and authoritative network, able to combine local expertise with global strategy. Their future lies in acting ever more as a coordinated whole, aligned with the WPA's Action Plans and responsive to the challenges of a rapidly changing world. By reinforcing their collective identity, expanding into underserved regions, prioritizing education and cross-centre collaboration, and maintaining a strong commitment to social responsivity, the Centres are uniquely positioned to strengthen clinical and applied academic psychiatry and interdisciplinary scholarship worldwide.

Andrea Fiorillo[1], Kristina Adorjan[2,3], Muhammad W. Azeem[4], Debasish Basu[5], Bianca Della Rocca[1], Linda Lam[6], Roisin Mooney[7], Pratima Murthy[8], Victoria Mutiso[9], David Ndetei[9,10], Tarek Okasha[11], Janardhan Reddy[8], Dan J. Stein[12], Kamaldeep S. Bhui[7]

[1]Department of Psychiatry, University of Campania "L. Vanvitelli", Naples, Italy; [2]University Hospital of Psychiatry and Psychotherapy, Bern, Switzerland; [3]Institute of Psychiatric Phenomics and Genomics, LMU University Hospital, Munich, Germany; [4]Department of Psychiatry, Sidra Medicine, Doha, Qatar; [5]Department of Psychiatry, Postgraduate Institute of Medical Education and Research, Chandigarh, India; [6]Department of Psychiatry, Chinese University of Hong Kong, Hong Kong; [7]Department of Psychiatry and Wadham College, University of Oxford, Oxford, UK; [8]Department of Psychiatry, National Institute of Mental Health and Neurosciences, Bangalore, India; [9]Africa Institute of Mental and Brain Health, Nairobi, Kenya; [10]Department of Psychiatry, University of Nairobi, Nairobi, Kenya; [11]Okasha Institute of Psychiatry, Faculty of Medicine, Ain Shams University, Cairo, Egypt; [12]Unit on Risk and Resilience in Mental Disorders, Department of Psychiatry and Neuroscience Institute, University of Cape Town, Cape Town, South Africa

1. Bhui KS, Fiorillo A, Stein D et al. World Psychiatry 2016;15:300.
2. Fiorillo A, Bhui KS, Stein DJ et al. World Psychiatry 2021;20:457.
3. Fiorillo A, Javed A, Azeem MW et al. World Psychiatry 2023;22:495-6.
4. Wasserman D. World Psychiatry 2024;23:165-6.
5. Wasserman D. World Psychiatry 2024;23:302-3.
6. Wasserman D, Iosue M, Petros NG et al. World Psychiatry 2025;24:284-5.
7. Wasserman D, Iosue M, Avan A. World Psychiatry 2025;24:452-3.
8. Schulze TG. World Psychiatry 2024;23:303-4.
9. Skokauskas N, Chaimowitz G, Elgabry D et al. World Psychiatry 2024;23:304-6.
10. Soghoyan A. World Psychiatry 2024;23:306-7.
11. Skokauskas N, Chaimowitz G, Elgabry D et al. World Psychiatry 2025;24:147-8.
12. Sampogna G, Al-Taiar H, Baessler F et al. World Psychiatry 2024;23:461-2.
13. Pinto da Costa M, Squeri T, Perez Gomez L et al. World Psychiatry 2025;24:459-60.
14. Torous J, Linardon J, Goldberg SB et al. World Psychiatry 2025;24:156-74.
15. Fiorillo A, Azeem MW, Basu D et al. World Psychiatry 2025;24:151-2.

DOI:10.1002/wps.70033

Ten years of growth, collaboration and innovation: celebrating the WPA Early Career Psychiatrists Section

The WPA Early Career Psychiatrists (ECPs) Section was established in 2015. Over the past decade, the Section has evolved into one of the most dynamic and representative voices within the WPA, championing the perspectives, innovations and energy of ECPs across the world.

The Section was founded to foster international collaboration, mutual learning, and the active participation of ECPs in shaping the global mental health agenda and the future of psychiatry[1]. Rooted in values of equity, diversity and mentorship, the Section has prioritized accessibility for ECPs, especially from low- and middle-income countries (LMICs) and under-represented regions and groups. What began as a small group has since expanded into a robust structure, with partnerships involving national psychiatric associations, medical schools, and advocacy networks.

Among the most significant achievements of the Section has been its ability to amplify the voice of ECPs. It has ensured their representation in scientific congresses and international panels, coordinated the organization of the ECPs international congresses in Greece (2016) and Tunisia (2019), and contributed to training innovations, such as promoting patient involvement in medical education in psychiatry. The Section has led or supported collaborative research, coordinated global surveys, and published on key topics, especially during the COVID-19 pandemic.

Launching the very successful World Psychiatry Exchange Program[2] has further strengthened global ties and knowledge sharing. In collaboration with the World Health Organization[3] and the International Federation of Medical Students Association[4], the Section has contributed to global mental health dialogues and advocacy efforts. Many Section members have gone on to hold senior positions in academia, clinical services, and policy, demonstrating the long-term impact of investment in early leadership development.

The Section was initially proposed to consolidate the efforts of ECPs involved in the previous WPA Early Career Psychiatrists Council, and of other ECPs who had been active at national, regional and international levels in other associations[5]. But the past decade has not been without its challenges. The COVID-19 pandemic, political unrest, economic inequalities, natural disasters and wars have disproportionately affected ECPs in many regions. Many continue to face limited training opportunities, stigma, and brain drain, particularly in low-resource settings[6]. Within this context, the ECPs Section has emerged not only as a professional space, but as a community of solidarity. The peer-to-peer connections, mentorship circles, and psychosocial support initiatives developed by the Section have provided lifelines for many members navigating burnout, isolation or displacement.

As the Section begins a new leadership term during its 10th anniversary year, the team has launched a renewed strategic agenda built around six strategic pillars:

- *Digitalization*. The Section has launched the WPA ECPs WhatsApp Community, with global, regional and thematic subgroups to enhance real-time interaction, mutual support, and rapid information sharing. New communication tools, including expanding social media presence and a streamlined membership registration system, are improving accessibility and visibility.
- *Globalization*. The Section is prioritizing outreach to external partners that are lacking formal affiliation with WPA components, to integrate diverse perspectives into its activities.
- *Expansion*. New working groups focused on education, research, advocacy and well-being are being launched. These will allow more ECPs to engage in projects, contribute to webinars and publications, and participate in other activities.
- *Leadership development*. ECPs should be actively encouraged to engage in WPA committees, scientific events, and global mental health policy platforms. A new mentorship framework is being developed to connect emerging professionals with established leaders in psychiatry.
- *Representation*. The Section remains committed to strengthening gender equity, regional diversity, and the inclusion of ECPs from LMICs, particularly those facing structural or institutional barriers[7]. Flexible engagement models are being explored to reach psychiatrists in countries not formally affiliated with the WPA.
- *Sustainability*. The Section's terms of reference are under revision, and a multi-year action plan has been developed to ensure continuity and institutional memory. Standard operating procedures and protocols are being formulated to enhance operational efficiency.

ECPs today are already reshaping the field with new perspectives on digital health, cross-cultural collaboration, emerging interventions, and ethical practice. By cultivating a culture of contribution and ownership, our Section is empowering a generation ready not just to participate, but to lead psychiatry into a more inclusive, responsive, and globally connected future.

As we celebrate this 10-year anniversary, we acknowledge with deep gratitude the many individuals who have contributed to this collective journey, including past and current WPA officers, regional representatives, mentors, collaborators, and all ECPs who have engaged with the Section in diverse ways. Their dedication, creativity and solidarity have shaped the Section's identity and propelled its growth. Whether through leading initiatives, contributing to scientific output, offering mentorship, organizing events, or simply showing up to participate in a discussion, each act of involvement has strengthened the ECP community.

The Section's vitality lies not only in its formal structure, but in the lived connections among its members, in the friendships formed across borders, the mutual support offered during difficult times, and the shared vision of a more inclusive and equitable future for psychiatry. This anniversary is not only a celebration of institutional success, but also of the human relationships that have sustained the Section and made it a meaningful professional and personal space for so many.

Ultimately, the ECPs Section is a stepping stone in a professional trajectory; a movement rooted in the conviction that early voices matter, that solidarity is essential, and that the future of psychiatry depends on inclusive, courageous, and collaborative leadership[8,9]. As we look ahead, our collective hope is that the Section will continue to be a space where ECPs can not only grow, but lead.

Hussien Elkholy[1,2], Mariana Pinto da Costa[3], Felipe Picon[4], Florian Riese[5], Mariana Paim Santos[6], Alex Vicente Spadini[7], Fairouz Tawfik[2], Rick Peter Fritz Wolthusen[8], Lamia Jouini[9]

[1]Department of Clinical Neuroscience, Brighton and Sussex Medical School, Brighton, UK; [2]Okasha Institute of Psychiatry, Neurology and Psychiatry Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt; [3]Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; [4]ADHD Outpatient Program and Development Psychiatry Program, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil; [5]University Hospital of Psychiatry, Zurich, Switzerland; [6]Associação de Psiquiatria do Rio Grande do Sul, Brazil; [7]Department of Psychiatry, Federal University of Rio Grande do

Sul, Porto Alegre, Brazil; [8]Department of Psychiatry, Harvard Medical School, Boston, MA, USA; [9]Department of Old Age Psychiatry, Malevoz Psychiatric Hospital, Wallis Hospital, Monthey, Switzerland

The authors recognize the efforts of other previous or current Section committee members: T. Nakamae, P. Puspanathan, T. Melapi, I. Rojnic Palavra, S. Raja, P. Fung, H. Kuga, K. Tan, S. Medved, S. Philip, T. Morar and F. Swilem.

1. Pinto da Costa M, Palavra IR, Fung P et al. Lancet Psychiatry 2018;5:15-6.
2. Pinto da Costa M, Cheung G, Larnaout A et al. World Psychiatry 2023;22:490-1.
3. Pinto da Costa M, Ng RMK, Reed GM. World Psychiatry 2021;20:148-9.
4. Pinto da Costa M, Dima K, Ng RMK. World Psychiatry 2019;18:243-4.
5. Fiorillo A, Pinto da Costa M, Nakamae T et al. Middle East Curr Psychiatry 2016; 23:3-9.
6. Wasserman D. World Psychiatry 2024;23:165-6.
7. Pinto da Costa M, Ng B, Sanchez T et al. World Psychiatry 2025;24:291-2.
8. Picon F, Elkholy H, Pinto da Costa M et al. In: Javed A, Fountoulakis K (eds). Advances in psychiatry. Cham: Springer, 2018:143-55.
9. Wasserman D. World Psychiatry 2024;23:302-3.

DOI:10.1002/wps.70028

Acknowledgement
This publication has been partially supported by an unrestricted educational grant from Rovi Biotech srl, which is hereby gratefully acknowledged.