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World Psychiatry

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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.

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Generative artificial intelligence in mental health care: potential benefits and current challenges

The potential of artificial intelligence (AI) in health care is being intensively discussed, given the easy accessibility of programs such as ChatGPT. While it is usually acknowledged that this technology will never replace clinicians, we should be aware of imminent changes around AI supporting: a) routine office work such as billing, b) clinical documentation, c) medical education, and d) routine monitoring of symptoms. These changes will likely happen rapidly. In summer 2023, the largest electronic medical records provider in the US, Epic Systems, announced that it is partnering with OpenAI to integrate ChatGPT technology[1]. The profound impact that these changes will have on the context and delivery of mental health care warrants attention, but often overlooked is the more fundamental question of changes to the nature of mental health care in terms of improving prevention, diagnosis and treatments.

Research on non-clinical samples suggests that AI may augment text-based support programs, but assessments have focused on perceived empathy rather than clinical outcomes. While the former is an important development, it is only the first step towards progressing from feasibility to acceptability and from efficacy to effectiveness. A century of accessible self-help books, more than 60 years of mental health chatbots (Eliza was created in 1959), nearly 30 years of home Internet with access to free online cognitive behavioral therapy and chatrooms, over a decade of smartphone-based mental health apps and text message support programs, and the recent expansion of video-based telehealth, together highlight that access to resources is not a panacea for prevention. The true target for AI preventive programs should not be replicating previous work but rather developing new models able to provide personalized, environmentally and culturally responsive, and scalable support that works effectively for users across all countries and regions.

Computer-based diagnosis programs have existed for decades and have not transformed care. Many studies to date suggest that new AI models can diagnose mental health conditions in the context of standardized exam questions or simple case examples[2]. This is important research, and there is evidence of improvement with new models, but the approach belies the clinical reality of how diagnosis is made or utilized in clinical care. The future of diagnosis in the 21st century can be more inclusive, draw from diverse sources of information, and be outcomes-driven. The true target for AI programs will be to integrate information from clinical exam, patient self-report, digital phenotyping, genetics, neuroimaging, and clinical judgement into novel diagnostic categories that may better reflect the underlying nature of mental illness and offer practical value in guiding effective treatments and cures.

Currently, there is a lack of evidence about how AI programs can guide mental health treatment. Impressive studies show that AI can help select psychiatric medications[3], but these studies often rely on complete and labelled data sets, which is not the clinical reality, and lack prospective validation. A recent study in oncology points to an emerging challenge: when ChatGPT 3.5 was asked to provide cancer treatment recommendations, the chatbot was most likely to mix incorrect recommendations with correct ones, making errors difficult to detect even for experts[4]. The true target for AI programs will be in realizing the potential of personalized psychiatry and guiding treatment that will improve outcomes for patients.

For AI to support prevention, diagnosis and treatment there are clear next steps. Utilizing a well-established framework for technology evaluation in mental health, these include advances in equity, privacy, evidence, clinical engagement, and interoperability[5].

Since current datasets used in AI models are trained on non-psychiatric sources, today all major AI chatbots clearly state that their products must not be used for clinical purposes. Even with proper training, risks of AI bias must be carefully explored, given numerous recent examples of clear harm in other medical fields[6]. A rapid glance at images generated by an AI program when asked to draw "schizophrenia"[7] visualized the extent to which extreme stigma and harmful bias have informed what current AI models conceptualize as mental illness.

A second area of focus is privacy, with current AI chatbots unable to protect personal health information. Large language models are trained on data scraped from the Internet which may encompass sensitive personal health information. The European Union is exploring whether OpenAI's ChatGPT complies with the General Data Protection Regulation's requirement that informed consent or strong public health justifications are met to process sensitive information. In the US, privacy issues emerge with the risk that clinicians may input sensitive patient data into chatbots. This problem caused the American Psychiatric Association to release an advisory in summer 2023 noting that clinicians should not enter any patient information into any AI chatbot[8]. In order to allow integration into health care, authorities will need to determine whether chatbots meet privacy regulations.

A third focus is the next generation of evidence, as current studies that suggest the ability of chatbots to perform binary classification of diagnosis (e.g., presence of any depression or none) offer limited practical clinical value. The potential to offer differential diagnosis based on multimodal data sources (e.g., medical records, genetic results, neuroimaging data) remains appealing but as yet untested. Evidence of the true potential for supporting care remains elusive, and the harm caused to the eating disorder community by the public release (and rapid repudiation within one week) of the Tessa chatbot highlights that more robust evidence is necessary than that currently collected[9]. Like other medical devices, evidence of clinical claims should be supported by high-quality randomized controlled trials that employ digital placebo groups (e.g., a non-therapeutic chatbot).

Fourth, a focus on engagement is critical. We already know that engagement with mental health apps has been minimal, and can learn from those experiences. We are aware that engagement is not only a patient challenge, as clinician uptake of this technology is also a widely cited barrier and will require careful attention to implementation frameworks. These consistently highlight that, while innovation is important, there must be a concomitant focus on the recipients (i.e., education and training for both patients and clinicians) as well as on the context of care (e.g., regulation, reimbursement, clinical workflow). The principles of the non-adoption, abandonment, scale-up, spread and sustainability (NASSS) framework remain relevant in AI and offer tangible targets for avoiding failure.

Fifth and related, AI models need to be well integrated into the health care system. The era of standalone or self-help programs is rapidly ending, with the realization that such tools may often fragment care, cannot scale, and are rarely sustainable. This requires, in addition to data interoperability, careful designing of how AI interacts with all aspects of the health care system. There is a need for collaboration not only with clinicians but also with patients, family members, administrators, regulators, and of course AI developers.

While generative AI technologies continue to evolve, the clinical community today has the opportunity to evolve as well. Clinicians do not need to become experts in generative AI, but a new focus on education about current capabilities, risks and benefits can be a tangible first step towards more informed decision-making around what role these technologies can and should play in care.

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The public mental health revolution must privilege lived experience voices and create alliances with affected communities

The paper by Kirkbride et al in this issue of the journal[1] presents a masterful and comprehensive overview of the existing evidence demonstrating associations between an array of adverse social experiences and circumstances and the development and persistence of mental ill-health. It proceeds by providing a rallying cry for a revolution to topple the dominant focus of psychiatrists and resource-allocation models by service commissioners on treating existing mental disorders. Although the authors are careful to acknowledge how fundamental the current approach is, they claim that it has little more to offer in terms of moving the needle on alleviation of mental distress in the population. They call for this prevailing approach to concede substantial ground to make way for primary prevention strategies that tackle the key social determinants of mental ill-health. They convincingly argue that this transformational shift is essential if we are to make any significant progress in reducing the onset and burden of mental disorders across the globe. They particularly highlight the modifiable properties of social determinants as promising targets for preventive interventions to rejuvenate the largely stagnant field of treatment innovation in psychiatry.

However, there seems to be an absence of the voices of those with lived experience of social adversity and mental health issues within this review and the roadmap it presents for improving mental health across the population and reducing inequities in mental ill-health. For far too long, the very people we are trying to help have been excluded from the spaces in which decisions are made about how to study and treat them. This simply cannot continue. Not only is it morally wrong, but it can lead to wasting precious funding resources on attempting to answer research questions that have no relevance to wider society, and to the delivery of services that are inaccessible, unacceptable or do not meet the needs of people within local communities[2]. In 2021, the World Health Organization published a report entitled "Nothing for us, without us"[3], which specifically advocated for the inclusion of individuals and communities with first-hand experience of mental health issues and social determinants in designing policies, interventions, and research programs to enhance effectiveness and equity by ensuring that these have relevance and buy-in from the populations they are targeting, and that nobody is left behind.

Therefore, the design, delivery and evaluation of primary mental health prevention and promotion strategies and interventions should at the very least be informed by those most affected by the social and mental ill-health inequalities emphasized by Kirkbride et al, and preferably involve those with lived experience in equal partnership[2,3]. Ideally, we would reach a point in the near future where those with lived experience will lead research and interventions to improve population mental health. Additional social and financial support plus a high degree of flexibility are likely to be required to ensure that people from the most marginalized sections of our society can be included in these conversations, as they often

face multiple barriers to involvement. This will be crucial to avoid reproducing the systemic inequities that plague our society.

There are an increasing number of examples of successful involvement of people with lived experience in both research and clinical practice, with some even involving them throughout the whole process from design to implementation and dissemination[4]. This reaps benefits not only in terms of increased robustness of research and enhancing its translation into practice[2], but also provides opportunities for those with lived experience to develop new skills, increase their self-esteem, and be empowered[3,4]. This in turn is likely to result in positive benefits for their mental well-being and future prosperity. Moreover, funding bodies in the UK (e.g., the Wellcome Trust, UK Research and Innovation, MQ mental health charity) and around the world are realizing the importance and value of including those with lived experience of mental ill-health in developing the content of funding calls, rating applications, and sharing decision-making, by providing them with seats at the table for funding panels. These practices could easily be extended to those with lived experience of social adversity, and indeed the Violence, Abuse and Mental Health Network (www.vamhn.co.uk), one of the national mental health networks funded by UK Research and Innovation, involved trauma survivors in the design of its grant funding calls and criteria for rating applications, as well as in the selection of which applications to fund.

It is also important to engage and partner with marginalized and minoritized people from local communities and community-based organizations to create preventive interventions that are accessible, acceptable, inclusive and engaging, which will ultimately underpin their effectiveness[3]. As Kirkbride et al flag in their review, there is often entrenched mistrust of mental health care providers among minoritized groups (especially those from ethno-racial and LGBTQ+ communities), due to historical and recent experiences of discrimination, which together with stigma can present a major hurdle to ensuring that the services provided are actually used by those who may require them the most[5,6].

Moreover, interventions may need to be adapted to meet the specific needs of marginalized and minoritized communities – for instance located in places that can be easily reached by public transport or are familiar and non-stigmatizing (e.g., shopping centres, barber shops, primary care health centres, cafés) – and provide support with intersecting issues such as poor living conditions, debt, physical health problems, discrimination and other forms of trauma. Indeed, mental health interventions that have been adapted for people from minoritized groups have shown some benefits over more universal treatments[7], and health care co-located with welfare advice services has demonstrated improved mental health and financial outcomes[8].

Therefore, it will be crucial to ensure that prevention efforts are co-designed with minoritized communities and ideally delivered in collaboration with grassroots and community-based organizations, so that whatever is developed is acceptable, accessible, inclusive, and subsequently effective. Centring the voices of those with lived experience of mental health issues and social adversities, such as sexual violence, will also be essential to minimize the likelihood that the policies and interventions developed cause further harm[9]. Without the involvement of the people and communities affected, many of the proposed public mental health interventions are doomed to fail.

I would therefore urge academics, clinicians and policy makers to privilege the voices of those with lived experience of social adversity, mental health issues, and marginalization as they march forward into this public mental health revolution. It will be crucial for them to strive to share power equally with the communities affected when designing, implementing and evaluating these preventive strategies, if they are to develop acceptable and effective interventions, and succeed in overthrowing the current state of affairs.

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Borderline personality disorder: a comprehensive review of diagnosis and clinical presentation, etiology, treatment, and current controversies

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Borderline personality disorder (BPD) was introduced in the DSM-III in 1980. From the DSM-III to the DSM-5, no major changes have occurred in its defining criteria. The disorder is characterized by instability of self-image, interpersonal relationships and affects. Further symptoms include impulsivity, intense anger, feelings of emptiness, strong abandonment fears, suicidal or self-mutilation behavior, and transient stress-related paranoid ideation or severe dissociative symptoms. There is evidence that BPD can be reliably diagnosed and differentiated from other mental disorders by semi-structured interviews. The disorder is associated with considerable functional impairment, intensive treatment utilization, and high societal costs. The risk of self-mutilation and suicide is high. In the general adult population, the lifetime prevalence of BPD has been reported to be from 0.7 to 2.7%, while its prevalence is about 12% in outpatient and 22% in inpatient psychiatric services. BPD is significantly associated with other mental disorders, including depressive disorders, substance use disorders, post-traumatic stress disorder, attention-deficit/hyperactivity disorder, bipolar disorder, bulimia nervosa, and other personality disorders. There is convincing evidence to suggest that the interaction between genetic factors and adverse childhood experiences plays a central role in the etiology of BPD. In spite of considerable research, the neurobiological underpinnings of the disorder remain to be clarified. Psychotherapy is the treatment of choice for BPD. Various approaches have been empirically supported in randomized controlled trials, including dialectical behavior therapy, mentalization-based therapy, transference-focused therapy, and schema therapy. No approach has proved to be superior to others. Compared to treatment as usual, psychotherapy has proved to be more efficacious, with effect sizes between 0.50 and 0.65 with regard to core BPD symptom severity. However, almost half of the patients do not respond sufficiently to psychotherapy, and further research in this area is warranted. It is not clear whether some patients may benefit more from one psychotherapeutic approach than from others. No evidence is available consistently showing that any psychoactive medication is efficacious for the core features of BPD. For discrete and severe comorbid anxiety or depressive symptoms or psychotic-like features, pharmacotherapy may be useful. Early diagnosis and treatment of BPD can reduce individual suffering and societal costs. However, more high-quality studies are required, in both adolescents and adults. This review provides a comprehensive update of the BPD diagnosis and clinical characterization, risk factors, neurobiology, cognition, and management. It also discusses the current controversies concerning the disorder, and highlights the areas in which further research is needed.

Key words: Borderline personality disorder, psychotherapy, dialectical behavior therapy, mentalization-based therapy, transference-focused therapy, schema therapy, suicidal behavior, adverse childhood experiences, neurobiology, social cognition

(World Psychiatry 2024;23:4–25)

The term "borderline" was introduced in the psychiatric literature by Stern[1] and Knight[2], to identify a patient group showing a level of functioning situated between neuroses and schizophrenic disorders. This patient group was not well defined. An important progress occurred with Kernberg's introduction of the concept of borderline personality organization[3,4], marked by the use of primitive defense mechanisms such as splitting or projective identification, identity diffusion (shifting between all-good and all-bad), and severely disturbed object relationships[3]. Reality testing was largely intact, differentiating individuals with borderline personality organization from psychotic patients[3]. Another early contribution was provided by Grinker et al[5], who empirically identified four features of the "borderline syndrome": anger, impaired close relationships, identity problems, and depressive loneliness.

In 1980, borderline personality disorder (BPD) was introduced in the DSM-III[6], based on a study by Spitzer et al[7], who drew both on research by Gunderson and colleagues[8,9] and on Kernberg's concept of borderline personality organization[3], by including specific problems of identity and interpersonal relationships characterized by sudden shifts from one extreme to another (e.g., from all-good to all-bad or vice versa). This early research showed that BPD could be discriminated with sufficient accuracy from both schizophrenia and (neurotic) depression, as well as from other personality disorders[10,11].

In the following more than four decades, a plethora of research has been carried out on BPD, much more than on any other personality disorder. This research has focused on the diagnosis of BPD, its etiology (including genetics, neurobiology, and interactions between genetics/neurobiology and adverse childhood experiences), epidemiology, course and prognosis, cognition, and the effectiveness of pharmacotherapies and psychotherapies[12-18].

BPD remains a challenging disorder, from both research and clinical perspectives. At present, for example, there is still controversy concerning its conceptualization as either a specific personality disorder or a level of general impairment in personality functioning[19-21]. The treatment of BPD remains challenging as well. As to pharmacotherapy, there is no consistent evidence showing that any psychoactive medication is efficacious for the core features of the disorder[16]. Indeed, no medications have been approved by regulatory agencies for treating BPD[16,22]. According to the UK National Institute for Health and Care Excellence (NICE), pharmacotherapy should only be used to treat discrete and severe comorbid

anxiety or depressive symptoms or psychotic-like features, or to manage acute crises, and should be administered for the shortest time possible[22]. Psychotherapy is the treatment of choice for BPD, with various approaches having proved to be efficacious in randomized controlled trials (RCTs)[14,17,22]. However, almost 50% of BPD patients do not respond sufficiently to psychotherapy[23], so that further research in this area is clearly warranted. Whether specialized methods of psychotherapy or more generalist approaches are required for the treatment of BPD is a debated issue[24-26].

This paper provides a comprehensive review of BPD diagnosis and clinical characterization, course, epidemiology, risk factors, neurobiology, social cognition and neurocognition, and management. Current controversies (e.g., categorical vs. dimensional approaches to diagnosis; specific vs. generalist psychotherapy interventions) are also discussed, and major areas in which further research is warranted are highlighted.

DIAGNOSIS AND CLINICAL CHARACTERIZATION

The DSM-5 characterizes BPD as a pervasive pattern of instability of interpersonal relationships, self-image and affects, and marked impulsivity, emerging by early adulthood and present in a variety of contexts, as indicated by five or more of a set of nine criteria[27] (see Table 1).

The DSM-5 alternative dimensional model requires for BPD the presence of moderate or greater impairment in personality functioning, manifested by difficulties in at least two of the following areas: an unstable self-image (identity); unstable goals and values (self-direction); compromised ability to recognize the feelings and needs of others (empathy); and intense, unstable and conflicted close relationships (intimacy). In addition, four or more of the seven following personality traits are required (at least one of which must be impulsivity, risk taking or hostility): emotional lability, anxiousness, separation insecurity, depressivity, impulsivity, risk taking, and hostility. Impairments in personality functioning and pathological personality traits are required to be relatively pervasive and stable[27] (see Table 2).

An important aspect omitted in the DSM-5 criteria for BPD is regression proneness (i.e., showing emotions or behaviors not adequate to age) in unstructured situations, one of the reasons for many of the treatment problems occurring with the disorder[28]. Regression proneness has been empirically demonstrated by use of unstructured psychological tests such as the Rorschach or the Thematic Apperception Test (TAT)[29-32]. In these tests, patients with BPD tend to show bizarre-idiosyncratic primary process thinking, usually associated with the activation of low-level defense mechanisms and object relations[31-33].

In the ICD-11, the categorical system of personality disorders has been replaced by a dimensional approach similar to the DSM-5 alternative model[34]. Of the DSM-5 personality disorders, only BPD remains distinct and unique, by use of the "borderline pattern specifier". In the ICD-11, a diagnostician's task is to rate the severity level of personality dysfunction as "mild", "moderate" or "severe". In addition, the patient may be described on five domains (negative affectivity, detachment, dissociality, disinhibition, and anankastia). While in the clinical setting most patients with BPD can be expected to be classified as having a severe personality disorder, the ICD-11 allows to rate BPD patients in whom some areas of personality functioning are relatively less affected as suffering from a moderate personality disorder[35].

Table 1 DSM-5 criteria for borderline personality disorder[27]

A pervasive pattern of instability of interpersonal relationships, self-image and affects, and marked impulsivity, beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

1. Frantic efforts to avoid real or imagined abandonment.
2. A pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation.
3. Identity disturbance: markedly and persistently unstable self-image or sense of self.
4. Impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating).
5. Recurrent suicidal behavior, gestures or threats, or self-mutilating behavior.
6. Affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability or anxiety usually lasting a few hours and only rarely more than a few days).
7. Chronic feelings of emptiness.
8. Inappropriate, intense anger or difficulty in controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights).
9. Transient, stress-related paranoid ideation or severe dissociative symptoms.

The ICD-11 borderline pattern specifier may be applied in the presence of at least five of the following requirements: a) frantic efforts to avoid real or imagined abandonment; b) unstable and intense interpersonal relationships, which may be characterized by vacillations between idealization and devaluation; c) identity disturbance, manifested in unstable self-image; d) a tendency to act rashly in states of high negative affect, leading to potentially self-damaging behaviors; e) recurrent episodes of self-harm; f) emotional instability due to marked reactivity of mood; g) chronic feelings of emptiness; h) inappropriate intense anger or difficulty controlling anger; and i) transient dissociative symptoms or psychotic-like features. Further manifestations which may be present include a view of the self as inadequate; an experience of the self as profoundly different and isolated from other people; and proneness to rejection hypersensitivity (see Table 3).

Proposals to describe BPD by the five-factor model of personality[36] characterize it by high levels of both neuroticism (anxiousness, angry hostility, depressiveness, impulsiveness, vulnerability) and openness (high openness to feelings and actions), and by low levels of both agreeableness (low compliance) and conscientiousness (low deliberation)[37,38]. Another approach to define and conceptualize BPD focuses on major dimensions of psychopathology: most researchers agree that the dimensions which capture the essence of the disorder are emotional dysregulation, impulsivity and behavioural dysregulation, and interpersonal hypersensitivity[38].

With nine DSM-5 criteria and a threshold for diagnosis of five positive criteria, there are 256 theoretically possible ways to meet

Table 2 Proposed criteria for borderline personality disorder in the alternative DSM-5 model for personality disorders[27]

A. Moderate or greater impairment in personality functioning, manifested by characteristic difficulties in two or more of the following four areas:

1. Identity: Markedly impoverished, poorly developed, or unstable self-image, often associated with excessive self-criticism, chronic feelings of emptiness; dissociative states under stress.
2. Self-direction: Instability in goals, aspirations, values or career plans.
3. Empathy: Compromised ability to recognize the feelings and needs of others associated with interpersonal hypersensitivity (i.e., prone to feel slighted or insulted); perceptions of others selectively biased toward negative attributes or vulnerabilities.
4. Intimacy: Intense, unstable and conflicted close relationships, marked by mistrust, neediness and anxious preoccupation with real or imagined abandonment; close relationships often viewed in extremes of idealization and devaluation, and alternating between overinvolvement and withdrawal.

B. Four or more of the following seven pathological personality traits, at least one of which must be 5, 6 or 7:

1. Emotional lability: Unstable emotional experiences and frequent mood changes; emotions that are easily aroused, intense and/or out of proportion to events and circumstances.
2. Anxiousness: Intense feelings of nervousness, tenseness or panic, often in reaction to interpersonal stresses; worry about the negative effects of past unpleasant experiences and future negative possibilities; feeling fearful, apprehensive or threatened by uncertainty; fears of falling apart or losing control.
3. Separation insecurity: Fears of rejection by – and/or separation from – significant others, associated with fears of excessive dependency and complete loss of autonomy.
4. Depressivity: Frequent feelings of being down, miserable and/or hopeless; difficulty recovering from such moods; pessimism about the future; pervasive shame; feelings of inferior self-worth; thoughts of suicide and suicidal behavior.
5. Impulsivity: Acting on the spur of the moment in response to immediate stimuli; acting on a momentary basis without a plan or consideration of outcomes; difficulty establishing or following plans; a sense of urgency and self-harming behavior under emotional distress.
6. Risk taking: Engagement in dangerous, risky, and potentially self-damaging activities, unnecessarily and without regard to consequences; lack of concern for one's limitations and denial of the reality of personal danger.
7. Hostility: Persistent or frequent angry feelings; anger or irritability in response to minor slights and insults.

Table 3 Requirements for the borderline pattern specifier in the ICD-11[34]

The borderline pattern specifier may be applied to individuals whose pattern of personality disturbance is characterized by a pervasive pattern of instability of interpersonal relationships, self-image and affects, and marked impulsivity, as indicated by five (or more) of the following:

- Frantic efforts to avoid real or imagined abandonment.
- A pattern of unstable and intense interpersonal relationships, which may be characterized by vacillations between idealization and devaluation, typically associated with both strong desire for and fear of closeness and intimacy.
- Identity disturbance, manifested in markedly and persistently unstable self-image or sense of self.
- A tendency to act rashly in states of high negative affect, leading to potentially self-damaging behaviors (e.g., risky sexual behavior, reckless driving, excessive alcohol or substance use, binge eating).
- Recurrent episodes of self-harm (e.g., suicide attempts or gestures, self-mutilation).
- Emotional instability due to marked reactivity of mood. Fluctuations of mood may be triggered either internally (e.g., by one's own thoughts) or by external events. As a consequence, the individual experiences intense dysphoric mood states, which typically last for a few hours but may last for up to several days.
- Chronic feelings of emptiness.
- Inappropriate intense anger or difficulty controlling anger manifested in frequent displays of temper (e.g., yelling or screaming, throwing or breaking things, getting into physical fights).
- Transient dissociative symptoms or psychotic-like features (e.g., brief hallucinations, paranoia) in situations of high affective arousal.

Other manifestations, not all of which may be present in a given individual at a given time, include the following:

- A view of the self as inadequate, bad, guilty, disgusting and contemptible.
- An experience of the self as profoundly different and isolated from other people; a painful sense of alienation and pervasive loneliness.
- Proneness to rejection hypersensitivity; problems in establishing and maintaining consistent and appropriate levels of trust in interpersonal relationships; frequent misinterpretation of social signals.

the criteria for BPD[39]. Thus, despite conceptual coherence[40], BPD appears to be a heterogeneous diagnostic category which may include patient subtypes[41]. A cluster analysis, for example, found three clusters: a large one with "core" BPD symptoms; an extravert/externalizing one characterized by high levels of histrionic, narcissistic and antisocial features; and a small one of patients with marked schizotypal and paranoid features[42].

Although still utilized with caution, the diagnosis of BPD in adolescents is no longer controversial. Early detection of BPD (or subthreshold features of the disorder) facilitates a timely treatment of these young patients, reducing individual suffering and societal costs[43]. In the past, several arguments were used against BPD diagnosis prior to the age of 18, including the not uncommon occurrence of affective instability and irritation regarding self-image in adolescents, and the potential harm due to stigmatization. Today, there is a consensus regarding the potential appropriateness and usefulness of BPD diagnosis in the youth. This is also reflected by the latest developments in the ICD-11 and DSM-5[27,34], where the age threshold for the diagnosis has been omitted. The diagnosis of BPD can be regarded as being as reliable and valid in adolescence as in adulthood[44,45]. A community-based study conducted in the US found a point prevalence for adolescents at around 1% and a cumulative prevalence of 3% up to the age of 22[46]. As in adults, prevalence rates in outpatient and inpatient psychiatric settings are considerably higher[47,48].

In older patients with BPD, symptoms shift to more depression, emptiness and somatic complaints[49,50]. Emotional dysregulation, unstable interpersonal relationships, anger and attachment insecurity persist, whereas impulsivity and identity disturbances decrease[49,50]. Self-harm may take other forms, such as non-adherence to medical regimes or misuse of medication[50].

Individuals with BPD are likely to have co-occurring lifetime mood disorders (83%), anxiety disorders (85%), substance use disorders (78%), and other personality disorders (53%)[51-53]. BPD and bipolar I or II disorder co-occur in about 10-20% of patients with either disorder[54,55]. Although BPD is often comorbid with major depressive disorder or bipolar disorder, the additional diagnosis of BPD should not be made in an episode of those disorders if there is no evidence that the typical BPD symptomatological pattern persists over time.

Among people with attention-deficit/hyperactivity disorder, the lifetime rate of BPD was found to be 37.7%[56]. Eating disorders are also common among individuals with BPD, with median rates of 6% for anorexia nervosa, 10% for bulimia nervosa and 22% for eating disorders not otherwise specified[53]. Of individuals with BPD, 30% were diagnosed with post-traumatic stress disorder (PTSD), and 24% of individuals with this latter disorder were diagnosed with BPD[57].

Although there is a considerable overlap between BPD and the construct of complex PTSD (CPTSD) introduced in the ICD-11 – both disorders include problems in affect regulation, self-concept and interpersonal relationships – there is evidence that they can be empirically differentiated[58,59]. In particular, difficulties in affect regulation in CPTSD are ego-dystonic, stressor-specific and variable over time, whereas in BPD they tend to be ego-syntonic and persistent. Moreover, in contrast with the unstable self-concept in BPD, individuals with CPTSD have a consistently negative sense of self. Finally, the high rates of impulsivity and suicidal and self-injurious behaviors of BPD are not observed in CPTSD[59].

The above high levels of comorbidity may be an artefact of the categorical approach to psychiatric disorders, as also evidenced by the considerable overlap between BPD and the general psychopathology or p factor[60-63]. It has been argued that this overlap may represent a more parsimonious way not only to explain the high "comorbidity" associated with BPD, but also its large negative impact on functioning[64].

BPD can be reliably diagnosed by semi-structured interviews. Several reliable and validated interview methods exist[65-69]. In addition, self-report questionnaires and projective techniques such as the Rorschach or the TAT have proved to be helpful, especially with regard to assessing the level of personality functioning [28,29,31,32,54] (see Table 4). Sensitive diagnostic instruments for BPD in the elderly, however, need to be developed[50].

COURSE

BPD seems to be less stable over time than traditionally believed[54]. Considerable rates of recovery and relatively low rates of relapse have been reported in both short-term and long-term naturalistic follow-up studies[54,82]. In a 10-year prospective follow-up study, 50% of patients with BPD achieved recovery (i.e., symptomatic remission and good social and vocational functioning during the past two years), while 93% of them showed symptomatic remission lasting two years, and 86% remission lasting four years[82]. Thirty-four percent of patients lost their recovery and 30% their remission status after a two-year long remission[82]. Of note, most individuals received pharmacotherapy or psychotherapy, so that the above remission rates may not reflect the natural history of untreated BPD[83].

A meta-analysis of studies on the long-term course (≥5 years) of BPD reported a mean remission rate of 60%, associated with high heterogeneity between studies (I^2=80.9%)[84]. Excellent recovery (i.e., remission of symptoms and good social and full-time vocational functioning) was achieved in 39% of BPD patients compared with 73% in other personality disorders[85].

Patients with BPD show poorer social functioning than those with other mental disorders, including major depressive disorder and other personality disorders[86,87]. Only approximately 16% of people with BPD were reported to be married or living with a partner[88]. Social functioning was found to be unstable and highly associated with the symptomatic status[83,88,89]. Those patients who experienced change in personality pathology showed some improvements in functioning[83,88-91]. There is evidence that changes in personality traits (defined by the five-factor model) are followed by changes in BPD psychopathology, but not vice versa[92]. Traits were found to be more unstable in BPD than in patients with other personality disorders, indicating a "stable instability"[93].

BPD features tend to decline over time, and this process seems to be in part influenced by temperament[94]. However, diagnostic instruments may not be sensitive enough to tap the shift in symptoms in older populations to more depression, emptiness and somatic complaints[49,50].

EPIDEMIOLOGY

The age of onset of BPD varies, but symptoms are usually manifest in early adulthood[27]. In the adult general population, rates for BPD range between 0.7 and 2.7%[95,96]. In primary care, psychiatric outpatients and psychiatric inpatients, prevalence rates of 6%, 11-12% and 22%, respectively, have been found[96,97]. In a US community sample, 2.7% of individuals had been diagnosed with BPD in their lifetime, with only slightly higher rates for women compared to men (3% vs. 2.4%)[52]. In a psychiatric outpatient setting, however, considerably higher rates of BPD were found in women compared to men (72% vs. 28%)[97]. There are gender differences in comorbidity: men with BPD display more frequently substance abuse and antisocial personality disorder, while women more frequently present with mood, anxiety and eating disorders, and PTSD[98].

The rate of death by suicide is higher among individuals with BPD than in patients with other personality disorders (5.9% vs. 1.4%)[99]. These results are consistent with those of a recent meta-analysis which reported suicide rates of 2 to 5% (mean 4%) over follow-up periods of 5 to 14 years among people with BPD[84]. Suicide attempts occurred in more than 75% of BPD individuals[100].

In addition, BPD patients have a higher prevalence of somatic comorbidities – such as endocrine, metabolic, respiratory, cardiovascular and infectious (e.g., human immunodeficiency virus infection, HIV; hepatitis) diseases – than persons without BPD[101,102]. Mortality by non-suicide causes is clearly increased, with 14% of

Table 4 Major diagnostic interviews, self-report questionnaires, and projective techniques available for borderline personality disorder (BPD)

Tool	Scope	Description
Structured Clinical Interview for DSM-5 Personality Disorders (SCID-5-PD)[65]	BPD diagnosis according to DSM-5	Semi-structured interview including an optional screening questionnaire (SCID-5-SPQ); assessment of all personality disorders along DSM-5 criteria
Structured Clinical Interview for the DSM-5 Alternative Model for Personality Disorders (SCID-5-AMPD)[66]	BPD diagnosis according to DSM-5 Alternative Model for Personality Disorders (AMPD)	Semi-structured interview consisting of three modules: Module I: Dimensional assessment of the four domains of functioning (identity, self-direction, empathy and intimacy) Module II: Dimensional assessment of the five pathological personality trait domains (negative affectivity, detachment, antagonism, disinhibition and psychoticism) Module III: Assessment of each of the six specific personality disorders of DSM-5 AMPD
Diagnostic Interview for Personality Disorders (DIPD-IV), BPD module[67]	BPD diagnosis according to DSM-IV	Diagnostic interview for DSM-IV personality disorders
Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD)[68]	BPD symptom change	Clinician-administered scale for assessment of change in DSM-IV borderline psychopathology
Structured Interview of Personality Organization – Revised (STIPO-R)[69]	Personality organization	Semi-structured clinical interview assessing personality organization in five domains (identity, object relations, defenses, aggression, moral values)
Borderline Personality Inventory (BPI)[70]	BPD diagnosis, screening and personality functioning	Self-report tool assessing BPD symptoms and diagnosis, and borderline personality organization according to Kernberg
Borderline Symptom List (BSL)[71]	Borderline-typical symptomatology based on DSM-IV-TR criteria	Self-report tool assessing subjective impairments of BPD patients along the subscales of self-perception, affect regulation, self-destruction, dysphoria, loneliness, intrusions and hostility
Level of Personality Functioning Scale Self-Report (LPFS-SR)[72]	Personality functioning	Self-report tool assessing impairment in personality functioning according to the DSM-5 AMPD
McLean Screening Instrument for BPD (MSI-PD)[73]	Screening measure for BPD along the DSM-IV criteria	Self-report true/false screening questionnaire, including one item for each DSM-IV BPD criterion, with the exception of two items for paranoia/dissociation
Personality Assessment Inventory (PAI)[74]	BPD features	Self-report inventory of adult personality, including clinical scales assessing borderline features (affective instability, identity problems, negative relationships, self-harm)
Personality Diagnostic Questionnaire-4 (PDQ-4)[75]	Screening tool for DSM-IV personality disorders	Self-report tool with true/false questions intended to provide an indication of key features of each personality disorder, followed up with additional questions
Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) – Self-Report[76]	BPD symptom change	Self-report scale for the assessment of change in DSM-IV borderline psychopathology
Dimensional Assessment of Personality Pathology – Basic Questionnaire (DAPP-BQ)[77]	Personality pathology	Self-report measure of personality pathology, based on a dimensional model; subscales include affective lability, identity problems and self-harm
Personality Inventory for DSM-5 (PID-5)[78]	Maladaptive personality traits	Self-report measure of five broad domains of maladaptive personality variation: negative affect, detachment, antagonism, disinhibition and psychoticism
Rorschach/Holtzman Inkblot Technique[79,80]	Personality functioning (e.g., primary process thinking, defense mechanisms, object relations)	Projective techniques based on 10 (Rorschach) or 45 (Holtzman) unstructured cards. Subjects are asked: "What might this be?"
Thematic Apperception Test (TAT)[81]	Personality functioning (e.g., primary process thinking, defense mechanisms, object relations, affect regulation)	Projective technique based on 20-30 cards with a specific thematic valence. Subjects are asked to make up as dramatic a story as possible for each card.

BPD patients and 5.5% of those with non-BPD personality disorders dying over a 24-year follow-up[99]. Compared with patients without BPD who had other mental disorders or medical conditions, BPD was associated with a 2.3-fold increase in mortality rate during a 2-year follow-up[101].

Patients with BPD die on average 14-32 years earlier than subjects in the general population[99], while some studies report lower lifetime loss (6-7 years)[101]. Loss of lifetime years is more pronounced in men[101]. Compared to individuals without BPD, men with BPD had a poorer lifetime expectancy than women with

BPD, with an odds ratio (OR) of 2.40 (95% CI: 1.93-2.54) vs. 2.21 (95% CI: 2.08-2.77)[101].

These data suggest recommending BPD patients to engage in regular medical check-ups[103]. Increased health problems and associated higher mortality may reflect both unhealthy lifestyle and more direct neurobiological dysregulation of the stress and immune system associated with high levels of early adversity in BPD. Indeed, chronic physical diseases are strongly associated with "immature" personality[104], for which BPD may serve as a prominent example.

BPD is associated with intensive treatment utilization, and with societal costs exceeding those of anxiety and depressive disorders, diabetes, epilepsy and Parkinson's disease[54,87,101,105]. Thus, BPD constitutes a significant public health concern.

RISK FACTORS

It is currently hypothesized that, in BPD, genetic factors and adverse childhood experiences interact to influence brain development via hormones and neuropeptides[54,106]. Adverse childhood experiences are thought to modulate gene expression and lead to stable personality traits that may predispose to BPD[54].

There is familial aggregation of BPD[54,107], with recent data from a Swedish population-based study estimating heritability at 46%[108]. The risk of receiving a BPD diagnosis was increased 4.7-fold for full siblings[108]. The hazard ratio in identical twins was 11.5 (95% CI: 1.6-83.3). However, no single nucleotide polymorphisms associated with BPD have been identified[38,109], and some evidence of a genetic overlap of BPD with bipolar disorder, major depression and schizophrenia has emerged[109]. Results of epigenetic studies yielded inconsistent results and are often limited by small sample size[38,110]. Further large scale studies that are sufficiently powered to detect effects of genes on BPD phenotype are required[38]. In addition, more reliable measures of this phenotype are needed.

Adverse childhood experiences – including physical, sexual and emotional abuse, and neglect – are significantly associated with BPD[111,112]. Consistent with these findings, BPD has been associated with high levels of disorganized and unresolved patterns of attachment[113]. Borderline personality traits were associated with prior significant negative experiences in 12-year-old children[107]. This effect was more pronounced when families had psychiatric histories. While multiple psychosocial factors, including maltreatment, are associated with an increased risk for BPD, these findings do not seem to be disorder-specific[111].

Inherited and environmental risk factors are thought to contribute independently and interactively to the etiology of BPD. Recent findings on familial clustering and heritability of clinically diagnosed BPD, which revealed a 54% contribution from unshared, individually unique environmental factors, point in this direction[108].

There is increasing evidence that BPD is associated with both early and later adversity, leading to vicious interpersonal cycles. This is, for instance, evidenced by high levels of revictimization in romantic relationships and bully-victim relationship with peers, leading to increasing levels of distrust in others and social isolation[114-118]. Moreover, there is growing evidence that social deprivation and societal inequality may increase the risk for BPD, which may be related to high levels of distrust and sensitivity to social rejection and injustice in individuals with BPD[119-121]. These results point to the need of considering vulnerability to BPD from a broad, socio-ecological and transactional perspective[113,115].

NEUROBIOLOGY

A large number of studies have been conducted on the neurobiological underpinnings of BPD. Although several brain areas and neurotransmitters have been identified as potentially involved, only few findings have been confirmed by meta-analyses.

At the neuroendocrinological level, dysfunctions of the hypothalamic-pituitary-adrenal (HPA) axis, with altered levels of cortisol, have been suggested to underlie the impaired stress responses characteristic of BPD. One meta-analysis found significantly lower mean basal cortisol levels in individuals with BPD compared to non-psychiatric controls, with a small effect size of g=–0.32 (95% CI: –0.56 to –0.06, N=546, n=12, I^2=53%)[122]. Yet, a more comprehensive meta-analysis found no significant differences in singular cortisol assessments between individuals with BPD and healthy controls or individuals with other mental disorders, although heterogeneity between studies was high and moderate, respectively[123]. In a sub-analysis of five studies investigating continuous cortisol output, BPD patients' cortisol response to psychosocial challenges was blunted relative to healthy controls as well as to individuals with other personality disorders[123]. It is unclear whether disturbed HPA axis functioning is specifically associated with BPD or may rather be understood as a consequence of trauma exposure common in many psychiatric disorders[124]. However, research evidence is consistent with the allostatic load hypothesis, suggesting that the blunted cortisol response in BPD reflects a compensatory down-regulation consequent to adversity and stress.

Oxytocin has been also implicated in BPD, with particular relevance for interpersonal functioning, given its purported role in attachment behavior and social cognition[125]. A recent meta-analysis found decreased oxytocin levels among women with BPD (standardized mean difference, SMD=–0.46, 95% CI: –0.90 to –0.02; N=131, n=4, I^2=64%)[126]. However, the number of studies included was small, heterogeneity was moderate, and there were no significant differences with other personality disorders[126]. Furthermore, the administration of exogenous oxytocin in BPD patients has yielded inconsistent and paradoxical effects[127]. Further research is required to determine the role of oxytocin in BPD, in particular whether the observed impairments in the oxytocinergic system reflect a transdiagnostic vulnerability factor associated with early adversity and disturbed parent-infant attachment[125], or psychopathology in general[126].

In terms of neural systems, the most widely held hypothesis suggests a fronto-limbic imbalance in BPD, in which emotion dysregulation is mediated by hyperactivity of limbic structures

(e.g., amygdala, hippocampus and anterior cingulate cortex) and abnormal functioning of prefrontal structures[128]. However, only tentative conclusions can be drawn on the neurobiology of BPD, as most neuroimaging studies are severely underpowered[129].

The most robust meta-analytic result of neuroimaging studies in BPD is hyperactivity of the amygdala and hippocampal area during emotional processing experiments[130-132], which seems to be accompanied by impairments in habituation of the amygdala to repeated negative stimuli[133-138]. While earlier meta-analyses found a reduction in hippocampal and amygdala volume in BPD [139,140], a more recent and comprehensive meta-analysis reported no gray matter alterations[141]. Although the amygdala is assumed to be involved in emotional evaluation and recognition of subjectively dangerous situations, its exclusive role in processing negative emotions has recently been challenged, as studies have shown that amygdala activation is only marginally involved in the prediction of subjective fear ratings[142], correlates with the experiencing of positive emotions[143], and might rather indicate saliency for faces than threats[144]. Furthermore, despite the common conceptualization of the amygdala as the brain's "fear center", inconsistent meta-analytic evidence has been found for its involvement in processing threats[145,146]. Hence, negative emotional experiencing cannot be confidently inferred from amygdala hyperactivity in BPD [147].

Research on abnormal prefrontal functioning lacks spatial specificity in BPD[147,148], and meta-analyses have yielded conflicting results, with an earlier one finding abnormal functioning in prefrontal areas[131], while the most recent and comprehensive one reported no significant differences to healthy controls[132], although again the marked heterogeneity of BPD may be an important factor explaining inconsistent findings.

Connectivity analyses could test assumptions of reduced prefrontal top-down regulation on limbic areas such as the amygdala. However, only very few studies have investigated connectivity during emotion regulation tasks in BPD[149]. A considerable number of studies have investigated resting-state connectivity in BPD, yielding conflicting results with respect to the fronto-limbic imbalance hypothesis[150-152].

Taken together, to date there is only weak evidence that a fronto-limbic imbalance underlies emotion dysregulation in BPD[147]. Moreover, most neuroimaging findings lack specificity to BPD and might rather relate to transdiagnostic factors of psychopathology[131,153] or to childhood maltreatment[134,147,154-157]. Recent research efforts point to the possible role in BPD of impairments in the temporo-parietal junction[158], which is thought to play a crucial role in distinguishing self from other, so that its impairments might underlie the typical self-other distinction problems (i.e., identity diffusion) observed in BPD patients. However, meta-analyses are not yet available and the small number of studies preclude drawing strong conclusions.

In summary, although brain areas and neurotransmitters have been identified as potentially involved in BPD, an integrated and empirically supported neurobiological model of the disorder does presently not exist. Research on the neurobiology of BPD is complicated by several factors, including the high prevalence of co-morbidities, the heterogeneity of the condition, the use of medication, as well as substantial differences in experimental designs.

SOCIAL COGNITION AND NEUROCOGNITION

Over the past decade, empirical studies on social cognition have advanced our understanding of interpersonal and emotional dysfunction in BPD. The disorder appears to be characterized by relatively severe impairments in mentalizing, i.e., the capacity to understand the self and others in terms of intentional mental states, as a result of largely affect-driven, externally-cued processing of social information. Results are not always consistent, which may be due to the type of tasks used (e.g., some social cognition tasks show ceiling effects or primarily rely on "cold" social cognition, whilst mentalizing impairments mainly tend to emerge in high-arousal contexts in BPD patients) and the influence of factors involved in the etiology of the condition (e.g., severity of trauma or attachment style).

A recent systematic review[159] of experimental studies on social cognition in BPD based on the Systems for Social Processes approach of the Research Domain Criteria included four meta-analyses, concerning more basic (i.e., emotion recognition accuracy and reaction time) and more complex (i.e., understanding of mental states and ostracism) features of mentalizing with regard to others. Individuals with BPD showed reduced accuracy for recognizing facial emotional expression in others compared to healthy controls, with a significant moderate effect size of g= –0.41 (95% CI: –0.57 to –0.25; n=18, I^2=21%). There was no evidence for differences with respect to reaction time in detecting facial emotions (g=0.27, 95% CI: –0.04 to 0.59, n=8, I^2=27%). As to the widely held hypothesis of an anger bias in BPD, the evidence of the systematic review was inconsistent, although the number of included studies was very small (n=4). Another meta-analysis found evidence for an attentional bias to negative and personally relevant negative words rather than an attentional bias towards facial stimuli[160].

Strong rejection sensitivity (ostracism) was found in BPD. Following perceived social exclusion, individuals with BPD experienced substantially more negative emotions and reported a greater threat to needs relative to healthy controls, with a large effect size (g=1.13, 95% CI: 0.67-1.59, n=10)[159]. Although there was significant heterogeneity and evidence for publication bias, people with BPD showed greater levels of ostracism compared to individuals with other mental disorders (e.g., social anxiety disorder, major depressive disorder), with a medium effect size (g=0.67, 95% CI: 0.16-1.18). These findings from experimental studies are consistent with those of other meta-analyses, reporting strong expectancy of social rejection assessed by self-report in BPD compared to normal controls[120,161,162]. However, heterogeneity between studies was again large, and there was evidence for publication bias.

Notably, one meta-analysis found a larger difference in negative affectivity following social inclusion (d=1.00, 95% CI: 0.76-1.25, I^2=78%) than social rejection (d=0.68, 95% CI: 0.57-0.80, I^2=68%) in individuals with BPD compared to non-BPD groups[120].

However, heterogeneity was high and significant. Although these findings await confirmation, disturbed perceptions of both social exclusion and inclusion might be one explanation for the marked instability in close relationships in BPD. Further evidence for this comes from a meta-analysis of 26 studies on romantic attachment in BPD patients[163]. The disorder was significantly correlated with attachment anxiety (r=0.48, I^2=77%), but also with attachment avoidance (r=0.30, I^2=74%)[163]. Heterogeneity was significant. Hence, a combination of both forms of attachment difficulties might underlie BPD, which is consistent with the assumption that the disorder, and its severe cases in particular, is related to a disorganization of the attachment system characterized by strong push-pull cycles in close interpersonal relationships[164,165].

The above-mentioned meta-analysis of experimental studies[159] also found, in BPD patients compared to healthy controls, a significantly poorer understanding of mental states in others, as assessed with Theory of Mind (ToM) tasks[166], with a medium effect size (g=–0.45, 95% CI: –0.75 to –0.16, n=24). However, there was high heterogeneity between studies (I^2=85%). Individuals with BPD also showed greater deficits in inferring others' mental states in comparison to people with other mental disorders, with a medium effect size (g=–0.53, 95% CI: –1.03 to –0.03). Heterogeneity was high (I^2=64%). These findings are largely consistent with those of other meta-analyses of studies using ToM tasks[167,168].

Moreover, in a meta-analytic evaluation[169], significant impairments were found in studies of mentalizing involving ToM tasks in BPD compared to healthy controls (d=0.36, 95% CI: 0.24-0.48, n=31, N=2,737, I^2=50%). Deficits in mentalizing assessed by self-report were more pronounced (d=1.84, 95% CI: 1.64-2.04, n=4, N=595, I^2=0%). These findings are consistent with a meta-analysis finding a strong correlation between deficits in mentalizing with regard to the self, assessed in terms of emotional awareness or alexithymia, in BPD compared to healthy controls (r=0.52, 95% CI: 0.41-0.61, n=15)[170].

Yet, one recent meta-analysis found evidence for a role of excessive mentalizing or hypermentalizing in BPD (r=0.26, 95% CI: 0.12-0.39, n=10), which was, however, comparable to other mental disorders[171]. Although hypermentalizing may be related to psychopathology in general rather than BPD in particular, these findings suggest that BPD is not simply associated with general deficits in mentalizing, but with a specific imbalance which can be expressed in hypomentalizing as well as hypermentalizing. This interpretation is consistent with research findings suggesting that BPD is associated with a predominance of automatic, affect-driven and largely externally-based mentalizing, with little possibility for more controlled, cognitive and internally-based mentalizing, specifically in high-arousal contexts[172]. However, more longitudinal research is needed, as there is evidence that mentalizing problems and BPD features reciprocally interact over time, and meta-analytic evidence for a specific mentalizing profile in BPD patients is currently lacking.

A meta-analysis of 3,543 participants[173] found that BPD symptomatology was associated with less frequent use of adaptive emotion regulation strategies (i.e., cognitive reappraisal, problem solving, and acceptance) and more frequent use of maladaptive ones (i.e., suppression, rumination, and avoidance). The role of rumination as a dysfunctional emotion regulation strategy in BPD was also confirmed by two recent meta-analyses[174,175]. Furthermore, a meta-analysis found stronger self-report of experienced shame in comparison to healthy controls, with a large effect size of d=1.44 (n=10, N=3,543)[176]. However, there was significant heterogeneity and evidence for publication bias.

Lastly, there is preliminary evidence of negative self-evaluation[159,177], lack of cooperation/trust[178,179], impairments in self-other distinction[180], disturbed interoception[181], and splitting[179] in BPD patients, but meta-analytic evaluations have yet to confirm these hypothesized deficits.

Deficits in neurocognition in BPD were demonstrated in a meta-analysis of 207 effect sizes across cognitive domains, reporting a medium overall effect size for impaired neuropsychological functions in BPD compared to healthy controls (d=–0.48, 95% CI: –0.58 to –0.43, N=9,332)[182]. However, heterogeneity was significant. The strongest impairments were found for decision making (d=–1.41, 95% CI: –0.91 to –1.91), memory (d=–0.57, 95% CI: –0.64 to –0.58), and executive functioning (d=–0.54, 95% CI: –0.64 to –0.43)[198]. These results are in line with other meta-analyses[183,184].

In summary, meta-analyses support a complex pattern of alterations in social cognition and neurocognition in BPD. The most robust findings are impairments in emotion recognition accuracy, an attentional bias towards negative stimuli, marked rejection sensitivity following social exclusion as well as inclusion, imbalances in mentalizing, dysfunctional emotion regulation, and deficits in neurocognition. Limitations are that most meta-analyses showed substantial heterogeneity, and results are often not specific to BPD. Further research is required to develop a more comprehensive understanding of the role of social cognition and neurocognition in BPD.

MANAGEMENT

As a first step of management, BPD patients need to be informed about the diagnosis, expected course, putative risk factors, and treatment options[54]. Psychotherapy should be recommended as the first-line treatment, with pharmacotherapy as a possible adjunctive treatment in specific situations. Clear boundaries should be set, response to provocative behavior should be avoided, and a consistent approach should be agreed upon with all involved clinicians, in order to prevent a situation in which some of them are regarded as "bad" and others as "good". If present, life-threatening behaviors need to be addressed first.

Managing life-threatening behaviors

Life-threatening behaviors (e.g., suicidal, self-mutilating or high-risk behaviors, attacks against others) must be given priority. Verbal interventions entail a calm attitude, understanding the crisis from the person's point of view, empathic open questions, and stimulating reflections about solutions. Sedative or antipsychotic

medications may be used for the treatment of crises, but for no longer than one week[185].

For understanding and managing suicidality, the following recommendations can be given[186,187]. The therapist needs to clarify the acute danger of committing suicide (e.g., has the patient already developed a plan on how to commit suicide; has the patient previously made a suicide attempt; is impulse control severely impaired, e.g. by substance misuse; is there a lack of social support system; is the patient trustful with regard to agreements?). It should then be explored whether there is a major depressive disorder requiring pharmacotherapy or inpatient treatment. If this is not the case, clarifying the trigger of the present suicidality is required (e.g., interpersonal loss, shift from all-good to all-bad). Suicide may be experienced by the patient as a solution of a problem (e.g., stopping anxiety, despair, loneliness, emptiness, or anger). Discussing what makes life intolerable may help to move the focus from suicide to life's wounds. Other solutions may emerge. Focusing on black-and-white images of the self or of others related to the triggering situation may be helpful.

Suicidal threats may be used by the patient to force the clinician not to abandon him/her (as others may have done). As a result, the clinician may feel as helpless or angry as the patient, or being tortured. The clinician is recommended not to counteract aggressively – e.g., by trying to get rid of the patient (thus confirming the patient's experiences and expectations). Instead, the clinician may convey that he/she is concerned and trying to help the patient to reduce his/her suicidal pressure, but that ultimately it will be up to the patient to decide what to do. It is recommended to make a contract that commits the patient not to act on suicidal impulses, but to discuss them in the sessions or to go to emergency psychiatric services if he/she feels that suicidal impulses cannot be controlled. Evidence-based psychotherapies for BPD include detailed recommendations about how to treat suicidality[187-189] (see below).

Pharmacotherapy

Up to 96% of patients with BPD seeking treatment receive at least one psychotropic drug[190]. Polypharmacy is common[191,192]: almost 19% of patients with BPD report taking four or more psychotropic drugs[193]. However, no class of psychoactive medications has consistently proven to be efficacious, and no medication has been approved by the US Food and Drug Administration (FDA) for BPD[194].

Pharmacotherapy is not recommended for the treatment of any core symptom of BPD, but only for addressing discrete and severe comorbid disorders such as severe depression or anxiety or transient psychotic symptoms, and only for the shortest possible time and as a treatment in crises[22]. It should be noticed, however, that there are only a few RCTs focusing on BPD with distinct comorbidities[16], as most trials excluded patients with comorbid major depressive disorder, bipolar disorder, psychotic disorders or substance-related disorders. Short-term symptoms of depression or anxiety that are part of the BPD emotional instability and can be related to specific triggering situations must not be misinterpreted as reflecting comorbid disorders. For insomnia in BPD, general advice about sleep hygiene without medication prescription is recommended[22]. For severe insomnia, Z-drugs (e.g., zolpidem or eszopiclone) may be prescribed[22]. Due to concerns over dependence, the use of Z-drugs is recommended only for severe insomnia, with the lowest possible dose and for no longer than four weeks[195].

Acute suicidality or psychotic crises may necessitate psychotropic medication, as well as severe agitation or dissociative states, or pronounced difficulties in controlling aggression. At present, no RCTs exist on the use of psychotropic drugs in manifest crises of patients with BPD[194]. Due to the high comorbidity of BPD with addictive disorders[196,197], the use of substances with dependence potential should be avoided as far as possible. Sedative antihistamines (such as promethazine) or low-potency antipsychotics (such as quetiapine) may be preferred. After the acute crisis has subsided, the medication should be discontinued.

Psychotherapy

Psychotherapy is regarded as the first-line treatment for BPD [22,54,198]. Guidelines do not recommend brief forms of psychotherapy lasting less than three months[22]. However, although a number of specialist treatments – i.e., dialectical behavioral therapy (DBT), mentalization-based therapy (MBT), transference-focused psychotherapy (TFP), and schema therapy (ST) – for BPD have been developed and empirically supported, their implementation in routine clinical practice remains patchy. If evidence-based methods of psychotherapy are not available, experienced mental health professionals may apply psychoeducation or crisis management[26].

Evidence has emerged for generalist models of treating patients with BPD, that incorporate features of specialized evidence-based treatments, and can be carried out by experienced clinicians without a training in those treatments[199]. Of note, however, these treatment models, which typically served as comparison conditions in trials of specialized methods of psychotherapy, followed manuals or manual-like guidelines, and therapists received supervision by experts as well[200-202]. Thus, as discussed in more detail below, further research is required to establish whether generalist models are as efficacious as the specialized treatments with respect to all outcomes.

Further efforts are needed to decrease the stigma associated with BPD among both the general public and health care workers. It often takes many years before individuals with BPD seek help and, when they do, they are unfortunately often still met with stigma with regard to the nature and treatability of their problems in many health care settings[203,204].

In the following sections, we discuss the various methods of psychotherapy that have proven to be efficacious for BPD in RCTs [17,205]. For family members of BPD patients who suffer from considerable burden, helpful psychoeducational methods have been developed[206].

Dialectical behavior therapy (DBT)

DBT[189,207,208] is a structured outpatient psychotherapy based on cognitive-behavioral principles. This therapy is "dialectical" in the sense that both acceptance and change are regarded as necessary for improvement. It consists of four components: individual therapy, group skills training, telephone coaching, and team consultations of therapists.

Individual therapy is conducted by the patient's primary therapist. It focuses on six main areas. Parasuicidal behavior is explored in detail, and problem-solving behaviors – including short-term distress management techniques – are emphasized. Therapy-interfering behaviors are addressed (e.g., non-adherence, breaking agreements), as well as behaviors with impact on the quality of life (e.g., substance abuse, high-risk sexual, interpersonal, legal, financial or health-related behavior). Acquired behavioral skills are discussed and applied to patient's daily life. Trauma history is addressed when the patient is ready, including remembering the abuse, validation of memories, acknowledging emotions related to abuse, reducing self-blame and stigmatization, addressing denial and intrusive thoughts regarding abuse (e.g., by exposure techniques), and reducing polarization or supporting a dialectical view of the self and the abuser[208]. The therapist consistently reinforces the patient's self-respect behaviors.

Group skills training focuses on deficits in behavioral skills, including the unstable sense of self, unstable interpersonal relationships, fear of abandonment, impulsivity and emotional lability. Training includes four modules: core mindfulness, interpersonal effectiveness, emotion regulation, and distress tolerance. Group meetings take place weekly for two hours. The four modules are worked through in about six months. Modules may be repeated, and the skills training group is recommended for at least one year. Patients are assigned homework to reinforce skills. Diary cards are used to document the use of skills and are discussed with the individual therapist.

Core mindfulness skills have been adopted from Eastern meditation practice. To target BPD patients' impulsivity and emotion-driven behavior, they are taught to observe and participate fully in the present moment. To target their tendency to idealize and devaluate both themselves and others, they are taught to focus on one thing at a time with a non-judgmental mindset. Doing so also prevents patients from ruminating about past and worrying about future events.

Interpersonal effectiveness skills training teaches patients to ask for what they need, to say "no", and to deal with interpersonal conflicts. Emotion regulation skills include identifying and labelling emotions; identifying obstacles to change of emotions, including parasuicidal behaviors; learning to avoid vulnerable situations; increasing events which lead to positive emotions; learning to tolerate painful emotions. Distress tolerance skills include techniques for self-soothing or distracting, as well as for transforming intolerable pain into tolerable suffering.

Telephone coaching can be used in times of crises between regular sessions. Patients can learn how to ask for help in an adequate, non-abusive manner. Reinforcement for parasuicidal behaviors is minimized by making an agreement that the patient is expected to call the therapist before enacting a parasuicidal behavior, and is not allowed to call the therapist for 24 hours after a parasuicidal behavior act, unless there are life-threatening injuries.

Weekly team consultations of therapists form an integral part of treatment, aiming to monitor treatment fidelity, enhance therapeutic skills, and maintain therapists' motivation in working with this particular group of patients. Team consultation may promote empathy and acceptance of the patient.

Mentalization-based therapy (MBT)

MBT[209] is a structured treatment that combines individual and group psychotherapy. It focuses on addressing suicidality and self-harm, emotional processing, and relational instability in BPD patients, through a consistent focus on improving their capacity for mentalizing and social learning.

BPD is characterized by imbalances in mentalizing, as expressed in high levels of automatic, affect-driven and externally-based mentalizing, and frequent loss of the capacity for balanced mentalizing, particularly within close interpersonal relationships. This is associated with a dominance of experiencing the self and others in non-mentalizing modes, such as: a) the psychic equivalence mode (equating thoughts and feelings with reality), b) the teleological mode (only recognizing observable reality as a determinant of mental states), and c) the pretend mode (characterized by excessive mentalizing severed from reality).

These unmentalized or "alien-self" experiences are assumed to give rise to very intense and often unbearable feelings (e.g., high levels of anger, sadness or rejection), and as a result there is a tendency to externalize these unmentalized feelings through acting-out behaviors (e.g., self-harm, substance abuse), in an attempt to regulate them.

MBT also focuses on improving the capacity for epistemic trust, i.e., the capacity to trust knowledge conveyed by others and to use this knowledge for salutogenetic purposes (i.e., to be able to benefit from positive resources in the social environment).

The therapeutic stance of the MBT therapist is guided by the following basic principles: a) management of anxiety and arousal is central in MBT, as high levels of arousal easily lead to a loss of mentalizing, whereas low levels typically result in pretend mode functioning (excessive mentalizing severed from reality); b) interventions are aimed at restoring more balanced mentalizing, as patients with BPD easily resort to automatic, highly affect-driven and externally-based mentalizing, with little ability for more balanced, controlled mentalizing that integrates cognition and affect, and externally-based and internally-based social information; c) the patient and the therapist are equal, conversational partners attempting to reconstruct and better understand what is happening in the patient's interpersonal relationships, and how interpersonal issues are associated with the patient's presenting problems; d) a focus on the recovery of mentalizing implies that the therapist is primarily concerned with the "how" of mental processes, rather than the "what" and "why"; e) contingent and marked responses of empath-

ic emotional validation are another key feature of MBT, aiming to restore a sense of agency and understanding in the patient.

MBT uses a spectrum of interventions, which include: supportive interventions (empathic and normalizing interventions that primarily serve to regulate anxiety and arousal, and foster epistemic trust by restoring a sense of agency through experiences of marked mirroring); interventions aimed at clarification and elaboration of subjective experiences; interventions aimed at restoring basic mentalizing (e.g., stop-and-rewind, stop-stand-and-explore, stop-stand-and-challenge); interventions aimed at mentalizing the therapeutic relationship; interventions aimed at translating and generalizing knowledge acquired within the therapeutic process to interpersonal relationships outside of the therapeutic context. Two types of MBT for BPD have been developed and empirically supported: intensive outpatient MBT and day-hospitalization-based MBT for adults[210].

MBT includes an initial phase, a treatment phase, and a final or ending phase, each with their specific goals and strategies that are directly rooted in the evolving understanding of the condition.

The initial phase involves: psychoeducation provided through an MBT introductory group course; case formulation developed collaboratively with the patient; a focus on developing a treatment alliance based on an understanding of the patient's attachment history; safety planning; formulation of a mentalizing profile, i.e., the identification of specific imbalances in mentalizing, including triggers of mentalizing problems.

The treatment phase comprises general and specific strategies. General strategies include: stabilization of risky behaviors; supportive, empathic validation to regulate anxiety/arousal and to enable the (re)activation of mentalizing; the use of elaboration and clarification to foster basic mentalizing, particularly of highly affective states; a strong focus on interpersonal relationships and events to enable an exploration of alternative perspectives (i.e., relational mentalizing); a focus on repairing alliance ruptures. Specific strategies include: management of impulsivity by mentalizing events that trigger impulsive behavior; activation of the attachment system in both group and individual therapy, allowing for the development of basic mentalizing; linking experiences in therapy to daily life, with a focus on social exclusion/inclusion and rejection; increasing mentalizing capacity when under stress; recovering mentalizing capacity when a loss of mentalizing occurs; mentalizing traumatic experiences when indicated.

The final phase focuses primarily on the following issues: review of the therapy with a focus on the experience of ending for both patient and therapist; a focus on issues associated with ending that trigger BPD-specific concerns (e.g., fears of abandonment or rejection); generalization of stable mentalizing and learned social understanding; considering how to continue the therapeutic process after ending.

Transference-focused psychotherapy (TFP)

TFP represents a specific extension of psychoanalytic therapy for treatment of individuals with personality disorders[187,211]. Within the framework of psychoanalytic object relations theory, unconscious conflicts activated in the transference are seen as expressions of conflictual, affectively invested internalized object relations. Unconscious conflicts are represented as dyadic units composed of a representation of the self interacting with a representation of a significant other, framed by a particular affect state. These dyadic structures come to be enacted, or lived, by the patient in his/her interactions with the therapist.

In TFP, the therapist's focus is on exploration and interpretation of patient's behaviors in the treatment that reflect the activation of specific transferences, associated internalized object relations, and the conflicts they imply. The activation of dominant internalized object relations is interpreted both in their defensive function, that is, as a protection against the opposite relationships that they attempt to avoid, and in their "impulsive" or expressive function, as a reflection of deeper primitive, affectively motivated behaviors pushing for actualization.

Within the setting of a borderline structure, unconscious conflict takes the form of a fundamental conflict, or split, between positively charged, idealized sectors of experience and negatively charged, paranoid sectors. Each internalized object relation can, at different moments, serve impulsive or defensive functions. These idealized and persecutory internalized object relations are activated and then enacted in the transference.

The main psychoanalytic techniques employed in TFP are interpretation, transference analysis, technical neutrality, and countertransference utilization. Affective dominance refers to material that, in the perception of the therapist, is most strongly present and affectively salient in the patient's verbal and, in particular, nonverbal communications at any moment of the session[211]. Affective dominance signifies the major area of conflict currently active in the therapy session, and thus, the material that becomes the most suitable and productive focus of the therapeutic intervention.

Interpretation is the establishment of hypotheses involving unconscious conflicts. They derive from the combined analysis of the content of the patient's communications, his/her nonverbal behavior, and the dominant countertransference. Interpretations focus predominantly, but not exclusively, on the transference. Affect dominance determines the focus of interpretation.

Transference analysis represents the main therapeutic instrument. It refers to the analysis of unconscious conflicts activated in the dyadic relations between patient and therapist that replicate the conflictual internalized relation between self and others ("objects") from the past, modified by present context.

Technical neutrality is the observing attitude of the therapist, who keeps a concerned objectivity in his/her interpretive interventions, and maintains himself/herself outside the patient's activated internal conflicts.

Countertransference utilization refers to the therapist's ongoing observation of his/her emotional reactions to the patient, utilizing them to more sharply understand the emotional conflicts activated in the transference, and to interpret the transference in this light without direct communication to the patient of his/her own countertransference.

An early stage of TFP involves clarification of self and object

representation of the activated internalized object relationship, their predominant affective implication, the distribution of self and object roles to patient and therapist, and their potential interchange. A more advanced stage involves the patient's emotional learning that he/she is, at a deeper level of unconscious experience, identified with both self and other in both idealized and persecutory internalized relationships, with decrease in the splitting of idealized and persecutory states of mind. In this advanced stage of treatment, the patient learns and tolerates the reasons for his/her splitting of polar opposite love- and hatred-dominated relationships, and integrates the concepts of his/her self and the respective concepts of significant other. Normalization of personal identity is achieved, and a realistic capacity for relationships with significant others develops. Modulation of affect states, increased affect control, and increased capacity for non-conflictual investment in work and profession, love and sex, and gratifying social relations may evolve.

Schema therapy (ST)

ST[212,213] draws on cognitive-behavioral, psychodynamic, attachment and emotion-focused approaches. It addresses four dysfunctional life schemas characteristic of BPD: the abandoned/abused child; the angry/impulsive child; the detached protector; and the punitive parent. In addition, some presence of the healthy adult is assumed. The development of the healthy adult is one of the goals of ST, first embodied in the therapist and internalized by the patient during the therapeutic process.

The abandoned/abused child mode is characterized by feeling isolated, lost, unloved, and frantic, obsessive with finding a parental figure who will take care of him/her. This mode is regarded as a core state of being for the BPD patient. ST recommends the therapist to envision BPD patients as functioning as a young child.

In the angry/impulsive child mode, the patient expresses rage about mistreatment and unmet emotional needs. This mode is activated in situations of real or perceived abandonment, deprivation or mistreatment. Tragically, this mode makes it even less likely that the patient's needs are met. In addition, the punitive parent may be activated and punish the angry child. Outburst of rage may be followed by cutting or other forms of self-punishment.

In the detached protector mode, the patient avoids investing emotionally in people or activities; he/she may feel numb or empty, withdraw socially, excessively fantasize or seek stimulation or distraction. This mode interferes with therapeutic progress.

The punitive parent mode represents the patient's identification with an abusive parental figure. By internalizing this figure, the inner abuse continues. In this mode, patients feel "evil" or "dirty" and may engage in parasuicidal behaviors. The therapist helps the patient to recognize this part of himself/herself, and gives it a descriptive name (e.g., "your punishing father"). Thus, the patient may achieve some distance from this part of himself/herself and may fight back.

Four processes are regarded as core mechanisms of change in ST: "limited reparenting", emotion-focused work, cognitive restructuring and education, and behavioral pattern breaking.

"Limited reparenting" is regarded as the most important change mechanism[235]. Therapists try to compensate for the deficits in parenting that patients with BPD experienced during their childhood, while maintaining professional boundaries. They act in a warm and sympathetic way, providing safety, stability and acceptance. They may disclose themselves if they believe it will be beneficial to patients. They provide the patients with their home phone number for use in crises, give extra session time, and have phone sessions and email exchange as needed. Patients who have problems related to separation and abandonment may be provided with check-in calls, flashcards or other transitional objects.

ST uses emotion-focused techniques, including imagery work, dialogues and letter writing. Patients are asked to bring up images and memories of difficult situations they experienced in the past. The therapist can enter into the childhood scenes, and protect and support the abandoned/abused child, functioning as the healthy adult. After the therapist has done so, the patient takes on the healthy adult role, by entering into the image and protecting the child mode. Traumatic memories are worked through more slowly and only with the patient's permission. ST uses dialogues between the therapist and the patient to nurture the abandoned child, to protect the misused child, and to fight the punitive parent. These dialogues can be done in imagery or through Gestalt chair work. The latter helps to locate the punitive voices outside the patient. By role-playing, the therapist helps the patient to strengthen his/her healthy adult mode. As a third technique, therapists encourage the patients to write a letter to those who have mistreated them in which they express their feelings and needs. The letters are not intended to be sent.

Cognitive techniques used in ST include education and cognitive restructuring. Patients are taught about normal needs and emotions. Thus, the therapist validates the patient's rights to have these needs met, while also teaching the patient to negotiate the desires in a reciprocal way, respecting others. This applies to emotions and specifically to anger. However, patients are taught to adequately express their emotions, not using a "black-and-white" thinking. In addition, patients are taught not to blaming themselves for setbacks during therapy.

Finally, the patients are guided to generalize to the life outside what they have learnt during sessions. For this purpose, traditional behavioral techniques may be used, such as relaxation training, assertiveness training, anger management, self-control strategies, or graduate exposure. Flashcards or dialogues may also be used. Therapists and patients identify the most serious behaviors as targets for change. *In vivo* exercises may be used to disconfirm distorted expectations, for example of others acting as punitive parents. In sessions, role-playing and behavioral rehearsals can be used.

ST includes three phases: bonding and emotional regulation, schema mode change, and development of autonomy.

The bonding and emotional regulation phase aims at establishing a relationship with the therapist which is an antidote to the abusive or punitive one that the patient experienced as a child. Thus, a "holding environment"[214], a safe place for the patient, is

developed. After that, childhood and adolescent experiences are explored. During these explorations, the patient is kept in the abandoned/abused child mode, in order to allow him/her to make a new relational experience. The patient begins to internalize the experience with the therapist as a healthy parent. Anger may be expressed, but in a controlled way, in order to avoid that it becomes counterproductive. All the patient's needs and longings that have been unmet are activated, allowing the therapist to engage in a limited reparenting behavior.

While working on changing schema modes, the therapist maintains a relationship with the abandoned/abused child. The therapist praises the patient and calls him/her "generous, loving, intelligent, sensitive, creative, empathic, passionate, or loyal"[215, p.335], reparenting the patient. The punitive parent mode may be triggered, and the patient may reject these affirmations.

If the patient is flooded with anxiety and painful emotions, the detached protector mode could be triggered. This is a survival mechanism developed by the patient, but can interfere with the therapeutic process. When it emerges in the therapeutic process, this mode is identified, and its benefits and costs are discussed. The situation can be addressed by adjusting the intensity and frequency of affective work carefully. Furthermore, the use of medication can be considered to reduce the intensity of affects.

In the final stage of treatment, the therapist shifts the attention from reparenting within the therapeutic relationship to developing independence outside sessions. The focus is on interpersonal relationships and on the sense of identity. Relationships are explored to see how the various modes are interacting. With regard to developing a sense of identity, the therapist and the patient work together to explore what resonates with the patient.

Efficacy of psychotherapy in BPD

A meta-analysis aggregating the effect sizes achieved by psychotherapy in comparison to treatment-as-usual (TAU) in BPD yielded an overall SMD of –0.52 (95% CI: –0.70 to –0.33, n=22, N=1,244), which corresponds to a clinically relevant reduction in symptom severity[17] (see Table 5). Thus, psychotherapy of BPD is among the few treatments for common mental disorders achieving medium or large effect sizes in comparison to TAU[217]. For self-harm (SMD=–0.32, 95% CI: –0.49 to –0.14, n=13, N=616), suicide-related outcomes (SMD=–0.34, 95% CI: –0.57 to –0.11, n=13, N=666) and psychosocial functioning (SMD=–0.45, 95% CI: –0.68 to –0.22, n=22, N=1,314), psychotherapy was significantly superior to TAU as well, but with low-quality evidence and effect sizes below clinical relevance[17]. There is no evidence that psychotherapy is associated with a higher rate of serious adverse events compared with TAU (risk ratio, RR=0.86, 95% CI: 0.14-5.09; n=4, N=571, p=0.86)[17]. Generic methods of psychotherapy (e.g., general psychiatric management, structured clinical management, client-centered therapy, supervised team management) were found to be inferior to specialized psychotherapies such as DBT, MBT or schema therapy[216].

For the main types of evidence-based psychotherapy, the effect sizes achieved in comparison with TAU in BPD patients do not differ significantly[17]. This applies to symptom severity (X^2=6.88, df=4, p=0.14, I^2=41.8%) and psychosocial functioning (X^2=0.67, df=3, p=0.88, I^2=0%). The most recent network meta-analysis confirmed the lack of significant differences between specialized psychotherapies in reducing BPD symptom severity, with only two exceptions: ST was superior to DBT (SMD=0.72, 95% CI: 0.03-1.41) and cognitive-behavior therapy (CBT) (SMD=0.90, 95% CI: 0.12-1.69)[216]. However, these results should be interpreted with caution, as some of these differences were based on only a few trials[216]. Between DBT, TFP and MBT, no statistically significant differences were found in reducing BPD symptom severity, with small between-group effect sizes[216]. For suicidal behavior, no differences in efficacy were found between specialized psychotherapies[216].

With regard to individual types of psychotherapy, most studies are available for DBT[17]. DBT achieved a medium clinically signifi-

Table 5 Meta-analytic evidence for efficacy of psychotherapies vs. treatment as usual (TAU) for borderline personality disorder (BPD)

	n	N	Outcome	SMD (95% CI)
Major forms of psychotherapy vs. TAU[17]	22	1,244	Severity of BPD symptoms	–0.52 (–0.70 to –0.33)
	13	616	Self-harm	–0.32 (–0.49 to –0.14)
	13	666	Suicide-related outcomes	–0.34 (–0.57 to –0.11)
	22	1,314	Functioning	–0.45 (–0.68 to –0.22)
Dialectical behavior therapy vs. TAU[17]	3	149	Severity of BPD symptoms	–0.60 (–1.05 to –0.14)
	7	376	Self-harm	–0.28 (–0.48 to –0.07)
	6	225	Functioning	–0.36 (–0.69 to –0.03)
Psychodynamic therapies vs. TAU[228]	4	213	Severity of BPD symptoms	–0.65 (–0.99 to –0.32)
	5	354	Suicide-related outcomes	–0.67 (–1.13 to –0.20)
	5	392	Functioning	–0.57 (–1.04 to –0.10)

Major forms of psychotherapy include dialectical behavior therapy, psychodynamic therapies, cognitive-behavior therapy, schema therapy, and acceptance and commitment therapy. Psychodynamic therapies include mentalization-based therapy, transference-focused therapy, and dynamic deconstructive therapy. SMD – standardized mean difference.

cant effect size compared to TAU for BPD severity (SMD= –0.60, 95% CI: –1.05 to –0.14, n=3, N=149, I^2=42%). It achieved small and clinically not significant effect sizes for self-harm (SMD=–0.28, 95% CI: –0.48 to –0.07, n=7, N=376, I^2=0%) and psychosocial functioning (SMD=–0.36, 95% CI: –0-69 to –0.03, n=6, N=225, I^2=31%)[17]. In these studies, DBT had a duration of 2.5 to 12 months[17]. A recent RCT found DBT of 6-month duration to be non-inferior to 12-month DBT with regard to self-harm (primary outcome), as well as for general psychopathology and coping skills, at 24-month follow-up[218]. There were no differences in dropout rates between treatments. A briefer form of DBT may reduce barriers to treatment access.

For psychodynamic therapies in BPD, ten RCTs presently exist (five for MBT[25,219-222], three for TFP[200,223,224], and four for other methods, such as dynamic deconstructive therapy[201,225-227]). In these RCTs, psychodynamic therapy was compared to TAU or to other active treatments. It had a duration of 5-24 months, except for one study, in which it had a 3-year duration[224]. A meta-analysis comparing psychodynamic therapies with TAU found medium effect sizes in favor of the former for core BPD symptoms (g=–0.65, 95% CI: –0.99 to –0.32, n=4, N=213, I^2=15.4%), suicide-related outcomes (g=–0.67, 95% CI: –1.13 to –0.20, n=5, N=354, I^2=40.1%) and psychosocial functioning (g=–0.57, 95% CI: –1.04 to –0.10, n=5, N=392, I^2=60.1%), with low or moderate heterogeneity[228]. Effect sizes were clinically significant, except for functioning. This meta-analysis did not find significant differences in efficacy between psychodynamic therapies and other active psychotherapies, including DBT and ST (g=0.05, 95% CI: –0.52 to 0.62, n=4, N=394, I^2=64%). Excluding one outlier[224] reduced heterogeneity (g=–0.08, 95% CI: –0.55 to 0.39, n=3, N=308, I^2=19%).

Due to the limited number of RCTs, meta-analyses specifically focusing on between-group effect sizes with ST are not available[229]. The most recent meta-analysis on psychotherapy for BPD included only three RCTs of ST[216]. As noted above, in reducing BPD symptoms, ST was found to be superior to DBT and CBT, but not MBT or TFP[216]. However, these results should be interpreted with caution, due to the limited number of RCTs on which they were based. With regard to individual studies, a large RCT (N=495) found combined individual and group ST to be superior to both TAU (d=1.14, 95% CI: 0.57-1.71, p<0.001) and predominantly group ST (d=0.84, 95% CI: 0.09-1.59, p=0.03) in reducing severity of BPD symptoms, with large effect sizes[230]. Predominantly group ST was not superior to TAU (d=0.30, 95% CI: –0.29 to 0.89, p=0.32)[230]. Both treatments were delivered over a period of two years, with combined individual and group ST encompassing 124 sessions and predominantly group ST 122-135 sessions. Another RCT found ST to be superior to TFP[224]. These results, however, have been critically discussed with regard to the question whether TFP was adequately implemented[231,232]. In a pilot study, brief ST (20 sessions) was not found to be superior to TAU[233].

Research on psychotherapy for BPD has several limitations. The number of studies is still relatively limited, and the quality of evidence is moderate[17]. In many studies, risk of bias was high [17,205], possibly inflating effect sizes[205]. Dropout rates are high[234] and differ considerably between studies[235]. Furthermore, treatment effects are found to be unstable at follow-ups[17,205]. Regarding publication bias affecting outcomes, results are heterogeneous[17,205]. Moreover, rates of non-response vary considerably between studies and treatments, which may also in part be due to different definitions of response used[23]. For psychotherapy alone, non-response was on average 48.8%[23] when the definition of response required either no longer meeting criteria for BPD or change of BPD symptomatology below a cut-off (e.g., 50% or 25% reduction)[23]. The mean rate of non-response was similar for DBT (47%), ST (42%) and psychodynamic therapies (42%)[23]. For TAU, it was 64%[23]. Thus, the proportion of non-responders is considerable, and psychotherapy needs to be further improved.

There is limited evidence that psychotherapy for BPD is also effective under real-world conditions. For instance, more than a dozen of naturalistic studies have found that MBT is associated with clinically significant improvements in BPD symptoms, general psychiatric symptoms, suicidality and self-harm[236]. For TFP, a naturalistic study reported a remission rate of 58% as well as improvements in BPD symptom severity and functioning (N=19)[237]. An inpatient treatment which combined TFP with modules of DBT skills training was reported to achieve significant improvements in identity diffusion and symptoms (N=32)[238]. In another naturalistic study, both DBT (N=25) and dynamic deconstructive psychotherapy (N=27) achieved significant reductions in symptoms of BPD, depression, and disability by 12 months of treatment[239]. This was not true for a non-randomized TAU condition (N=16). A naturalistic study found no differences in outcomes between MBT and DBT after 12 months of treatment[240].

Psychotherapy in adolescents

A recent Cochrane review concluded that adolescent patients with BPD do benefit from psychotherapy, but to a lesser extent than adult patients[17]. Disorder-specific treatments such as DBT, TFP and MBT have been adapted for adolescents. Studies often include young patients with subthreshold BPD pathology, and use naturalistic or even hybrid study designs with randomized assignment in a naturalistic setting. In these studies, high attrition rates are quite common.

Some reasonably robust studies on psychotherapeutic interventions for adolescents with BPD are, however, available. A quasi-experimental investigation compared DBT (N=29) with TAU (N=82) among suicidal outpatient adolescents who also met DSM-IV criteria for BPD[241]. The DBT group had significantly fewer hospital admissions, but no differences were found in suicide attempts. In a Norwegian randomized control trial of 77 adolescents with recent and repetitive self-harm, DBT (N=39) was compared to enhanced usual care (EUC) (N=38)[242]. Participants met at least two DSM-IV criteria for BPD plus the self-destructive criterion, or at least one DSM-IV BPD criterion plus at least two below-threshold criteria. The authors found DBT to be superior to EUC. The former remained superior in reducing self-harm, but not for other outcomes (including BPD symptoms), over a follow-up period of 52 weeks[243]. For DBT, a recent meta-analysis including

five RCTs and three controlled clinical trials reported a medium effect size compared to control groups (g=–0.44, 95% CI: –0.81 to –0.07, n=7, I^2=80%) in reducing self-harm, and a small effect size (g=–0.31, 95% CI: –0.52 to –0.09, n=6, I^2=44%) in reducing suicidal ideation[244].

The adolescent identity treatment (AIT)[245] integrates behavioral elements with TFP. In a naturalistic study, 60 adolescents diagnosed with BPD or subthreshold BPD pathology received either DBT or AIT[246]. Both treatments significantly improved BPD symptoms, depression, and psychosocial and personality functioning. Overall, AIT was found to be not inferior to DBT and even more effective in reducing BPD symptoms.

TFP was evaluated in a naturalistic day-clinic setting[247]. One hundred twenty adolescents with personality pathologies (BPD as a majority) received either TFP or TAU. Contrary to the TAU group, patients treated with TFP showed a significant reduction in self-harm.

MBT was compared with TAU in 80 adolescents exhibiting self-harm behavior and comorbid depression, of whom 73% met the criteria for BPD. MBT was more effective than TAU in reducing self-harm and depression[248]. A reduction in BPD traits after the end of MBT was also reported.

The efficacy of the psychoanalytic-interactional method (PiM) was examined in an inpatient setting[249]. This RCT included 66 adolescents with the primary diagnosis of a mixed disorder of social behavior and emotions (F92 according to the ICD-10) compared with a mixed control group (waiting list and TAU). The ICD-10 F92 diagnosis was used as an indicator of BPD features. The sample comprised severely impaired patients with high rates of comorbidity. Patients in the treatment group had a significantly higher rate of remission (OR=26.41, p<0.001) and a significantly greater improvement in behavioral problems and strengths. At six-month follow-up, treatment effects were stable. A subsequent analysis assessed 28 adolescents fulfilling DSM-IV diagnostic criteria for BPD who had started inpatient treatment[250]. At the end of treatment, 39.3% of these patients no longer met the diagnostic criteria and were therefore classified as remitted.

However, a recent systematic review and meta-analysis of psychotherapy for adolescents with BPD or BPD features[251], including ten RCTs with a high risk of bias and very low quality, found that only a few trials demonstrated superiority of the intervention over the control condition. Thus, the authors stated that it is difficult to derive conclusions about the efficacy of psychotherapy in BPD adolescents, and that further high-quality studies with larger samples are required.

CONTROVERSIES

Diagnostic issues

A first debated issue is whether BPD should be regarded as a separate disorder ("there has been a notable absence of sound scientific evidence that it is a unified syndrome"[19, p.394]). In fact, the BPD criteria were found to show a high loading only on a general personality pathology factor, whereas other personality disorders showed loadings either on both the general and a specific factor or largely only on a specific factor[62].

Furthermore, BPD has been critiqued for missing stability in studies with long-term follow-ups, with some typical symptoms of BPD being associated with a higher stability than others[252-254]. However, the percentage of BPD patients who retain their personality disorder diagnosis in a 2-year follow-up (44%) is not substantially different from that of patients with obsessive-compulsive (40%), schizotypal (39%) and avoidant (50%) personality disorder[252]. Furthermore, the decrease in proportion of criteria met across time does not differ significantly between the various personality disorders[252].

Some authors have argued that the high overlap with the general factor of personality pathology, and the intrinsic experience of self and interpersonal dysfunction, suggest that the BPD criteria reflect general impairments in personality functioning rather than a distinct personality disorder[60,62]. This notion is consistent with Kernberg's concept of borderline personality organization [3,255], and is compatible with the DSM-5 and ICD-11 dimensional model of personality disorders[35,60].

Another critical issue is the number of criteria that have to be fulfilled in order to be able to assign a diagnosis of BPD. A patient with intense feelings of emptiness, highly unstable interpersonal relationships, severe identity disturbance, and self-harm, for example, may not fulfill the diagnostic criteria due to missing a fifth criterion, despite severe impairment in functioning. Furthermore, with five of nine criteria required for the diagnosis, there are 256 possible ways to meet the DSM-5 criteria of BPD[39], suggesting considerable heterogeneity among BPD patients. This heterogeneity represents a challenge for research on etiology and treatment[38].

Another critical argument refers to the fact that clinical features typical of BPD are well represented within the ICD-11 system, with its two-step approach of firstly assigning a core personality disorder diagnosis (mild, moderate, severe) based – among others – on self and interpersonal functioning, and secondly the specification via trait dimensions, most notably negative affectivity (e.g., emotional lability, anxiety), disinhibition (e.g., reckless behavior, impulsivity), and dissociality (e.g., hostility, aggression)[21,35]. On the other hand, proponents of a categorical model emphasize that BPD is a clinically useful diagnosis and one of the best researched ones, especially with regard to the development and testing of psychotherapeutic interventions[254]. Moreover, it is argued that some of the most important concepts related to our understanding of mental disorders and psychopathology – such as mentalization and its neurobiology, trauma, and relationship dynamics – have been stimulated by research on BPD[256-258].

The final decision to include a "borderline specifier" in the ICD-11 was preceded by intense discussion and controversy[19]. This decision has been seen as a political and practical compromise in order to strengthen the acceptance of the new system[19,21]. Considering that there is a lot of ongoing research and funding related to BPD, and that several academic careers have been built upon its research and treatment, abolishing it has been likely seen as too far-reaching. Additionally, the new system, including both options,

will likely lead to interesting research options (e.g., studying milder forms of personality disorder in combination with typical borderline domains, or comparing the old versus the new model)[21].

Treatment issues

Some meta-analyses suggest limited differences in efficacy between specialized and non-specialized treatments for BPD, particularly at long-term follow-up and when controlling for publication bias[205]. This has led some authors and guidelines to conclude that non-specialist treatments may be as effective as specialist ones [199]. Of course, non-specialist treatments may have the advantage of being more cost-effective and thus the potential to greatly increase access to effective psychotherapy for patients with BPD. Yet, as noted, several meta-analyses have instead found clinically significant differences in efficacy between specialist and non-specialist treatments for BPD[17,216]. Moreover, non-specialist treatments evaluated in clinical trials are typically manualized, with clinicians being trained and supervised in the approach, and thus may often not be truly "non-specialized" treatments.

Because of their problems with self-coherence and trust in others, patients with BPD might be particularly sensitive and responsive to treatments that offer coherence, consistency and continuity[24]. This assumption is also borne out by studies suggesting that the effect sizes of specialist treatments for BPD considerably decrease when offered under suboptimal conditions[259]. Moreover, some studies suggest that specialist treatments may be particularly more effective compared to non-specialist ones in more complex patients[260,261]. Finally, the effectiveness of "non-specialist" treatments evaluated in RCTs has dramatically increased over time, suggesting that they have increasingly incorporated effective principles of "specialist" treatments or, at the very least, have discontinued the use of iatrogenic practices such as unfocused exploratory and supportive interventions[24].

Although more research concerning the (cost-)effectiveness of specialist and non-specialist treatments, and their implementation in routine clinical care, is needed to investigate the above assumptions, the good news is that there is growing convergence among different treatment approaches as regards effective practices in patients with BPD.

CONCLUSIONS

BPD is a common mental disorder, associated with considerable functional impairment, intensive treatment utilization, and high societal costs. The construct of BPD is internally consistent and more homogeneous than often assumed[262]. However, it is still controversial whether BPD is better represented by a categorical or dimensional approach[19]. Future research is required to clarify this issue. This is also true for the elucidation of the risk factors, the neurobiological underpinnings, and the role of social cognition and neurocognition in the disorder.

With regard to treatment of BPD, pharmacotherapy is presently only recommended for severe and discrete comorbid mental disorders and for the short-term treatment of crises. Psychotherapy has proven to be efficacious in BPD[17] and is recommended as first-line treatment[22]. With regard to the different types of psychotherapy, there is presently no reliable evidence that one method is superior to others[17,216]. Some differences in efficacy that were recently reported are based on a few trials[216]. As a limitation, rates of non-response and relapse are relatively large[23]. Thus, psychotherapy needs to be further improved.

Future studies of psychotherapy in BPD are recommended to focus on patients at risk of non-response and on improving long-term effects, as well as on reducing self-harm behavior and suicidal ideation[263]. Taking the high dropout rate into account[234], another focus should be on patients prematurely terminating treatments. By studying dropouts, researchers can learn which aspects of a treatment are experienced by patients as not beneficial or even harmful, and in which way treatments may be improved. Thus, patients who drop out of a treatment can provide important information[264].

As another limitation, the quality of psychotherapy studies was found to be modest[17,216]. Further high-quality studies are required, in both adults and adolescents. Taking the shift from categorical to dimensional concepts into account[20], research on psychotherapy of BPD (and of personality disorders in general) needs to take dimensional outcome measures (e.g., Level of Personality Functioning Scale[27]), as well as personality traits, into account. Treatment research on dimensionally defined (severe) personality disorders is required[265].

In addition, high-quality head-to-head comparisons of the major forms of psychotherapy with a sufficient statistical power, adequate treatment implementation, and control of bias and researcher allegiance are needed. Such trials may also examine presumed mechanisms of change. For these head-to-head comparisons, proponents of each approach need to be included on an equal basis (adversarial collaboration)[266]. Funding organizations are encouraged to support these comparative trials, since large samples may be required to detect small but clinically significant differences, implying considerable study costs. As the differences in efficacy between the major psychotherapeutic approaches do not seem to be substantial at the group level[17,216], identifying what works for whom seems to be a promising strategy. Individual participant data meta-analysis may be helpful in this regard[216].

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Functional magnetic resonance imaging in schizophrenia: current evidence, methodological advances, limitations and future directions

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Functional neuroimaging emerged with great promise and has provided fundamental insights into the neurobiology of schizophrenia. However, it has faced challenges and criticisms, most notably a lack of clinical translation. This paper provides a comprehensive review and critical summary of the literature on functional neuroimaging, in particular functional magnetic resonance imaging (fMRI), in schizophrenia. We begin by reviewing research on fMRI biomarkers in schizophrenia and the clinical high risk phase through a historical lens, moving from case-control regional brain activation to global connectivity and advanced analytical approaches, and more recent machine learning algorithms to identify predictive neuroimaging features. Findings from fMRI studies of negative symptoms as well as of neurocognitive and social cognitive deficits are then reviewed. Functional neural markers of these symptoms and deficits may represent promising treatment targets in schizophrenia. Next, we summarize fMRI research related to antipsychotic medication, psychotherapy and psychosocial interventions, and neurostimulation, including treatment response and resistance, therapeutic mechanisms, and treatment targeting. We also review the utility of fMRI and data-driven approaches to dissect the heterogeneity of schizophrenia, moving beyond case-control comparisons, as well as methodological considerations and advances, including consortia and precision fMRI. Lastly, limitations and future directions of research in the field are discussed. Our comprehensive review suggests that, in order for fMRI to be clinically useful in the care of patients with schizophrenia, research should address potentially actionable clinical decisions that are routine in schizophrenia treatment, such as which antipsychotic should be prescribed or whether a given patient is likely to have persistent functional impairment. The potential clinical utility of fMRI is influenced by and must be weighed against cost and accessibility factors. Future evaluations of the utility of fMRI in prognostic and treatment response studies may consider including a health economics analysis.

Key words: Schizophrenia, functional magnetic resonance imaging, biomarkers, negative symptoms, functional outcomes, cognition, treatment response, therapeutic mechanisms, precision medicine, clinical utility

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While functional neuroimaging in schizophrenia emerged in the literature somewhat later than structural neuroimaging, its promise was just as great or greater, as have been its challenges. Fortunately for the field, and for people suffering from schizophrenia, the maturational arc of this technique is in its ascendancy, with a number of new developments that have accelerated our understanding of brain function in this illness from the group to the subgroup to the individual level.

The present paper aims to serve as a comprehensive review of functional neuroimaging in the various phases of schizophrenia. The focus is on functional magnetic resonance imaging (fMRI), both resting state and task-based, rather than other types of functional neuroimaging – e.g., positron emission tomography (PET), electroencephalography (EEG), magnetoencephalography (MEG), and arterial spin labeling (ASL). We provide a critical summary of the literature on fMRI in schizophrenia, including diagnostic markers, neural correlates of negative symptoms and cognitive deficits, and markers of treatment resistance and therapeutic response. The utility of fMRI to understand therapeutic mechanisms, guide precision treatment, and dissect patient heterogeneity is also reviewed. Lastly, methodological considerations and advances, limitations, and future directions of research in the field are discussed.

Neuroimaging research in schizophrenia began with the advent of computed tomography (CT) and then MRI scans, which demonstrated that there were structural differences in the brains of people with that diagnosis, considered as a group, compared to healthy controls[1]. These early investigations were followed by functional neuroimaging studies using PET and then fMRI, revealing that brains of people with schizophrenia, again considered as a group, also functioned differently[2-5]. Over time, the field has shifted its focus from regional brain activation to more global activation and connectivity. Despite a wealth of evidence for differences in brain activation and connectivity between samples of people with schizophrenia and samples of healthy controls, findings are variable[6]. fMRI-based diagnostic markers remain elusive, but recent work using machine learning approaches for diagnostic prediction, or aimed at the identification of dimensional, transdiagnostic brain-based biomarkers, holds promise[7,8].

Regarding the various phases of schizophrenia – clinical high

risk (CHR), first episode and chronic – there has been an increasing focus on the first episode and CHR phases. The field began studying chronic patients in the late 1980s and 1990s, and then added the study of first-episode patients some years afterward, followed by the study of CHR individuals several years after that [9,10]. Similar brain networks seem to be implicated across these populations; however, there is often greater confidence with fewer confounds in earlier illness phase subjects, while sample sizes and statistical power are typically larger in later phase patient studies. In recent years, collaborative multi-center research has been critical to advance our understanding of these different illness phases [11]. Larger sample sizes, achieved via "pooling" of data – e.g., via the Enhancing Neuro Imaging Genetics through Meta Analysis (ENIGMA) consortium[12,13] – have helped increase statistical power, and clarified the robustness of findings previously achieved using smaller samples.

Given their strong associations with functional outcomes, the neural correlates of negative symptoms and cognitive deficits have been significant areas of investigation in schizophrenia[14,15]. Potential neural markers of negative symptoms have been identified in fMRI studies of early and chronic schizophrenia, but results suggest that they may vary by symptom construct, and that inconsistencies in the conceptual framework underlying the assessment of negative symptoms may hamper progress[15,16]. Regarding cognitive impairments, task-based fMRI has been instrumental in allowing for real-time assessments of brain function while patients complete cognitive tasks in the scanner. Early work characterizing small patient groups produced robust patterns of either heightened or reduced neural activation; however, recent work shows that there may be heterogeneity among patients in terms of which circuits or networks are engaged during tasks[17,18], just as there is such variability among individuals without psychiatric illness[19,20]. Different people may use different neural strategies to complete the same cognitive tasks[21-23]. Further, neural activation patterns during cognitive processing may relate to cognitive performance rather than diagnosis[24].

The heterogeneity of schizophrenia is a critical clinical consideration, which is highlighted throughout this review, acknowledging that no two patients are exactly alike. For much of the history of neuroimaging investigation, schizophrenia has been treated as a single construct using categorical, group-based approaches, despite significant variability among positive and negative symptom expression, neurocognitive and social cognitive performance, treatment response, functioning, and many other facets of the illness[25,26]. There is a recognized need for dimensional approaches across cases and controls, and for the transdiagnostic identification of brain-behavior relationships[27,28]. Of late, the application of multivariate and multimodal data-driven integration approaches and machine learning models in large, consortia-based samples, to identify brain-based biomarkers of diagnosis, symptom constructs, functional outcomes, treatment response and beyond, has shown how clinical heterogeneity can be linked to biological heterogeneity, and provided some hope for potential clinical utility of fMRI[8].

Potentially greater success in relating neural activation to behavioral constructs may be forthcoming through the identification of subtypes or biotypes of illness that may have different outcome trajectories and prognoses[29]. If these are established at the first episode, they may guide decisions around treatment, particularly those interventions which are expensive and resource intensive[30]. fMRI markers may be particularly informative regarding treatment resistance and response, understanding therapeutic mechanisms, and guiding precision treatment.

Perhaps the greatest chance of successful clinical application of fMRI is in guiding pharmacological and neurostimulation treatment. With respect to treatment response, replicated resting state findings identifying the neural circuitry correlates of non-response to conventional antipsychotics could accelerate the use of clozapine[31], a life-saving medication for some, rather than subjecting patients to multiple unnecessary antipsychotic trials. In addition, an understanding of therapeutic mechanisms using pre/post designs in clinical trials can better inform clinicians of potential benefits and harms of particular treatments, and provide the opportunity for improvement in therapeutic development. Finally, an understanding of individual differences can be useful for therapeutic targeting, e.g., using neurostimulation approaches in a personalized manner based on an individual's functional connectivity profile[32,33].

Methodological considerations and advances are also discussed in this paper, covering developments in experimental design, data acquisition, and pre-processing and analytical choices. Notably, significant developments in scanner hardware have allowed for higher resolution acquisitions in shorter periods of time, improved motion correction, and harmonization across sites to support multicenter consortia-based research, an essential advance that has led to more replicable findings for the field[34,35]. In conjunction, precision medicine-based approaches that are now being applied to fMRI, such as deep phenotyping via longer resting state fMRI scans, may more definitively characterize individual variation in brain activity and reliable functional connectivity features, to support individualized biomarker identification and targeting of neurostimulation treatments[36,37].

Availability and advances in reproducible neuroimaging software pipelines, facilitated by code sharing and open science initiatives, have also allowed for more standardized fMRI analyses across labs[38,39]. Data pre-processing and analytical decisions substantially affect neuroimaging results and conclusions[40], emphasizing the importance of such developments for reproducibility of findings. Advances in network theory and the use of multivariate analyses have also allowed for interpretation of the brain's function as a set of networks, and provided insight into collinearity across brain regions and behavioral tasks, mitigating the multiple comparison problem[41-43]. Additionally, tools for moving analyses from volume- to surface-based approaches have better aligned with our knowledge of brain anatomy and allowed for the assessment of individualized brain topography and connectivity profiles[44,45].

While fMRI is providing valuable insights into the pathophysiology of schizophrenia, the limitations of the field are many. Technical limitations and physiological constraints of fMRI, sources of noise and artefacts, the multiplicity of analytical choices, small

sample sizes, the heterogeneity of the illness, and sampling bias related to illness severity or comorbidities have all contributed to reproducibility and generalizability issues[46]. The relationship between cost of fMRI and clinical utility, and the accessibility of the technology for those who live in more remote areas, are important factors as well. The field is also facing challenges regarding the conceptual framework underlying much of the fMRI research to date, for example with a shift from categorical to dimensional and individualized approaches[47,48].

Despite these limitations, the field is far ahead of where it was even a decade ago. Recent publications have brought fMRI reproducibility and generalizability issues to the forefront once more[49]. However, major advances in methodology and standardization, including via the Human Connectome Project, multi-center collaborations which dramatically increase sample sizes to better deal with type 1 and 2 error, reproducible methodologies, and progress in data-driven and precision-based approaches, have given rise to a new age of fMRI research in schizophrenia[13,34,38,50]. The increasing use of fMRI in clinical trials has also been an important development, with many potential future directions in terms of guiding treatment approaches. Relatively new understanding of the value of within-person sampling to generate more robust findings at the individual level may also change our thinking about how we use this technology[51].

This paper comprehensively reviews findings in each of these areas relevant to fMRI in schizophrenia, critically considering both important advances and limitations. Overall, it serves to summarize where the field of fMRI in schizophrenia has been, where it is at present, and its future potential.

DIAGNOSTIC MARKERS

Case vs. control regional and whole brain activation

The application of fMRI for examining brain-based abnormalities in schizophrenia was preceded by approximately two decades of work with functional neuroimaging methods such as xenon inhalation and PET. These latter studies laid the foundation for methods and scientific themes that were carried forward to fMRI investigations. Similarly, ideas from cognitive neuroscience, which intertwined with xenon inhalation/PET and EEG, heralded the advent of fMRI. Contextualizing the emergence of fMRI studies of schizophrenia in the mid-1990s requires discussion of findings from and methodologic challenges inherent to those other neuroimaging modalities.

In one of the first functional imaging studies of schizophrenia, Ingvar and Franzén used ^{133}xenon inhalation to document decreased blood flow to frontal brain regions[52]. In the late 1970s and early 1980s, this idea was carried forward with cerebral blood flow and glucose metabolism studies at rest, but especially using cognitive paradigms such as the Wisconsin Card Sorting Test to examine changes in cerebral blood flow during a cognitive challenge[2,3,53]. These early studies led to the conceptualization of schizophrenia as an illness characterized by regionally specific frontal hypoactivation, primarily in the dorsolateral prefrontal cortex (DLPFC) during task engagement, but also in the anterior cingulate cortex during attentional control[54].

While these studies aimed to establish pathophysiologic markers of schizophrenia, others subtyped the illness based on findings including activation of Broca's area and subcortical structures during hallucinations, and greater involvement of temporal lobe activation in the context of the presence of disorganization and formal thought disorder[55-58]. Though not designed for establishing diagnostic markers, these early studies provided a scientific framework for demarcating schizophrenia with neuroimaging measures.

The advancement of image processing methods, and analytic approaches such as statistical parametric mapping, allowed standardized hypothesis testing of regionally specific neural dysfunction[59]. These advances further helped fMRI to carry forward the work of xenon inhalation/PET studies, but without the radiation exposure. Early fMRI studies characterized diagnostic differences in patients with schizophrenia relative to healthy controls across a variety of cognitive states. This included further support for deficits in DLPFC functioning during working memory, with specificity for schizophrenia, building upon earlier observations of "hypofrontal" blood flow[4,5]. Related fMRI studies of executive functioning reported decreased anterior cingulate cortex activation during attentional monitoring[60]. Additional findings across other cognitive domains and clinical contexts included decreased superior temporal gyrus activation during auditory processing[61], increased temporal lobe activation during hallucinations[62], abnormal limbic activation during facial emotion processing[63], and abnormal sensorimotor activation during pursuit eye movements[64].

Findings from case-control fMRI studies of schizophrenia advanced our understanding of network-related abnormalities that characterize the syndrome. Beyond regionally specific dysfunction of structures, such as the DLPFC during executive processing, meta-analyses illustrated large-scale dysfunctional activation across a network of regions including subcortical structures, cognitive control regions, and the frontoparietal network[65,66]. Similarly, fMRI and PET studies of episodic memory demonstrated abnormal DLPFC-hippocampal activation during recall, implicating impaired frontal-hippocampal coactivation that extends beyond a regionally specific deficit[67,68].

Meanwhile, concurrent evidence began to isolate synchronous functional networks that characterize the intrinsic functional architecture of the brain, independent of task-based activation, starting with the identification of the default mode network (DMN)[69-71]. Functional connectivity studies of schizophrenia demonstrated abnormal coupling between the DLPFC and the hippocampus in relation to psychosis and working memory[72-74], and abnormal intrinsic thalamocortical connectivity at rest[75,76]. Novel data-driven methods for fMRI analysis, reviewed in more detail below, also allowed for the identification of large-scale network-specific abnormalities in schizophrenia, including the DMN[77]. These findings supported the decades-old "dysconnectivity" hypothesis of schizophrenia[78]. While not directly quantifying diagnostic specificity,

this first wave of neuroimaging via PET and fMRI established key pathophysiologic markers of schizophrenia that have been further leveraged by more advanced analytic methods.

Case vs. control modular and global connectivity

The demonstration of distributed co-activation across the brain, and the identification of a set of replicable resting state brain networks, drove a shift from studies examining local activation of particular brain regions in schizophrenia vs. healthy controls to functional connectivity studies exploring how different brain areas interact and form networks. With this shift came the rise in popularity of resting state fMRI, which is ideally suited for examining intrinsic connectivity.

Early studies of functional connectivity utilized undirected seed-based approaches, correlating the activity over time between selected regions of interest. Many focused on the DMN, as regions comprising this network were found to be implicated in self-referential thinking and mentalizing. Both hypoconnectivity[79,80] and hyperconnectivity[81,82] within the DMN in people with schizophrenia vs. healthy controls were reported[83]. These studies were followed by seed-based whole-brain voxel-wise approaches to examine connectivity more globally.

Seed-based analyses of resting state connectivity demonstrated widespread connectivity abnormalities in schizophrenia compared to healthy controls, but results were mixed regarding locality of seed regions and directionality (i.e., hypo- or hyper-connectivity)[6]. Earlier evidence suggested that schizophrenia is related to hypoconnectivity, particularly of the frontal lobe, in comparison to healthy controls[84]. Aligning with this, a meta-analysis of whole-brain seed-based resting state connectivity demonstrated hypoconnectivity within and between multiple networks, including the DMN, ventral attention/salience network, and thalamus networks in schizophrenia compared to healthy controls[85]. These findings support a large-scale disconnected brain networks model of schizophrenia.

Effective connectivity differs from typical functional connectivity, as it is based on a mechanistic model of causal influence between regions of the brain[86]. Dynamic causal modeling[87] is a technique which has been used to demonstrate differences in effective connectivity of the DMN in first-episode psychosis[88], of the frontoparietal network during working memory performance[89], as well as of prefrontal regions in relation to cognition and clinical symptoms[90] and of the hippocampus in relation to clinical symptoms[91] in schizophrenia vs. healthy controls.

Recent work using spectral dynamic causal modeling of resting state fMRI fronto-striato-thalamic circuits suggests that dysconnectivity of the subcortex is present in first-episode psychosis, and dysconnectivity between the cortex and subcortex is seen in later stages of schizophrenia[92]. Local connectivity between spatially adjacent regions has also been examined in schizophrenia using regional homogeneity, with meta-analyses showing abnormal localized connectivity[93,94], including in the medial prefrontal cortex within the DMN[95].

More complex, multivariate approaches, such as spatial independent component analysis (ICA), allow for data-driven exploration of regions with temporal synchronicity across the whole brain to parcellate systems or networks, without pre-selection of regions of interest[96,97]. ICA has been used to detect altered functional connectivity in people with schizophrenia compared to healthy controls, including in the DMN[77,98], frontoparietal/cognitive control network[99,100], and salience network[101]. A meta-analysis of (whole-brain or network-specific) seed-based functional connectivity studies based on ICA brain templates in schizophrenia vs. healthy controls revealed hypoconnectivity between regions from multiple networks, including the DMN as well as auditory and somatomotor networks[102].

Graph theoretical approaches provide a way to quantify the organization and function of brain networks modeled as a set of nodes and edges, including global and local properties[103,104]. Evidence from graph theoretical analyses of functional connectivity suggests that the brains of people with schizophrenia show aberrant network properties, including reduced efficiency, disrupted hub connectivity, and altered modularity compared to healthy controls[105], generally exhibiting a disruption in the balance of regional integration and segregation (i.e., reduced small-worldness)[106-108]. A meta-analysis of functional graph-analytical studies in schizophrenia demonstrated decreased small-worldness, as well as reduced local organization/efficiency, compared to healthy controls[109].

More recently, dynamic connectivity approaches have been used to explore time-varying connectivity states or modes in schizophrenia, with the suggestion that the variability of functional connectivity findings in this disorder may be driven in part by the use of static analyses[110]. Dynamic functional connectivity analyses have provided evidence for people with schizophrenia spending more time in weaker between-network connectivity states[110] and less in switching between states[111,112]. They have also further supported DMN dysfunction[113,114].

Converging evidence implicates dysconnectivity of the DMN, frontoparietal and salience networks, including the striatum, as well as of cortical-subcortical interactions (e.g., thalamocortical) as potential diagnostic markers of schizophrenia. Indeed, a transdiagnostic multimodal meta-analysis identified schizophrenia-specific dysconnectivity of the DMN, frontoparietal, salience and limbic networks, with converging functional dysconnectivity and reduced gray matter volume in the insula, striatum and thalamus[115].

Though an abundance of fMRI-based case-control differences have been observed, the search for clinically diagnostic functional imaging markers of schizophrenia continues. Inconsistent findings may be a consequence of the heterogeneity present within schizophrenia and across people with schizophrenia and healthy controls, which may be better characterized using dimensional or more individualized approaches rather than categorical ones[8]. Machine learning approaches hold promise for parsing heterogeneity and identifying predictive neuroimaging features.

fMRI biomarkers of schizophrenia

With all the evidence of functional connectivity differences in schizophrenia, and with the growth of machine learning approaches, the question of whether a brain scan could be used to diagnose schizophrenia reliably has been a concern since the early days of this century. One of the earliest studies[116] used a sample of task-based fMRI data from an auditory oddball task in approximately 20 individuals with schizophrenia, bipolar disorder, or no psychiatric disorder. Using temporal lobe and default mode networks and some basic clustering approaches, the authors reported that they were able to classify the participants with 90% or higher accuracy. Although data-driven techniques are reviewed later in relation to heterogeneity, we focus here on machine learning through the lens of diagnostic classification.

Part of the attraction of machine learning approaches is the possibility of scanning an individual who is either at risk or whose diagnosis is in dispute, and automatically getting a high-confidence, objective judgement as to a patient's diagnosis[8,117]. There have been a multitude of studies over the past few decades attempting to develop such an algorithm. A review of studies using the support vector machine (SVM) algorithm to classify functional or structural scans found that most of them reported an accuracy of 80% or higher in distinguishing schizophrenia cases from controls[118]. While SVM was the dominant algorithm in the past, deep learning techniques have shown equivalent or improved promise in being able to distinguish schizophrenia cases from healthy controls on the basis of a scan from a neuroimaging dataset[119,120].

With such promising data over almost 20 years, why do we not have diagnostic scans for schizophrenia in use already? There are a number of problems. Notably, many of the studies, including some recent ones, have focused on a very small number of subjects, 20 or 30 per diagnostic group. Smaller samples are prone to overfitting in their models, and their results often do not generalize to a larger dataset[121]. Moreover, a model built on a dataset from one particular type of scanner and scanning protocol often does not perform well on data collected in another setting[122]. As larger and more heterogeneous resting state datasets are becoming increasingly available, machine learning algorithms which can generalize across the varieties of scanning settings around the world are being developed[123].

A further limitation is that confirming whether someone has schizophrenia or no mental disorder is rarely of clinical utility. Studies to date have generally worked with clinically diagnosed and medicated individuals with schizophrenia and contrasted them to age- and gender-matched individuals with no history of psychiatric disorders. This facilitates the machine learning training process, as whether the algorithm provides the correct answer is determined by the clinical diagnosis. However, this does not match the clinical situation. Predicting whether someone who is currently not on antipsychotic medication is likely to develop a full psychotic disorder, or which of several possible diagnoses may apply, is where the classification systems could be more useful. This has been addressed by studies showing that schizophrenia and bipolar disorder, and to some extent schizoaffective disorder, are separable[124,125], or that a system trained to use fronto-striatal features in schizophrenia will not falsely identify obsessive-compulsive disorder or any other psychiatric diagnosis[126]. Studies that recruit medication-naïve or first-episode participants are also showing promise[127], and getting sufficient samples of people at risk, to predict who does or does not develop psychosis, is a current international interest[128].

Just as the machine learning algorithms have to be trained to identify schizophrenia while not being confused by the heterogeneity of scanner characteristics, they also need to be trained across a wide set of diagnoses and clinical scenarios, in order to help the clinical process. A biomarker of chronic schizophrenia may not predict conversion to psychosis in CHR cases, or response to a given treatment, or which circuits are the most amenable to neuromodulation. But the capacity of machine learning approaches to address these questions is developing, as predicting prognostic trajectories for high-risk or first-episode subjects is an active area of exploration[129–131].

fMRI biomarkers in the clinical high risk phase

Early studies exploring resting state functional connectivity in CHR populations identified DMN hyperconnectivity[132] or a failure to suppress the DMN under high memory load[133] relative to healthy comparison participants. Later, a greater DMN connectivity was linked to poor insight[134].

Dysconnectivity within the cortico-striatal-thalamo-cortical networks has been reported by multiple groups[132,135-143] – specifically, hypoconnectivity in corticostriatal, thalamocortical and thalamo-cerebellar areas, and hyperconnectivity within sensorimotor cortical areas. Corticostriatal[137] and cerebellar-talamo-cortical[143] dysconnectivity has been linked to positive symptoms in CHR.

CHR participants in the North American Prodrome Longitudinal Study second cohort (NAPLS-2)[144] who later converted to psychosis had more prominent hypoconnectivity between the thalamus and prefrontal and cerebellar areas, and more pronounced thalamic hyperconnectivity with sensorimotor areas[135]. Disrupted functional connectivity of the insula with other hubs in the salience network[145] has also been associated with psychotic conversion. Further, adding measures of within- and between-network connectivity to validated clinical predictors from the NAPLS psychosis-risk calculator[146] was found to improve model performance[147].

More recently, a study from the Shanghai At Risk for Psychosis (SHARP) program[128], including a large unmedicated CHR sample, found that abnormal modular functional connectome organization predicted psychotic conversion, replicating prior work in a smaller medicated sample[148]. Using longitudinal data from NAPLS-2, it was found that CHR participants who later converted to psychosis showed a reduction in global efficiency and an increase in network diversity relative to CHR participants who did not convert, and this finding was primarily driven by the DMN[149].

Resting state fMRI data from NAPLS-2 were also used in a high-

dimensional brain-wide functional mediation framework to identify brain regions mediating the relationship between baseline behavioral symptoms and conversion to psychosis among CHR subjects[150]. Positive mediators were primarily distributed in the sensorimotor system, insular and opercular areas, and the striatum. Negative mediators were mainly located in the DMN and visual system[150].

Clearly, emerging functional connectivity research in the period before the onset of psychosis is revealing evidence of dysconnectivity in brain networks known to be relevant in information processing, neurocognition and psychosis. Replication of these findings in additional samples – including NAPLS-3 and the Psychosis-Risk Outcomes Network (ProNET) – will be important, along with the implementation of creative analytic techniques, to better understand the evolution, early identification and potentially pre-emptive treatments in the early stages of emerging psychotic illness.

fMRI markers of negative symptoms

Negative symptoms are a major determinant of poor functional outcome in people with schizophrenia[151-156]. Both first- and second-generation antipsychotics have limited benefit for this illness dimension[157-159]. The elucidation of the neural networks that serve as the substrate for these symptoms may be important for the development of new treatments.

A critical issue in the investigation of the neural basis of negative symptoms is the conceptual framework underlying their assessment. Of particular importance is the separation of negative symptoms into primary and enduring (deficit symptoms) vs. secondary ones. Deficit symptoms are regarded as intrinsic to the illness, whereas secondary negative symptoms may be due to exacerbations of psychosis, extrapyramidal side effects of antipsychotics, depression and/or understimulating environments[160-162]. There are limited functional imaging studies focused on the deficit syndrome. However, one study reported aberrant cerebellar neural activity and cerebro-cerebellar functional connectivity, involving executive dysfunction, in patients with this syndrome[163].

A major obstacle to the focus on the deficit syndrome in neuroimaging studies is the need to use trained investigators to administer an extensive diagnostic interview[164]. This has led to the development of the concept of persistent negative symptoms[157]. This concept also tries to minimize the heterogeneity associated with broadly defined negative symptoms, through the restriction to those that persist for six months or more and are present during periods of clinical stability and in the absence of prominent positive, depressive or extrapyramidal symptoms[157]. Here too there is a paucity of functional neuroimaging studies. The extant literature largely focuses on negative symptoms without invoking the deficit syndrome or persistent negative symptoms conceptual frameworks.

According to a common conceptualization, there are three subgroups of people with schizophrenia along a continuum from positive to negative symptoms: predominantly positive, predominantly negative, and mixed[161]. Indeed, functional connectivity between the salience and default mode networks has been related to both positive and negative symptoms[165]. Alternatively, negative symptoms may be conceptualized as a disease dimension, suggesting that there are distinct brain networks involved in negative vs. positive symptoms. In this latter context, and for patients with chronic schizophrenia, altered DLPFC-cerebellum[166], striatal-orbital medial frontal cortex[167], and medial fronto-temporal[168] functional connectivity have all been associated with negative symptoms. In patients earlier in their disease course, altered functional connectivity between crus II of the cerebellum and the anterior supramarginal gyrus has been associated with negative symptoms[169]. Early in the disease course, but not at a more chronic stage, greater negative symptom burden has also been associated with decreased activation in the cerebellum during a verbal Stroop task[170]. Irrespective of the stage of illness course, an inverse correlation has been observed between negative symptom burden and activation of motor cortex, including the supplementary motor area and precentral gyrus[170].

The various negative symptoms may also differ in their neural correlates. Indeed, in a fMRI study using a two-tone auditory oddball task, the severity of alogia, avolition/apathy and anhedonia/asociality was inversely correlated with blood oxygenation level-dependent (BOLD) signal during the target tone in distinct sets of brain regions[16]. There was an inverse correlation between anhedonia/asociality and the activity of the posterior cingulate and precuneus, which are typically considered to be part of the DMN. The severity of alogia was instead associated with decreased activity in the bilateral thalamus, right caudate and left pallidum, suggesting that this symptom may reflect a deficit in the ability to engage in voluntary motor behavior[16].

fMRI markers of cognitive deficits

Cognitive deficits are a core feature of schizophrenia and represent one of the main obstacles to clinical and functional recovery in affected individuals. Deficits are present both in general intelligence and in specific neurocognitive domains, as well as in social cognition[14]. Both social and non-social cognitive impairments appear to be distinct constructs from those of symptom profiles[171,172], and have been proposed as potential treatment targets[173,174].

Overall cognitive performance in schizophrenia is reported to be on average two standard deviations below that seen in unaffected individuals[175]. Impairments are also typically seen in specific domains, including memory, verbal and visual learning, executive functions, attention, and processing speed[176,177]. Particularly impairment in working memory, which involves the short-term storage and manipulation of information, has been proposed as a core deficit in schizophrenia[178]. Processing speed, which refers to the amount of time it takes for an individual to process and accurately respond to information in his/her environment, has also been reported as one of the most affected neuropsychological functions in schizophrenia[179]. Due to the ease of

use of processing speed assessments, they have been proposed as potentially useful tools for screening in clinical settings, or for the evaluation of specific interventions[179]. There is significant evidence that cognitive deficits are already present at the time of the first episode of psychosis[180], as well as in CHR individuals, albeit with high variability within different cognitive domains[181-183]. Whether further cognitive decline occurs after the first psychotic episode is less clear, and studies have reported both decline and amelioration[184,185].

Social cognition represents the cognitive capability to process, store and apply information about other people and social situations. Individuals with schizophrenia have difficulties in identifying emotions, feeling connected and reacting emotionally to others, and inferring people's thoughts[186-189]. As such, impairments in social cognition have been demonstrated to be a key correlate and predictor of functional outcome[173,174]. Social cognition is often divided into lower-level (e.g., emotion recognition and simple mental representation) and higher-level mentalizing (e.g., belief and intention inference; theory of mind) processes[173,190-192].

Evidence suggests that social cognition and neurocognition are distinct but related constructs[173,193], with meta-analytic results showing a stronger relationship between social cognition and functional outcomes[174,194]. Meta-analyses in CHR individuals have also demonstrated deficits across social cognitive domains, including emotion processing and theory of mind[195,196].

Neurocognitive impairments were established early on as fundamental features of schizophrenia, resulting in a wealth of neuroimaging studies examining cognition[1]. Initial fMRI studies focused on regional activity during specific cognitive tasks, demonstrating aberrant activation in the DLPFC during working memory tasks in people with schizophrenia vs. healthy controls[197,198]. Variability in such findings was also soon evident, including both decreases and increases in DLPFC activation during working memory performance, prompting meta-analyses to integrate results and identify potential moderating factors[199].

Meta-analyses of fMRI studies have focused on particular domains of neurocognition, including working memory, episodic memory, and executive functioning. A meta-analysis on DLPFC activation during working memory tasks[199], and a selective review of fMRI studies of working memory deficits in schizophrenia[200], support the role of DLPFC dysfunction in working memory impairments in schizophrenia. An early meta-analysis of fMRI studies of working memory in schizophrenia also identified abnormal activation of the DLPFC, anterior cingulate cortex, and insula compared to healthy controls[66]. More recently, a meta-analysis corroborated dysfunction of these areas, as well as of the posterior parietal cortex and supplementary motor area, noting that these identified regions are nodes of the cognitive control network and salience network[201].

Meta-analyses have also focused on fMRI studies of episodic memory in schizophrenia, identifying aberrant activation in regions including the left inferior prefrontal cortex, hippocampus, and left cerebellum versus healthy controls[202]. A meta-analysis of 41 functional neuroimaging studies of executive functioning (sometimes referred to as cognitive control) in schizophrenia revealed decreased activation in the DLPFC, anterior cingulate, and thalamus[65].

These findings have been largely confirmed in a review of neural correlates across neurocognitive domains in different phases of schizophrenia, noting that many of the neural abnormalities evident in chronic schizophrenia appear to be present to some degree prior to illness onset[203]. In relation to this, a meta-analysis of fMRI studies using neurocognitive tasks in CHR individuals demonstrated reduced activation of the inferior parietal lobule and medial frontal gyrus compared to healthy controls, and only of the inferior parietal lobule when looking at a subset of four studies using working memory tasks[204]. The regions of the brain implicated in these different cognitive functions are widely distributed and often overlapping[203]. Indeed, these deficits may not be discrete[205], and the DLPFC has been suggested as a potential common substrate for many cognitive impairments[206].

As mentioned, neuroimaging studies in schizophrenia suggest that cognitive performance depends on distributed brain systems or networks, rather than isolated regions[207]. A systematic review examining associations between resting state functional connectivity and neurocognition within and across domains found that aberrant connectivity between regions of the cortex and subcortex (cortico-cerebellar-striatal-thalamic loop) was associated with deficits in executive functioning, working memory, and processing speed, and that abnormal connectivity between regions of the DMN and the frontoparietal (e.g., DLPFC) and cingulo-opercular (e.g., anterior cingulate cortex) networks was related to multiple cognitive domains[208]. Notably, unique associations between particular cognitive domains and specific abnormalities in functional connectivity were not detected, supporting the idea of a disruption in shared mechanisms across neurocognitive domains resulting in generalized cognitive impairments observed in people with schizophrenia[208].

A recent meta-analysis also reviewed studies looking at the association between structural brain metrics and cognitive domains in schizophrenia, and mapped these structural findings onto resting state functional brain networks[209]. The frontoparietal (cognitive control) network was associated with the most cognitive domains, and the somatomotor, dorsal attention, and ventral attention networks were also implicated in multiple cognitive domains[209]. In general, more complex cognitive processes, such as reasoning and executive function, as well as social cognition, were associated with more networks[209].

Though relatively fewer studies have examined the neural correlates of social cognition in schizophrenia, there is considerable evidence for regional activation and functional connectivity abnormalities in relation to social cognitive deficits. Lower- and higher-level social cognition are believed to be subserved by partially dissociable but interacting networks in the brain[210-213]. Lower-level social cognition is thought to depend on a frontoparietal and insular "simulation network", including the inferior parietal lobule, inferior frontal gyrus[214,215], anterior cingulate cortex, and anterior insula[216,217]. Higher-level social cognition is thought to rely on a cortical midline and lateral temporal "mentalizing network", including the medial prefrontal cortex, temporoparietal

junction, and precuneus[218,219]. These lower- and higher-level social cognitive networks show overlap with the resting state frontoparietal and salience/ventral attention networks, and the DMN, respectively[220].

Meta-analyses of fMRI studies using emotion perception and theory of mind tasks in schizophrenia compared to healthy control groups have demonstrated altered brain activation in regions of the simulation and mentalizing networks[221-225]. Decreased activation in regions of the mentalizing network have also been identified in a meta-analysis of fMRI studies of theory of mind in individuals with CHR[226], though no differences in brain activation were found between at-risk and control groups in a recent meta-analysis of fMRI studies examining negative emotion perception[227].

Past work has identified associations between resting state connectivity among social cognitive regions and social cognitive performance outside the scanner in schizophrenia[168,228,229] and first-episode psychosis[230], as well as symptom severity in schizophrenia[231]. However, findings have been inconsistent, and such investigations lack insight into online social processing. Task-based fMRI studies have demonstrated greater functional connectivity in regions of the simulation and mentalizing networks during mentalizing in schizophrenia compared to healthy controls [232,233], though hypoconnectivity has also been reported between social cognitive regions during social processing tasks[234,235]. Such inconsistent findings are likely driven by case-control designs, often small samples, and varied analytical approaches. It should also be noted that conceptualizations of social cognition vary, and differences in the constructs being measured and reported domain scores may also contribute to variable results [236].

Studies in larger samples have used data-driven, computational approaches to elucidate the neural circuitry of social cognitive impairments. Associations between functional abnormalities in both the simulation and mentalizing networks and poorer social cognitive performance have been identified across individuals with schizophrenia and healthy controls during rest[237], a facial imitation task[21], and a more complex and naturalistic empathic accuracy task[24]. In particular, worse social cognitive performance has been linked to more distributed activation across the mentalizing and simulation networks[21], and greater intra- and inter-network connectivity across these social cognitive networks[24,237], indicative of decreased network efficiency and segregation. This work also suggests that neural activation patterns during social processing may relate to cognitive performance rather than diagnosis across schizophrenia and healthy controls. Evidence suggests that this pattern may exist transdiagnostically, across schizophrenia and autism for example[238].

Notably, both non-social[239] and social cognitive[186] domains have been proposed as candidate endophenotypes for schizophrenia. Given their associations with functional outcomes[174], they have also been identified as promising treatment targets. Accordingly, targeting brain circuitry important for these processes offers a potential novel therapeutic advance with implications for cognitive performance and, ultimately, functional outcomes[240].

fMRI IN RELATION TO TREATMENT: RESPONSE/RESISTANCE, MECHANISMS AND THERAPEUTIC TARGETING

Antipsychotic medication

Given that schizophrenia is likely a heterogeneous disorder involving multiple underlying pathological mechanisms[241], attempts to identify rational therapeutic targets have been challenging[242]. Functional brain imaging can be a powerful tool to better understand not only the underlying neural circuit dysfunction in schizophrenia, but how different interventions can modify these dysfunctional brain circuits. The incorporation of pre- and post-treatment fMRI in clinical trials offers an opportunity to investigate mechanisms of treatment response. Biologically based evidence can further support the efficacy of interventions in modifying brain function, and may provide evidence of "target engagement" even in cases where the clinical or functional outcomes are challenging to measure explicitly.

From 18 to 24% of patients with schizophrenia demonstrate complete treatment resistance from the first episode[243-245], and a similar percentage show only partial or inadequate response[246]. Ultimately, nearly 40% of patients are classified as non-responders to first-line antipsychotic medications, resulting in the overwhelming majority of health resource utilization associated with psychosis[247]. All effective and currently approved antipsychotic medications target dopamine D2 receptors, which are concentrated in the striatum[248,249]. A wide array of evidence is consistent with the hypothesis that there are two functional subtypes of schizophrenia with respect to treatment response: the hyperdopaminergic and normodopaminergic[250-252].

Cross-sectional[250] and prospective[253] PET studies suggest that elevated dopamine synthesis capacity in the striatum is characteristic of antipsychotic treatment responders, while treatment-resistant cases of schizophrenia have normal striatal dopamine functioning at baseline. Therefore, it is noteworthy that PET striatal dopamine synthesis capacity has recently been associated with differential patterns of cortico-striatal functional connectivity as measured by resting state fMRI[254,255]. However, striatal PET imaging may not be an easily translatable biomarker, since it is expensive, invasive, and involves exposure to ionizing radiation. Resting state functional connectivity is a promising neuroimaging technique to evaluate antipsychotic response. As resting state fMRI does not require an active task, it is especially practical in populations that may find traditional fMRI tasks difficult to perform[256]. Several investigators have used resting state functional connectivity of the striatum, a region rich in D2 receptors and the major site of antipsychotic action, to evaluate its potential to predict treatment response.

Evidence from several studies suggests that striatal circuits could be critical in mediating clinical response in people with psychosis. Resting state fMRI baseline striatal connectivity has been found to predict clinical response to antipsychotic treatment in a cohort of first-episode patients who had undergone no or minimal prior treatment[257]. This "striatal connectivity index" demonstrated 80%

sensitivity and 75% specificity for the prediction of acute antipsychotic response in an independent cohort of multi-episode patients. Confidence in these results was enhanced by independent data from a small longitudinally studied cohort of early-phase schizophrenia patients[258], in which antipsychotic treatment resulted in similar normalization of frontostriatal connectivity. Similarly, the role of baseline striatal connectivity in predicting treatment response in schizophrenia was supported by another study[259] in which greater hippocampal baseline connectivity followed by a connectivity increase over time to the caudate was associated with better response. Two recent prospective studies have produced comparable results[126,260].

Cross-validation of resting state functional connectivity patterns predictive of treatment response in patients with different clinical characteristics and environments is important to test the stability of the predictor. Accordingly, striatal resting state functional connectivity was explored in two cohorts of patients scanned on different MRI platforms: a cohort of medication-naïve first-episode patients and a cohort of unmedicated patients with schizophrenia[261]. In both cohorts, striatal resting state functional connectivity was predictive of subsequent treatment response to antipsychotic medication. Collectively, these independent and convergent replications suggest that striatal connectivity may be a critical mediator, and perhaps predictor, of antipsychotic drug effects on the brain.

Other functional networks have been studied in relation to their potential to predict antipsychotic treatment response. Functional connectivity of the DMN[262] has been investigated in the above mentioned two cohorts[261]. In both of them, resting state functional connectivity of the hippocampus, one of the principal regions of the DMN, was predictive of subsequent treatment response.

A recent systematic review and meta-analysis quantifying the utility of pre-treatment resting state fMRI in predicting antipsychotic response reviewed 22 datasets with 1,280 individuals, and concluded that striatal and DMN resting state functional connectivity were consistent predictors of antipsychotic treatment response[263]. The meta-analysis based on 12 datasets revealed an overall 81% sensitivity and 76% specificity to predict categorically defined treatment response.

Few studies have evaluated patterns of resting state functional connectivity in patients meeting criteria for treatment resistance, and differences in methodology have precluded meaningful conclusions[31]. More interesting are studies aimed to characterize patterns of resting state functional connectivity linked to the superior therapeutic action of clozapine in those not responding to trials of first-line antipsychotic medications. Because clozapine, unlike first-line antipsychotics, binds to dopamine D2 receptors with low affinity and has a uniquely rich pharmacology (with significant activity at other dopaminergic, muscarinic, adrenergic, histamine and serotonergic receptor subtypes[264-266]), distinctive resting state functional connectivity patterns associated with its efficacy should be expected. In treatment-refractory participants enrolled in a trial of clozapine, response to this drug was associated with an increase in corticostriatal resting state functional connectivity between the dorsal caudate and the frontoparietal network, which was also predictive of response at pre-treatment[267]. Although these findings need to be replicated with larger cohorts of treatment-refractory patients, they may indicate that changes in corticostriatal connectivity may represent a downstream mechanism of action common to all antipsychotic medications.

Another prospective neuroimaging study evaluated changes in clinical symptoms and patterns of resting state functional connectivity in schizophrenia patients who started treatment with clozapine[268]. A first step data-reduction of item-level clinical scales revealed four distinct patterns of treatment response to clozapine. Interestingly, those clinical patterns mapped onto distinct neuroimaging resting state functional connectivity features, that are thus relevant to clozapine-induced symptom change and can provide neuro-behavioral targets linked to clozapine efficacy.

Psychotherapy and psychosocial interventions

Though evidence is limited, fMRI studies have also shown that psychotherapy has the potential to induce functional brain changes in individuals with schizophrenia. For instance, cognitive behavioral therapy has been associated with increased functional connectivity between the DLPFC, dorsomedial prefrontal cortex and caudate[269], as well as between the DLPFC and amygdala/visual cortex[270], with prefrontal connectivity changes predicting long-term recovery[271].

Cognitive remediation and related psychosocial interventions have also been associated with increases in functional connectivity in frontal cortex[272] and increased frontal activation during task-based fMRI[273-275]. Activation in areas other than the frontal cortex have also been observed, including the anterior cingulate and parietal cortex[275,276]. Recent reviews investigating cognitive remediation in individuals with schizophrenia revealed positive associations between cognitive improvements and functional and structural changes in frontal brain regions[277,278]. Interestingly, a study examining changes in functional connectivity following cognitive remediation found that patients who received treatment showed more normalized brain network patterns, comparable to those observed in healthy controls[279]. Social cognitive training has also been shown to influence neural function in regions that support social cognition, such as the postcentral gyrus and amygdala, while improving emotion-processing abilities[280,281].

Studies in this field have usually included small patient samples, and additional research is required to comprehensively grasp the neural mechanisms involved in the effects of psychotherapy and psychosocial interventions, further explore ways to optimize them for improved functional outcomes, and demonstrate if such changes are transitory or persist over time.

Neurostimulation

A variety of neurostimulation methods have been used to treat schizophrenia, including electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), transcranial direct

current stimulation (tDCS), and deep brain stimulation (DBS).

ECT is being used in treatment-resistant schizophrenia or as augmentation in clozapine-resistant patients[283,284]. Baseline fMRI imaging has revealed patterns of dyssynchronous dynamic connectivity involving prefrontal-temporal regions as a prognostic marker of response to ECT[285]. Following ECT, a decreased coupling between the right amygdala and the left hippocampus, and an increased functional connectivity between the hippocampus and a range of cortical regions, have been reported[286,287].

rTMS and TDCS are becoming significant tools for addressing symptoms of schizophrenia that are not mitigated by conventional treatments[288], such as cognitive impairments[289,290], negative symptoms[291,292], and refractory hallucinations[293-295]. Early rTMS targets were identified via local changes in brain activity[296,297]. However, fMRI research has demonstrated that rTMS exerts deeper and broader effects by propagating along neural networks connected to the target site[298-303].

fMRI-guided rTMS targeting has been used for refractory auditory hallucinations. Several studies have targeted the temporoparietal junction, generally using an "inhibitory" protocol[293-295], as it represents a core region of overactivity within neural circuits associated with hallucinations[304]. Studies examining post-treatment changes found increased network connectivity in regions of the auditory/sensorimotor, central executive, and default mode networks[305], and normalized connectivity between the default mode and language networks, and within the auditory and central executive networks[306]. Another protocol using "excitatory" rTMS, with a functionally identified target in the language region of the superior temporal sulcus, observed a decrease in hallucinations[307].

Additional studies have shown both a reduction in activation after rTMS delivery to the temporal lobe and a corresponding decrease in hallucinations[308]. Moreover, a unique fMRI-based case study has suggested that there may be efficacy for hallucinations in very late onset schizophrenia via theta-burst stimulation (TBS)[309]. However, a recent meta-analysis did not find strong evidence for a reduction in hallucinations following rTMS or tDCS [293].

Neurostimulation to reduce negative symptoms has targeted the DLPFC[292], based largely on early neuroimaging work implicating the prefrontal cortex in schizophrenia and negative symptoms[310,311] and the antidepressant effects of rTMS to the DLPFC[312]. While fewer studies have used neuroimaging to assess the mechanistic effects of rTMS for negative symptoms, task-induced activity in the DLPFC has been shown to increase[313], and left DLPFC stimulation has been associated with a decrease in negative symptoms and a corresponding change in dynamic connectivity of the cortico-thalamo-cerebellar circuit[314]. Similarly, reduced negative symptoms and large-scale modulation of functional interactions have been noted with intermittent TBS of the left DLPFC[315]. Related studies focused on social cognitive deficits support modulation of neural circuitry during social-emotional evaluation with rTMS to the DLPFC[316].

Two potentially powerful ways by which evolving fMRI approaches can improve rTMS is the identification of novel circuit-based targets and personalizing treatment. As an example of the former, a data-driven analysis identified connectivity between the DLPFC and the cerebellar vermis as the most significant predictor of negative symptom severity in a sample of people with schizophrenia, and validated this in an independent sample by demonstrating a relationship between increased DLPFC-cerebellar connectivity and reduction in negative symptoms after rTMS to the cerebellar vermis[166]. This aligns with evidence suggesting that individual variability in functional connectivity can affect response to brain stimulation. Indeed, reductions in depression following DLPFC stimulation have been associated with anticorrelation (i.e., negative correlation) of the rTMS sites with the subgenual cingulate cortex[317]. The proximity of the rTMS target to an individually calculated optimal target based on anticorrelation with the subgenual cingulate cortex has also been found to predict treatment response in depression[318,319], raising the possibility that individualized rTMS targeting may improve treatment outcomes[33]. The combination of personalized functional connectivity mapping to identify target locations, and electric field modeling to maximally stimulate critical regions, may individually optimize neurostimulation treatment[320] and be applicable to novel treatment targets in schizophrenia, such as social cognition[32].

Findings in schizophrenia with tDCS, a more portable method for neurostimulation, have also been examined in relation to fMRI, but data are preliminary. Functional connectivity of the superior temporal gyrus has been suggested as a potential prognostic marker for response to tDCS[321]. Separate studies focused on cognition have reported positive effects with tDCS in schizophrenia and associated changes in neural circuitry[322]. Negative symptoms have also been targeted by tDCS, showing reductions in symptom ratings and associated prefrontal circuitry changes[323,324].

DBS is an invasive surgical treatment based on implantation of a small electrode capable of modulating localized aberrant neural circuits[325,326]. The largest human trial to date in schizophrenia included only seven participants, four of whom showed significant reductions in symptoms with electrodes placed in the subgenual anterior cingulate cortex or the nucleus accumbens[327], based in part on prior success for these regions in depression[328] and obsessive-compulsive disorder[329]. A single case study of DBS in the substantia nigra showed clinical improvements, including a complete cessation of hallucinations[330].

DBS within schizophrenia has faced several challenges, including difficulty or failure recruiting participants[331], ethical considerations around vulnerability[332], and concerns about increased surgical risks in people with this disorder[333,334]. It is, therefore, critical that future DBS trials are informed by a deeper understanding of the neural circuitry of the specific symptoms or behaviors being targeted, or systems which might have broader impact. Ideally, such targets should be established at the individual level, to optimize treatment outcomes.

Functional imaging can also identify broader mechanisms of psychosis to provide targets for novel interventions. As mentioned, there is substantial evidence supporting a disturbance in thalamo-cortical and thalamo-striatal connectivity in schizophrenia, which has been suggested as a crucial system that contributes to a wide range of underlying cognitive deficits and clinical symp-

toms[335,336]. The thalamus includes multiple nuclei that interact with subcortical and cortical regions[337-339], modulating cortical connectivity and maintaining or coordinating task-relevant cortical representations[340]. Interestingly, lesions to associative thalamic nuclei can result in psychosis symptoms[341]. Targeting specific thalamic nuclei may provide an opportunity for broad clinical impact. Emerging treatment modalities such as focused ultrasound, allowing deep brain neuromodulation of specific brain regions[342], may provide a novel mechanism to modulate thalamic connectivity and function to treat schizophrenia.

fMRI AND DATA-DRIVEN APPROACHES TO DISSECT HETEROGENEITY

High levels of heterogeneity of brain metrics is the norm, even in non-clinical populations[19,37]. A growing body of evidence suggests that schizophrenia encompasses even greater variability in both fMRI task activation[17,18,343] and resting state functional connectivity[344-346] than is present in the general population. Recent work has shown that there is minimal overlap in brain abnormalities among those who share the same diagnosis, indicating that differences at the group level may conceal biological heterogeneity and interindividual variations among people with schizophrenia[26]. Consequently, relying exclusively on case-control research will be inadequate to advance efforts for clinical translation of neuroscience results.

The Research Domain Criteria (RDoC) initiative shifts away from the conventional case-control research model, calling for integration of multi-level data (e.g., deep phenotyping across measures of genes, circuits, physiology, cognition and behavior) to characterize the full range of transdiagnostic brain-behavior dimensions within and across domains[47,347]. European initiatives – e.g., the Psychiatric Ratings using Intermediate Stratified Markers (PRISM) project – have similarly called for a shift to transdiagnostic research[348]. The ultimate aim is to identify subsets of individuals with more homogeneous biological profiles that map onto specific clinical features, which may inform stratification for clinical trials and biologically targeted transdiagnostic treatment approaches. Both dimensional brain-behavior research approaches and biotyping approaches align with this framework.

The neural circuitry of specific symptom, behavioral or cognitive domains can be mapped via brain-behavior associations, often assessed using linear models. Such approaches have been used to map the underlying neurobiology of symptom profiles (e.g., negative symptoms[166,167], hallucinations[304]), identify targets for brain stimulation[166], and predict clinical outcomes and medication response[349,350]. Utilizing linear analysis can delineate variability which exists across a given population, as opposed to relationships which are driven by a particular disorder. For example, case-control research has indicated that disruptions in social cognition in schizophrenia[173,187] are linked to differences in social cognitive neural circuit activation[223]. However, when examining the relationship between social cognition and related circuits across schizophrenia and controls, social cognitive network connectivity was associated with social cognitive deficits but not diagnosis[24].

Biotyping is another approach to tackling the challenge of heterogeneity[28,29,348], wherein data-driven methods, such as clustering, are used to identify subgroups with common neurobiological characteristics. Subgroups with shared brain-behavior relationships may be more homogeneous in therapeutic response and etiology[351,352]. Indeed, transdiagnostic work has identified subgroups with shared patterns of brain activation[21], functional connectivity[230], gray and white matter structure[353,354], and other multivariate biomarkers[355], which may have implications for prognosis and targeted treatment development. However, clustering approaches can, at times, separate participants into discrete groupings even when they exist along an underlying continuum[19,356].

Multimodal fusion techniques such as similarity network fusion[357] – which can integrate different data types and identify individuals with similar profiles across clinical/behavioral, structural and functional neuroimaging, and other metrics (e.g., genetics, peripheral biomarkers) – may prove a powerful tool for dissecting heterogeneity and deriving reliable biotypes. For example, fusion across structural imaging and behavioral measures in people with schizophrenia, autism and bipolar disorder identified novel, reliable and separable biotypes with distinct neural circuit-cognitive profiles, whereby effect sizes for between-group differences were greater with data-driven subgroups than those found using conventional diagnostic groupings[354].

Advanced analytical approaches such as multivariate statistics may allow for the identification of unique and common neural circuitry underlying clinical/behavioral scores[41,43]. Multivariate approaches can also provide insight into which behavioral domains represent shared constructs of underlying risk factors with common neurobiology[358], case-control differences during cognitive processing[233,359,360], or differences across genotypes[361]. In this way, neurobiology can inform the understanding of clinical domains[27]. Likewise, multivariate approaches can identify common and distinct neurobiological markers and behaviors across related sets of psychiatric disorders[362].

As previously described, recent shifts in research frameworks have also led to the use of predictive multivariate machine learning techniques, moving from explanatory to predictive analyses[7,363]. Machine learning techniques are ideally suited for making predictions from neuroimaging data, given that they are designed for multivariate analyses of high-dimensional data[364]. Machine learning models using fMRI data have been utilized to make binary classifications[365,366], and regression-based prediction approaches are becoming increasingly popular to make individual-level predictions of behavior, clinical symptoms, and functioning[367], or examine deviations from a normative distribution[368]. Generalizability of machine learning models established on the basis of a given sample can be evaluated using simulations that resample data, such as bootstrapping and cross-validation, but should ideally involve applying the model in a new external validation sample[30,369].

Machine learning has also been used to provide more individualized parcellation of brain regions on a common template, improving the predictive power of functional connectivity[370]. In-

dividualized deviations from common group parcellations using support vector regression have been related to both positive and negative symptoms, in contrast to atlas-based connectivity[371]. Ideally, future applications of machine learning to predict behavior or cognition at the individual level[372] may serve to inform clinician decisions.

The use of functional connectivity data in association with other modalities (neuroimaging, genetic, electrophysiological) to improve prediction performance also holds great promise. However, its implementation will necessitate building models which use carefully selected predictors, and testing their accuracy, generalizability and clinical utility in real-world clinical settings[373].

Prediction of treatment response at the individual patient level will also be of great value. For example, using machine learning algorithms and the resting state functional connectivity of the superior temporal cortex, medication-naïve first-episode psychosis was identified with an accuracy of 78.6%, and treatment response at the individual level was predicted with an accuracy of 82.5% [374].

METHODOLOGICAL CONSIDERATIONS AND ADVANCES

A common refrain in neuroimaging is the need for larger, representative studies. An underpowered study reduces the true positive rate for significant findings in the usual null-hypothesis framework, making reproducibility of any findings an overarching concern. Consortia of researchers to address the need for larger, more representative datasets are needed in neuroimaging just as they are in clinical trials[11].

The consortia approach can allow to collect large samples, as in the Function Biomedical Informatics Research Network (FBIRN), the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP), the Social Processes Initiative in Neurobiology of the Schizophrenia(s) (SPINS), the NAPLS and the ProNET studies, and the ongoing Accelerating Medicines Partnership (AMP) - Schizophrenia (SCZ) Programme[375-379]. In these projects, the focus is making the study parameters as similar as possible, so that the samples are homogeneous, the clinical assessments are the same across the whole sample, and the imaging techniques are prescribed prior to data collection to reduce site differences. This can increase power by reducing heterogeneity. Other consortia work with already-collected data[13]: the prospective meta-analysis technique used by the ENIGMA Schizophrenia Working Group, for example[12], prescribes the imaging processing techniques to be applied across dozens of datasets, removing the data processing and analysis as a source of heterogeneity. This kind of approach can lead to *post-hoc* datasets of thousands or tens of thousands.

The power of large samples is key, with international representation and increased inclusivity, but it also leads to innovative approaches for identifying and addressing heterogeneity. How much of the variability in published results is due to differences in the statistical approach, or to differences in characteristics of the sample? For example, in the meta-analysis of subcortical volumes in the ENIGMA Schizophrenia Working Group[12], a moderation analysis demonstrated that hippocampal volume deficits were more severe in samples with a higher proportion of unmedicated patients, adding to our understanding of sources of heterogeneity. At the same time, the drive to combine datasets directly, rather than doing a meta-analysis, has led to applications to fMRI measures of harmonization techniques known as ComBat (named for "combating batch effects when combining batches"), borrowed from genetics, with notable successes[381]. Standardized pipelines to reduce sources of noise while being sensitive to individual variation are becoming the norm, improving the chances for reproducible results[39].

As previously noted, recent advancements in MRI research approaches have opened new opportunities to address individual heterogeneity, collectively called precision fMRI. First, advances have been made in imaging sequences on MRI scanners. Hyperband fMRI can improve image quality via higher spatial and temporal resolution[34]. In addition, multi-echo fMRI images might be less susceptible to the effects of human motion[35]. Second, novel "personalized" MRI data processing approaches can better account for individual variability in brain morphology. Using cortical surface-based fMRI pipelines to account for differences in folding patterns across individuals will increase the power to detect clinically relevant effects.

Furthermore, fMRI data can map individual functional topography[44,370,382], which can provide additional advantages for finding associations with symptoms[371] or cognition[383]. Mapping individual functional topography requires more prolonged and more frequent within-individual scans[51], and is therefore mostly conducted in studies where multiple MRI sessions are available, but can build a more reliable, stable and individually specific "functional connectome"[37,50,384].

When planning the next generation of fMRI research experiments, one additional consideration will be what participants will do inside the scanner. Participants could be asked to complete any number of cognitive tasks (task-based fMRI), they could watch movies (sometimes referred to as "naturalistic viewing"[385]), or lie still (i.e., resting state fMRI). Resting state fMRI has the advantages of not needing additional equipment and having simpler task instructions that can still be followed when participants have more severe symptoms or cognitive deficits. However, the "resting state" is also less engaging, and so participants are more likely to move[386] and fall asleep[387] than when a task or movie is present. While much of the original work with task-based fMRI involved fitting a task model to the fMRI data (i.e., region-based analysis), it is crucial to consider that analytic tools that were primarily developed for resting state fMRI – that is, the calculation of functional connectivity and network-based modelling – are equally, if not more, useful when applied to task-based or naturalistic viewing data.

Task-based and resting state functional connectivity could lead to different biomarkers due to different "brain states". Examining connectivity during task states provides additional information on the relationship between connectivity and cognition[20,388]. Therefore, renewed interest in functional connectivity during different brain states is emerging, with some newer tasks being

developed to study paranoia[389]. Considering both resting state and task-based functional connectivity is essential to enhance interpretability and sensitivity to brain-behavior relationships [24,237].

LIMITATIONS

Although fMRI has been highly impactful in psychiatry research in the past three decades, it is associated with several kinds of limitations which have until now hampered its deployment in clinical settings. If fMRI is to become a useful diagnostic/prognostic tool in the care of patients with schizophrenia – e.g., to predict conversion to psychosis from at-risk states, to predict response to certain antipsychotic medications, or to guide precision treatment – these limitations will need to be overcome.

We divide these limitations into three categories: technical, experimental and conceptual. Technical limitations are those concerning data collection and analysis. Experimental limitations are those that come up in the conduct of clinical fMRI research, such as sample size and power limitations, and sampling biases. Conceptual limitations refer to issues in interpretation of fMRI findings in clinical schizophrenia research. This survey of limitations helps provide a realistic assessment of the current state of the field.

While fMRI has provided valuable insights into the pathophysiology of schizophrenia, it is important to keep in mind what it is measuring. fMRI is an indirect measure of brain activity. It is not able to delineate activity differences across neurotransmitter systems, which would help identify putative pharmacological targets. The spatial resolution of fMRI is closely associated with the signal-to-noise ratio, and influenced by field strength, brain coverage, acquisition technique, and temporal resolution[390]. The temporal resolution of fMRI is limited by the hemodynamic response time, and the BOLD response peaks about 5-6 seconds after stimulus onset, which is much slower than the neural response. However, early work revealed that jittering stimuli presentation and the use of event-related designs could help to overcome these obstacles [391,392], and there is increasing evidence to suggest that early phases of the BOLD response may provide information about neural activity with higher temporal resolution[393].

Recent advances in echo planar imaging (EPI) acquisition have allowed for increased spatial and temporal resolution. Multi-band accelerated EPI (also known as hyper-band), popularized and made readily available by the Human Connectome Project[34,394], allows for the collection of multiple brain slices simultaneously, increasing the speed of whole brain coverage and spatial resolution[395-397]. Ultra-high magnetic fields improve the signal-to-noise ratio and enhance the BOLD contrast, allowing for greater spatial resolution, and are becoming more commonly used in schizophrenia research[398], but high-field fMRI has its own technical and methodological challenges and is not widely available[399].

fMRI is sensitive to a variety of noise sources, including scanner artefacts, participant motion, and cardiac and respiratory activity. Technological improvements have helped to mitigate motion artefacts: accelerated imaging reduces the opportunity for participants to move, but increased resolution also heightens sensitivity to participant motion[400]. Improved scanner hardware has resulted in reduced signal distortion, blurring and dropout[394,401].

Evidence suggests that multi-echo fMRI may provide a promising avenue for mitigating motion artefacts[35,402]. Multi-echo reads fMRI data at multiple time points for each slice acquisition, removing non-BOLD signal (such as scanner and motion artefacts). It has also been shown to allow greater reliability in shorter scan durations[403], which may be critical to implement functional imaging in clinical samples. However, while software tools for multi-echo analysis exist[404], multi-echo sequences are not available on all MRIs, and require higher technical knowledge to implement and analyze. The influence of motion on fMRI metrics remains a prominent concern in studies of functional connectivity[405], particularly as clinical populations such as people with schizophrenia frequently show greater in-scanner motion[406-408].

Despite hardware improvements, residual sources of noise and artefact are inescapable in any imaging technology, and must be addressed in the image reconstruction and data analytic process. Pipelines for modelling and removing physiological noise and participant motion have been widely utilized to mitigate these effects[409-412]. For example, global signal regression (GSR) is a potentially powerful denoising strategy[413] which is effective at minimizing associations between motion and connectivity in resting state fMRI data[411,412]. However, it has the potential to remove signals of interest[414], introduce spurious anticorrelations[415], and distort group differences[416,417]. There is also some evidence to suggest that the global signal differs in people with schizophrenia compared to healthy controls[418,419]. Thus, while GSR may mitigate multiple noise sources, it has the potential to remove important signal characteristics, and many publications present dual sets of results (both with and without GSR), without making claims as to which represents the "ground truth"[420].

More broadly, the sheer multiplicity of analytic choices required in fMRI research – from raw signal to processed images and then to statistical brain-behavior relationships and group comparisons – vastly increases the number of "researcher degrees of freedom"[421], thereby increasing the possibility of false positives and non-replicability. Additionally, the three most widely utilized software packages for analyzing fMRI data have subtle differences in implementation of basic pre-processing and analytic steps[422], potentially yielding different results even under similar assumptions. Moreover, these software differences can have varying effects on output across different task conditions[423], software versions[424], or even different hardware configurations and operating systems[425].

A recent landmark study[40] illustrated the magnitude of the challenge in generating reproducible results in fMRI studies. A single fMRI dataset was distributed to 70 independent research teams, along with a pre-specified set of hypotheses to test, resulting in three key findings: a) no two groups utilized the same processing pipeline; b) the degree of concordance across groups was approximately midway between pure chance and complete agreement; and c) the researchers were generally inaccurate in their predictions about the results, with an "optimistic" bias to-

wards expecting significant results.

Due to increasing awareness of these issues, at least three sets of solutions have been proposed for future research: a) the use of stable, uniform and openly-annotated pipelines and platforms[426-430]; b) benchmarking approaches to quantifying and reporting the residual degree of artefact and variability present in a given set of outputs[431-434]; and c) performing "multiverse" analysis, which entails reporting results from a multiplicity of analytic approaches within a single paper[435,436].

Experimental limitations, including small sample sizes and sampling bias, have also contributed to reproducibility and generalizability issues in fMRI research, as has variability across studies in participant sampling. As previously described, participant heterogeneity, the use of small samples, and focus on case-control comparisons have contributed to inconsistent findings in the field and impeded biomarker identification, but the shift towards larger, multi-site samples, deep phenotyping, and dimensional vs. categorical approaches holds considerable promise.

Though it is a non-invasive technique, fMRI requires participants to remain still and supine, often for an extended period of time, within a noisy, confined space, inherently limiting the potential sampling pool. A recent study found lower trait anxiety scores in healthy fMRI study participants across multiple centers, indicative of sampling or self-selection bias[437]. These could result in failure to generalize across study contexts and the full range of the population.

As mentioned, greater in-scanner head motion has been reported in clinical populations[406-408]. fMRI in-scanner head motion has been associated with cognitive performance[438] and IQ[439]. Accordingly, there is evidence that participants with greater cognitive and functional impairment tend to be more often excluded through quality control procedures[440], precluding the analysis of data from those who may be the most in need of interventions.

In clinical studies, unstable illness and comorbidities are often exclusion criteria. It is challenging to study inpatients, and even more difficult to include those who are so ill as to require substitute decision making. Many patients use substances and are often excluded from research, because these substances may act on the same systems as the illness itself[441,442]. The effects of antipsychotic medication on the brain are also not yet fully understood[443,444], often acting as a confound in studies including medicated patients[445]. This limits the generalizability of most fMRI studies. Moreover, the validity of selected cognitive and clinical assessments, either in or out of the scanner, is another critical consideration that can influence the reliability of brain-behavior associations[446]. fMRI is also expensive and not necessarily readily available in lower-income and more rural areas, and its potential clinical utility is influenced by and must be weighed against these factors.

In addition to these technical and experimental issues, the field is also increasingly grappling with challenges to the conceptual framework underpinning much conventional neuroimaging research to date. As previously highlighted, most fMRI studies examine functional connectivity differences between cases and controls, but functional connectivity across the brain is a multifaceted phenomenon that may be, to some extent, a "moving target". While some of its aspects are consistent for an individual across time and condition, other components are not highly reliable across testing sessions[447]. Specifically, individual connections (edges) demonstrate a "poor" reliability (average intraclass correlation coefficient = 0.29), while large within-network functional connectivity values are more stable[448]. Moreover, functional connectivity changes dynamically within a scanning session[449], and this dynamic variability is itself a heritable phenomenon that may influence cognitive and psychiatric traits[450].

Additionally, while functional connectivity has traditionally been measured using canonical boundaries for nodal regions (albeit with varying degrees of spatial resolution), there has been a recently emerging trend towards individualized definition of functional connectivity network boundaries[20,37,44,451-453], following demonstrations that these individual differences are heritable[454], increase statistical strength of brain-behavior associations[48,383,455], and are relevant to the study of psychopathology, including schizophrenia[36,456].

Similarly, fMRI studies of task activations generally share the implicit assumption that there is a single region, or set of regions, underlying a given functional process (e.g., memory or response inhibition). However, it has long been acknowledged that the human brain can meet a given set of task demands using different strategies[457,458]. Consequently, it has recently been suggested that a "complexity" approach to brain-behavior relationships, allowing a many-to-one mapping of brain states to behavior, will be more productive than comparing groups on single-region activations[459]. This approach is congruent with the recent search for subgroups of patients that share a similar "biotype" – i.e., the pattern of overall brain organization may identify subgroups of patients with distinct pathophysiology[355,460-463]. It is also important to note that non-canonical functional network patterns may be marked by relevant demographic and clinical differences that should not be ignored[464]. These recent changes to the underlying conceptual framework of fMRI studies in schizophrenia are discussed in greater detail in the section below.

FUTURE DIRECTIONS

Within each section of this paper, the evolution of approaches, techniques and strategies of fMRI research in schizophrenia has been reviewed (see Table 1 for a summary). For example, initial studies started with small sample sizes comparing chronic patients to healthy controls. By contrast, current studies more commonly include people in the earlier stages of illness (including CHR subjects) and may employ large consortium-based approaches to enhance sample size. The sections of this paper themselves have a historical arc, starting with diagnostic case-control approaches to identify group differences, moving to more recent efforts to use fMRI for personalized treatment in a precision medicine paradigm, such as individually-targeted neurostimulation. This final section serves to bring together aspects of each of the preceding sections, with a view to the future.

Table 1 Summary of functional magnetic resonance imaging (fMRI) research on schizophrenia

	Advances	Challenges
Diagnostic markers	Functional neuroimaging analyses have evolved from regional approaches to global connectivity, including advanced analyses to characterize key pathophysiologic markers of schizophrenia and clinical high risk more comprehensively. Machine learning approaches hold promise for parsing heterogeneity and predicting conversion from clinical high risk to psychosis.	Despite an abundance of fMRI-based case-control differences, findings are inconsistent, and the search for clinically useful functional imaging markers of schizophrenia continues. Heterogeneity across people with schizophrenia and healthy controls may impede diagnostic biomarker discovery, and small, single-site samples limit generalizability.
Markers of negative symptoms	Potential neural markers of negative symptoms have been identified in fMRI studies of early and chronic schizophrenia, and results suggest that these may vary by symptom construct, highlighting the importance of symptom delineation when investigating their neural basis.	Negative symptoms are a major determinant of poor functional outcomes in schizophrenia which lack effective treatments, yet few functional neuroimaging studies have focused on them, and different conceptualizations of negative symptoms may obscure results.
Markers of cognitive deficits	Particular neural networks have been implicated in non-social and social cognitive deficits in schizophrenia, with recent dimensional analyses suggesting that neural activation patterns during cognitive processing may relate to cognitive performance rather than diagnosis across schizophrenia and healthy controls.	Inconsistencies in functional neural correlates of cognitive performance are likely due, in part, to variability in cognitive abilities, and how they are conceptualized and measured.
fMRI in relation to treatment: response/ resistance, mechanisms, and therapeutic targeting	fMRI has provided insights into potential treatment response markers and mechanisms through pre- and post-intervention analyses of antipsychotics, psychotherapy and psychosocial interventions, and neurostimulation. For instance, striatal resting state functional connectivity has emerged as a potential marker for antipsychotic treatment response. The use of functional imaging to guide neurostimulation treatments – such as DBS, rTMS and tDCS – allows for more precise targeting of symptom-related circuits, and recent advances in individualized targeting may optimize target engagement and treatment response.	The mechanisms of many therapeutic agents in schizophrenia are poorly understood. The identification of therapeutic targets has been hampered by symptom heterogeneity likely involving multiple underlying pathological mechanisms and contributing to variable response rates.
fMRI and data-driven approaches to dissect heterogeneity	Heterogeneity in schizophrenia may be better characterized using dimensional or more individualized rather than categorical approaches, including linear models for mapping brain-behavior associations, biotyping through data-driven clustering, and advanced multivariate techniques to identify distinct and shared neural features with other psychiatric disorders.	It is unclear how to best quantify or classify heterogeneity (e.g., biotypes versus dimensional approaches), and translate heterogeneous results to clinical practice.
Methodological considerations and advances	Collaborative research and consortia approaches have facilitated the aggregation of large and diverse neuroimaging datasets and shared analytical pipelines, offering international representation, enhanced statistical power, and standardization, as well as improved reliability and generalizability. Improved imaging sequences, personalized data processing approaches, and mapping individual functional topography via deep phenotyping offer opportunities to address individual heterogeneity using precision fMRI.	Refined measurement techniques are required to capture individual variability in brain organization and connectivity profiles, as well as changes in state-related brain signatures.

DBS – deep brain stimulation, rTMS – repetitive transcranial magnetic stimulation, tDCS – transcranial direct current stimulation

In the diagnostics arena, initial enthusiasm was generated by small sample size studies showing apparently clear differences between patients and non-psychiatric controls using fMRI. For example, several studies demonstrated reduced prefrontal activation in people with schizophrenia on the "N-back task" of working memory[465]. However, conceptual issues related to heterogeneity were apparent even in these early studies, some of which demonstrated increased prefrontal activation, attributed to "cortical inefficiency", such that patients might use greater prefrontal resources even while achieving lower accuracy[466]. Of note, as early as 1998[197], with very small sample sizes, individual level maps of activation were examined, and the authors concluded: "Five of six patients, including two who were neuroleptic-naïve, failed to activate DLPFC. In addition, a tendency for overactivation of parietal cortex was seen". While the authors attributed much of this variability to motion (which in part was likely correct), they were prescient insofar as no one patient uses exactly the same set of voxels (brain regions/circuits) to perform a task in the scanner[459]. These observations were not followed up for nearly 20 years, as the template for the vast majority of studies was a case-control comparison, followed in some cases by conducting a brain-behavior correlation with task performance for regions showing between-group differences. Work emerging over the past five years has substantially changed the way we think about heterogeneity in brain activation and network connectivity patterns across individuals, providing a potential roadmap forward.

With larger sample sizes and data-driven statistical approaches, it has become increasingly clear that there are relatively distinct patterns of activation amongst subgroups of patients. At the same time, these patterns may not differ when taking patients with schizophrenia and comparing them to non-psychiatric controls, or to other diagnostic groups, such as bipolar disorder. For

instance, in tasks related to social cognition, data-driven analyses aimed at heterogeneity dissection showed that subgroups of patients used different brain areas (and potentially neural strategies) to complete the same facial emotion imitation task in the scanner[21]. However, non-psychiatric controls also used the same range of networks/strategies, and there was no difference in the frequency of patients or non-psychiatric controls in each strategy-defined group. Nevertheless, there was a relationship between strategy/network utilization and social cognitive performance, such that participants in the "deactivating" group demonstrated better performance relative to people in the "hyperactivating" and "intermediate" groups. Additional investigations in larger samples (e.g., from the Human Connectome Project) show that the relationship between task-related fMRI network utilization and behavioral performance across a variety of cognitive tasks may fall along dimensions[19]. However, the dimensional position of any individual participant may vary as a function of task.

Does this mean that between-group (i.e., schizophrenia versus non-psychiatric control) comparisons are uninformative? Recent data suggest that with large enough sample sizes, collected from multiple centers, certain findings of small effect are reliable. For example, using resting state fMRI, it does appear that cortico-striato-thalamo-cortical network differences are present when comparing patients with schizophrenia to controls[126]. At the same time, there is individual variability within each group, and accounting for personalized intrinsic network topography can strengthen results[44]. It is also likely that the robustness of these findings can be increased by using higher quality fMRI acquisitions (e.g., multi-echo fMRI) of longer duration. Indeed, repeated acquisitions may be of highest value to obtain more precise functional mapping at the individual level. Specifically, just 10 minutes of multi-echo data using a repeated within-person longitudinal design yielded better test-retest reliability than 30 minutes of single-echo data in independent datasets[403].

The collection of very large sample sizes (in the thousands) to conduct cross-sectional group-wise or brain-behavior correlational analyses is very expensive and may only yield very small effect sizes[49]. Moreover, the findings of such studies are not applicable at the individual patient level. Thus, rather than a study of 1,000 patients scanned once, it may be more fruitful to conduct a study of 100 patients scanned 10 times each. Longitudinal studies may yield substantially greater effect sizes than a cross-sectional approach. In fact, a recent meta-analysis showed that effect sizes may be 290% greater in longitudinal studies[467]. At the individual level, data aiming to identify personalized signatures of brain function show that even six scans may be sufficient to robustly identify each person[468].

Such longitudinal approaches may also provide the opportunity to address important clinical questions in the treatment of schizophrenia, aligning with the precision medicine method that has been successful in specialties outside of psychiatry. One urgent clinical question in the treatment of schizophrenia is prognosis – patient outcomes are highly variable, and up to 40% of patients are ultimately classified as treatment resistant. Relatedly, it is of particular interest whether fMRI measures can capture the likelihood that a given patient will respond to conventional treatments, or will require clozapine. In short-term clinical trials, or in observational studies examining longer-term clinical, cognitive or functioning trajectories, study visits can be paired with an MRI scan. Importantly, this may not be an infinite requirement. It is plausible that a finite number of functional brain map trajectories correspond to specific clinical trajectories, or to treatment response profiles. If a large-scale prospective study can identify these profiles, subsequent clinical studies might require only one or two scans to determine a patient's trajectory, potentially informing clinical decisions. In early stage psychosis, for instance, some patients quickly improve and are able to resume work or school, while others struggle considerably, may be re-hospitalized, or require more intensive wrap-around care. Having this information within the first few weeks of care in an early psychosis program would allow for more efficient use of finite resources for those patients who require it most.

Remaining at the individual level, knowledge of the specific set of networks that a patient used during a task, or his/her individualized functional connectivity profile, can serve as essential information for targeting neurostimulation. For example, more personalized targets are associated with greater improvement in memory performance[299,469] and depressive symptoms[319]. Therefore, targeting toward a group mean of peak connectivity may result in maximal treatment efficacy for a subset of individuals, but will miss the optimal target for a substantial number of other individuals. Currently funded clinical trials are seeking to determine if fMRI can be clinically useful in order to improve targeting of neurostimulation treatment aimed at cognitive performance, negative symptoms and/or depressive symptoms in people with schizophrenia. If shown to be useful, personally-refined, image-guided interventional psychiatry may become a reality, blending precision medicine and personalized medicine into one[32].

However, if the field increasingly moves towards individualized approaches, it is incumbent upon us to be conscientious and equitable in terms of which individuals we study. Currently, several groups of patients with schizophrenia are under-represented in fMRI studies. The most ill patients, some of whom are not able to provide informed consent, are greatly under-represented in research. Ethics committees, patient advocates, clinicians and researchers must collaborate to change this. In other fields of medicine, those in the most need often participate in clinical trials. Additionally, women are under-represented in schizophrenia research[470], partially due to differences in prevalence and sex-based variability in illness severity. However, women's health research is underfunded in general[471], and a greater effort must be made to include women with schizophrenia in fMRI research, and particularly in clinical trials employing fMRI. Moreover, people of minoritized ethno-racial backgrounds are under-represented in this research[472]. Encouragingly, funders are making efforts to provide and promote opportunities for more inclusive research, and requiring justifications regarding sample recruitment related both to ethno-racial diversity and sex/gender diversity. Finally, diversity in age is required in our samples: for example, adolescents at risk for schizophrenia may have a functional signature

that changes across the lifespan.

The ultimate question is whether fMRI can be clinically useful in the care of patients with schizophrenia. Early clinical guidelines suggested that neuroimaging should be part of routine practice in a first episode of psychosis, in order to identify possible "organic" causes. However, any advantage of fMRI is largely unrelated to rare, potentially identifiable causes of psychosis. Instead, fMRI research should address potentially actionable clinical decisions that are routine in schizophrenia treatment – i.e., which medication should be prescribed if an fMRI scan shows a signature of treatment resistance to conventional antipsychotics, or whether a given patient is likely to have persistent functional impairment based on early neuroimaging data, thus requiring display of significant psychosocial resources. In such cases, the economic cost of fMRI, and in some cases the challenge of travel to a center for a patient living in a more remote area, may be worth it. Future evaluations of the utility of fMRI in prognostic and treatment response studies may consider including a health economics analysis to make a tangible clinical impact.

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The need for a consensual definition of mental health

The first conceptualization of mental health can be traced back to 1948, when J.C. Flugel, Chairman of the First International Congress of Mental Health, proposed to define it as "a condition which permits the optimal development, physical, intellectual and emotional, of the individual, so far as this is compatible with that of other individuals". In 1950, at the second session of the Expert Committee on Mental Health of the World Health Organization (WHO), mental health was defined as "a condition subject to fluctuations due to biological and social factors, which enables the individual to achieve a satisfactory synthesis of his own potentially conflicting, instinctive drives; to form and maintain harmonious relations with others; and to participate in constructive changes in his social and physical environment". Neither definition included the concept of well-being (and neither was very influential).

In 2004, the WHO provided a definition of mental health as "a state of well-being in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community"[1]. This definition has been highly influential, and several subsequent definitions of mental health have been organized within the same framework, in which a key role is assigned to the person's well-being (the "hedonic" perspective) and his/her self-actualization (the "eudaimonic" perspective).

According to the American Psychological Association, for instance, mental health is "a state of mind characterized by emotional well-being, good behavioral adjustment, relative freedom from anxiety and disabling symptoms, and a capacity to establish constructive relationships and cope with the ordinary demands and stresses of life"[2]. For the Public Health Agency of Canada, mental health is "the capacity of each and all of us to feel, think, and act in ways that enhance our ability to enjoy life and deal with the challenges we face. It is a positive sense of emotional and spiritual well-being that respects the importance of culture, equity, social justice, interconnections and personal dignity"[3].

This emphasis on positive feelings and self-actualization in the definition of mental health has been a matter of debate. First, this view is difficult to reconcile with the many challenging life situations in which well-being may even be regarded as unhealthy (indeed, people in good mental health are often sad, angry or unhappy; and it would be problematic to regard as unhealthy a person feeling desperate after being fired from his/her job in a situation in which occupational opportunities are scarce). Second, this view would exclude from the definition of mental health the many adolescents who struggle to find their place in the community, the many elderly people who are not able anymore to work productively and fruitfully, and the many migrants and other members of minority groups who are marginalized and therefore unable to make a contribution to their community.

To overcome the above emphasis on the hedonic and eudaimonic perspectives, a group of experts proposed in 2015 a new definition of mental health as "a dynamic state of internal equilibrium", to which several components contribute in varying degrees, including "basic cognitive and social skills; ability to recognize, express and modulate one's own emotions, as well as empathize with others; flexibility and ability to cope with adverse life events and function in social roles; and harmonious relationship between body and mind"[4]. This definition allows for the possibility of experiencing crises (e.g., adolescence, retirement) which certainly do not generate a state of well-being, but may lead to a new equilibrium, with a higher level of complexity. Moreover, the definition acknowledges the fact that mentally healthy people may experience negative emotions such as fear, anger, sadness or grief, while at the same time possessing sufficient resilience to timeously restore their state of internal equilibrium.

In 2022, the WHO's *World Mental Health Report* redefined mental health as "a state of mental well-being that enables people to cope with the stresses of life, to realize their abilities, to learn well and work well, and to contribute to their communities"[5]. This definition confirms the emphasis on well-being (apart from adding the specifier "mental") and seems to soften the emphasis on productivity of the previous definition by replacing the expression "work productively and fruitfully" with "learn well and work well". Furthermore, when describing "the intrinsic and instrumental value" of mental health, the report mentions several aspects of the alternative definition proposed in 2015[4], including cognitive skills, understanding and managing emotions, and empathizing with others.

However, the statement that mental health is "a state of mental well-being" remains a matter of concern. In fact, although a comprehensive review has reported as many as 191 components of the well-being construct[6], the concept is still conceived by many within a hedonic perspective. For instance, the American Psychological Association defines well-being as "a state of happiness and contentment, with low levels of distress, overall good physical and mental health and outlook, or good quality of life"[2].

Thus, there is not a consensus at the moment about the definition of mental health, in spite of the increasing popularity of this concept and the high frequency with which it is used in the literature, in public health and clinical contexts, and in policy documents. Sometimes the fuzziness of a concept may favor its success, but this is certainly not what all the stakeholders involved in the field wish to pursue.

It seems to be agreed that mental health is not just the mere absence of mental illness, but the relationship of the concept with that of mental well-being remains unclear or equivocal; the requirement for productivity and/or contribution to the community may lead to regard entire sections of the population as mentally unhealthy, thus "blaming the victims" of stigmatization, discrimination and exclusion; and the acknowledgement that healthy human life experience may be sometimes joyful and satisfactory, but at other times sad, disgusting or frightening seems to be lacking in several definitions.

On the other hand, the importance of components such as basic cognitive skills (i.e., paying attention to a task, remembering

past and recent information, being able to solve simple problems and make decisions); the basic ability to function in social roles and to entertain social relationships; emotional regulation (i.e., being able to recognize, express and modulate one's own emotions); flexibility (i.e., being able to modify one's own goals and plans in the light of new events or unpredicted difficulties, and adapt to changes required by different life periods or contingent situations); and a harmonious relationship between body and mind (since the quality of this interaction is instrumental to the overall experience of being in the world[7]) does not seem to be sufficiently recognized.

Future developments in the definition of mental health would benefit from a more systematic and substantial contribution of experts by experience, as well as from a greater conceptual sophistication.

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Functional neurological disorder: defying dualism

Functional neurological disorder (FND) is classified in the DSM-5-TR as "functional neurological symptom disorder (conversion disorder)" and in the chapter on mental disorders of the ICD-11 as "dissociative neurological symptom disorder".

Neurologists, who most commonly make the initial diagnosis, are usually barely aware of such classification systems, and use a variety of terms – such as "functional", "psychogenic" or "non-organic" – to describe symptoms of paralysis, tremor, seizures or blindness that were once encompassed under the label of "hysteria". This diversity of terms reflects a disorder that has been passed back and forward between neurology and psychiatry for 150 years. Over time, the FND pendulum has swung between a brain disorder in the late 19th century to a purely psychological condition in the 20th century. Today, FND researchers are suggesting that the pendulum rest in the middle. Defying dualism in FND may cause dissonance in clinicians, in those seeking tidy explanatory theories, and in classification systems. But it is an essential platform towards understanding FND and improving care for the millions of people around the world who have it.

For those who grew up with "conversion disorder" in the DSM-IV, the idea was simple, hydraulic and comfortingly Freudian. Someone has a stressful event, which is repressed and converted to motor or sensory symptoms, that may or may not be symbolic, perhaps reducing the stress, sometimes to the point of *belle indifférence*. Conversion disorder was often considered a rare condition, which could only be diagnosed by exclusion, and would often respond quickly to psychological therapy. Historian E. Shorter declared that "hysteria" had largely disappeared in favour of other somatic symptoms such as fatigue[1].

In the last 20 years, this narrow view of the condition has been systematically dismantled by the evidence. FND is a common condition, one of the commonest seen by neurologists in both outpatient and inpatient settings, making up 5-15% of patients[2]. It accounts for 50% of people rushed into hospital with suspected status epilepticus, and 8% of people admitted to hospital with suspected stroke. FND symptoms are usually not transient. A 14-year study of people with functional limb weakness found that 80% still had their symptoms at follow-up. Physical disability and distress are as high as in epilepsy or Parkinson's disease[2].

FND is a diagnosis of inclusion, with a diagnostic stability similar to other conditions in neurology and psychiatry[2]. People with FND have clinical features that are characteristic of the disorder. Hoover's sign describes impairment of *voluntary* hip extension in the presence of normal *automatic* hip extension during contralateral hip flexion. A functional tremor stops or entrains to the rhythm of the examiner in the tremor entrainment test in a way that does not occur in other tremor disorders. People having a functional seizure typically experience a brief prodrome with autonomic arousal and dissociation, followed by an event in which their eyes are closed, and there are either vigorous tremor-like movements, or they fall down and lie still for more than a minute in ways that only occur in this condition.

Injury, pain and infection are common triggers to functional motor and sensory disorders, and appear at least as relevant as adverse experiences[2]. Stressful events, adverse childhood experiences, and psychiatric comorbidity remain important in the story of many people with FND. The frequency of adverse childhood experiences (odds ratio: 3-4) and recent stress (odds ratio: 2-3) is increased, but not that different to many other conditions where they are considered a risk factor and not "the cause"[3]. There are patients in whom a conversion model still makes sense, but others for whom it is preposterous. The dropping of the requirement for a recent stressful event in the DSM-5, and the change of the name of the condition from "conversion disorder (functional neurological symptom disorder)" in the DSM-5 to "functional neurological symptom disorder (conversion disorder)" in the DSM-5-TR, are in keeping with that. A wider set of hypotheses, considering multiple levels from the neuron to society, is required to make sense of FND.

The "predictive brain" offers a potential solution to puzzling

disorders such as phantom limb phenomena, in which strong predictions that a limb "is still there" outweigh sensory input to the contrary. Similarly, in functional paralysis, one hypothesis is that the brain predicts a limb that "is not there" (and thus cannot be moved) so strongly that it outweighs sensory input telling the brain that the limb is normal[4]. The predictive brain builds on older notions of "ideas" or "beliefs" being important in FND, or of conditioned responses to threat, illness or injury that operate below the level of awareness. Neurodevelopmental conditions – including autism spectrum disorder, attention-deficit/hyperactivity disorder, and joint hypermobility – may be more common in people with FND because of an impairment in this predictive and interoceptive machinery.

The first functional neuroimaging study of an FND patient appeared in 1997. The shock news was that FND could be seen in the brain. A number of networks have then been found to be relevant to FND, including those involved in attention, motor control, salience and emotion regulation[2]. Perhaps the most interesting and replicated finding is hypoactivation of the network involved in sense of agency – the parts of the brain that let you know that it is "you" who made a movement – including the right temporoparietal junction. Poor activation of this network is consistent with what we see clinically ("it looks like a voluntary movement") *and* what the patient is telling us ("it doesn't feel like under my control"). A diagnostic biomarker for FND may even one day become available[5]. For example, a study of resting state functional imaging was able to classify FND from healthy controls using brain scans alone with an accuracy of 72%[6].

If one considers FND a disorder of higher voluntary movement, it is hardly surprising that it has often been confused with wilful exaggeration or malingering. But a whole range of clinical and neuroscientific evidence, including geographical and historical consistency as well as remarkable responses to neurophysiological experiments, such as increased accuracy in tests of sensory attenuation, show that feigning offers a poor explanation for the clinical phenomenon of FND[7].

Treatment for FND reflects this new multidisciplinary approach, starting with an explanation of the disorder that emphasizes diagnosis by inclusion, mechanisms in the brain, but also relevant psychological risk factors when present. FND-focused physiotherapy promotes automatic over voluntary movement, has important differences to physiotherapy for recognized neurological conditions, and shows a lot of promise in randomised trials[8]. FND-focused evidence-based psychological therapy addresses adversity, but also recognizes the physiology of functional seizures and their similarity to panic[9].

The International FND Society, founded in 2019, embodies this co-operative approach, and is complemented by new patient-led organizations such as FND Hope and FND Action. Together they are defying the dualism which has prevented progress and understanding of this common disabling condition.

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Euthanasia for unbearable suffering caused by a psychiatric disorder: improving the regulatory framework

Medical assistance in dying (MAID) – defined as voluntary euthanasia and/or physician-assisted suicide – for people with a terminal illness is becoming available in more jurisdictions around the world. By contrast, MAID in people with a non-terminal illness and, more specifically, in people with a psychiatric disorder remains a controversial topic.

Belgium is one of the very few countries where euthanasia for unbearable mental suffering caused by a psychiatric disorder is allowed. According to the 2002 Belgian Euthanasia Law, the eligibility criteria are: a) the euthanasia request is made by a legally competent adult patient; b) the request is voluntary, repeated, well-considered, and not the result of external pressure; c) the patient is in a medical condition without prospect of improvement; d) the patient experiences constant and unbearable mental suffering that cannot be alleviated; and e) the suffering is the result of a serious and incurable psychiatric disorder. To assess the fulfilment of these criteria, the attending physician must consult two independent physicians, including a psychiatrist. At least one month should pass between the date of the patient's request and the performance of euthanasia. After the euthanasia is performed, the attending physician must report this to the Federal Control and Evaluation Commission for Euthanasia, which is tasked with the *a posteriori* control[1,2].

According to the official data in 2020, MAID accounted for 1.9% of all deaths in Belgium. Between 2002 and 2021, a total of 370 patients received euthanasia for unbearable mental suffering caused by a psychiatric disorder. This corresponds to 1.4% of the total number of euthanasia cases, although in recent years the incidence slightly decreased to between 0.9 and 1%. The most common diagnoses (data on 2002-2019, N=325) were mood disorders (55.7%) and personality disorders (19.4%), followed by psychotic disorders (6.2%), anxiety disorders and post-traumatic stress dis-

order (6.2%), autism spectrum disorder (4.6%), eating disorders (1.5%), and other and/or combination of disorders (6.5%).

Recently, the fundamental rights compliance of the Belgian Euthanasia Law, as applied to euthanasia for mental suffering caused by a psychiatric disorder, was scrutinized in two ground-breaking court decisions[3,4].

In the first of these, the European Court of Human Rights examined whether a euthanasia of a 64-year-old woman with treatment-resistant depression and a personality disorder had violated the state's responsibility to protect her right to life, as well as the right to respect for private and family life of her son, who had only been informed about the euthanasia after it had been performed[3].

The Court held that the Belgian legal framework governing euthanasia for mental suffering caused by a psychiatric disorder complied with the conditions set out in an earlier case law on end-of-life decisions. More specifically, it was argued that the Belgian law contains a procedure that can guarantee that a euthanasia request is voluntary. In addition, as required for MAID concerning particularly vulnerable persons, the law provides for increased protective measures for euthanasia in people with mental suffering. In this regard, the Court noted the importance of the obligation to consult two independent physicians, including one psychiatrist, as well as to observe a waiting period.

By contrast, the Court still found a human rights violation in the way the *a posteriori* control of euthanasia was regulated. In the case at hand, the physician who had performed the euthanasia was the chair of the Federal Commission. Since in monitoring the legal compliance of that case of euthanasia the Commission had relied completely on the anonymous part of the registration document, the chair had inadvertently taken part in approving the euthanasia case without anyone having noticed his involvement. However, as this monitoring should be independent, reporting should not be anonymous if physicians involved in euthanasia are allowed to sit on the Commission[3].

In the second case, the Belgian Constitutional Court was petitioned by a judge who was looking into the liability of a physician who had performed the euthanasia of a 38-year-old woman with a personality disorder[1-4]. As in previous rulings, the Court confirmed that the Euthanasia Law and its constituting elements and safeguards do not violate the constitution. Since the Belgian Euthanasia Law does not contain any sanctions, the Court was asked to shed light on the penalties that should apply. In accordance with the general provisions of the Criminal Code, any infraction, even of an administrative nature, could be considered murder by poisoning. The Constitutional Court held that this would be disproportionate for the physicians involved in euthanasia, as they would run the risk of being convicted for murder even for infringing upon a legal condition of minor importance. Ruling that this violated the principles of non-discrimination and equality, the Court instructed the Belgian legislature to diversify the applicable system of penalties, with lighter penalties for violations of procedural conditions that are less important to guarantee the fulfilment of the eligibility criteria.

The evaluation of a request for MAID in the context of a psychiatric disorder is clinically challenging. First, the assessment of the decisional capacity of psychiatric patients who request MAID may be more complex than for other patients[1,2,5]. It is emphasized by opponents of MAID in people with a psychiatric disorder that their competence can be severely impacted by the illness[1,6,7]. Although a cautious approach is therefore necessary, there is no reason to presume that people with a psychiatric disorder cannot possess the required decisional capacity. This capacity should be assessed case by case and held to a high standard, considering the nature and possible consequences of the request. In this light, it is highly advisable to conduct a formal evaluation of the capacity of psychiatric patients who request MAID.

Second, there is no consensus or authoritative guidance on how to define or measure unbearable mental suffering[1,7,8]. This entails a risk that unbearable mental suffering is too readily accepted. Although treatment refractoriness is a clinical reality, MAID should only be considered after all reasonable biological, psychological, social and recovery-oriented treatment options have failed. When a patient refuses such treatments, this should not lead physicians to conclude that the mental suffering cannot be alleviated and the psychiatric illness is without prospect of improvement. Hence, the request for MAID should not be granted.

In 2017, the Flemish Society of Psychiatry published recommendations to guide clinicians in these difficult decisions[7]. They recommend following a two-track approach in the evaluation of a euthanasia request by a psychiatric patient. One track should examine the fulfilment of the eligibility criteria. Importantly, it is suggested to always involve at least two psychiatrists, who preferably are experts of that specific psychiatric disorder. In the second track, the psychiatric patient should be actively supported in exploring all remaining therapeutic and recovery-based options. This two-track approach combines respect for the autonomy of the patient with the obligation to protect that person's right to life. It implies that, while the euthanasia request is being assessed, the psychiatric patient continues treatment and his/her psychiatrist remains involved.

These recommendations inspired the Belgian Order of Physicians to adopt more stringent deontological standards for physicians who consider a euthanasia request from a psychiatric patient. These physicians are now obliged to comply with additional due care criteria: at least two of the three physicians involved should be psychiatrists; the physicians should come to a jointly formulated opinion about the fulfilment of all due care criteria; euthanasia should not be performed unless all reasonable treatment options have been tried and failed; and patients should be encouraged to involve their relatives in the euthanasia procedure. Combined, the legal and deontological due care criteria help ensure that a euthanasia request for mental suffering caused by a psychiatric disorder is appropriately addressed.

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Physician-assisted death for psychiatric disorders: ongoing reasons for concern

Physician-assisted death (PAD) – i.e., the prescription and administration of lethal medications by physicians – is increasingly available as an option for people struggling with psychiatric disorders. Although PAD was initially promoted as a means of easing suffering for people with terminal conditions, a growing number of jurisdictions have extended access to all causes of intractable and severe suffering, including psychiatric conditions.

At present, Belgium, the Netherlands and Luxembourg, along with Spain and Switzerland, either explicitly authorize or *de facto* permit lethal assistance in such cases[1]. Canada is scheduled to join this group in March 2024. It is difficult to ascertain how often PAD is used for psychiatric disorders; however, among all PAD cases in Switzerland, 8% of those in Swiss residents and 17% of those in people traveling from other countries for this purpose had documented mental disorders[2]. Overall, available data suggest that the frequency of PAD use in people with psychiatric disorders is increasing[1].

A growing literature is debating the ethics of PAD in psychiatry. For jurisdictions that permit PAD in terminal illnesses, it is commonly argued that to preclude its use for non-terminal conditions that cause immense suffering, including psychiatric disorders, is discriminatory. To proponents of psychiatric PAD, it appears unquestionable that these conditions can cause severe suffering and may be resistant to available treatments, that most people with a psychiatric diagnosis are competent to decide that death is preferable to an indefinite continuation of their current state, and that clinicians can reliably ascertain whether these criteria have been met[3].

I have previously detailed in this journal[4] my concerns about PAD for people with psychiatric disorders. Among the reasons I noted for caution in embracing PAD are its application to disorders very different from treatment-resistant depression (which is often held up as the model of an intractable condition that causes great suffering), including autism, eating disorders, dissociative disorders, and personality disorders. The high proportion of patients with personality disorders seeking PAD, and the well-known reactivity of these conditions to environmental circumstances, raise the question of just how deeply rooted the distress being expressed by such patients might be. Whether a person is experiencing severe suffering, a key criterion for eligibility, is entirely subjective, leaving evaluators with little choice but to accept the patient's assertion that this is the case. Given that intractability is usually judged only by the lack of response to those treatments that a patient is willing to accept, it is common that potentially effective interventions have never been tried by patients seeking PAD. Finally, whether the underlying disorder is driving the person's choice is very difficult to ascertain, leaving the decisional competence requirement little role to play in these cases.

Here, I want to consider what we can learn from the experience with psychiatric PAD, primarily from reports published over the last five years. There has always been concern that PAD would become a replacement for the provision of psychiatric care, especially where such care is not easily accessed. Recent reports from Canada underscore this concern, as exemplified by the account of a woman who sought help at a hospital for suicidal ideation[5]. She was told that the mental health system was "completely overwhelmed", no inpatient beds were available, and she would have to wait six months to see a psychiatrist as an outpatient. At that point, the counselor assessing her asked if she had ever considered PAD, explained how it worked, and noted that it would alleviate her suffering. All this occurred even though PAD was technically not yet authorized in Canada for people with mental disorders, and reinforces reports from other Canadian jurisdictions.

Along with concern about PAD being used as a substitute for care are data suggesting that patients who are suicidal – and thus should be treated for their intention to end their lives – are disproportionately seeking PAD. A review of studies on the prevalence of personality disorders among PAD requesters noted that in several reports they represented more than 50% of the sample; the authors underscored the substantial frequency of suicidal behavior in personality disorders, its fluctuating nature, and the existence of evidence-based treatments to address it[6]. Another review focused on the disproportionate use of psychiatric PAD for women, who accounted for 69-77% of cases in several series[7]. The authors noted that women also attempt suicide more frequently and typically favor less violent means, such as medication overdose. Hence, they suggested that PAD may be serving as a substitute for self-inflicted suicide, especially for women, and encouraged further research on this question.

The momentous nature of a decision to seek PAD – an irreversible and final procedure – suggests the need for great care in evaluating whether the criteria for eligibility are met. However, this appears often not to be the case. A review of 66 cases of PAD from the Netherlands found that, in 55% of cases, documentation of decisional capacity was limited to a global judgment, without assessment of specific capacity-related abilities[8]. Moreover, there

was disagreement about capacity among evaluating physicians in 12% of cases in which PAD was carried out anyway. The authors concluded that the decisional capacity of psychiatric patients seeking PAD receives neither a high level of scrutiny nor is subject to a high threshold, an approach that seems to be accepted by the committees that review these cases. In some jurisdictions, a patient with a psychiatric disorder need not be evaluated by a psychiatrist prior to PAD, heightening the probability of inadequate evaluation.

A recent case report from the Netherlands illustrates another reason for careful evaluation: the possibility that a patient has been misdiagnosed and thus has not received effective treatment[9]. In this case, intolerable auditory hallucinations that motivated the request for PAD were found to be due to intrusive thoughts and responded to cognitive-behavior therapy. The authors recommend an "obligatory second opinion by a psychiatrist specialized in the patient's disorder", which is not currently required.

Where does this leave us? These data suggest that many of the initial worries about psychiatric PAD are being reinforced by ongoing practice. This procedure is susceptible to being used as a replacement for care; it appears to be sought by patients, especially women, as a substitute for trying to end their own lives; and the challenging evaluations of the required criteria seem often to be performed in a perfunctory manner. Although data are not yet available, it is worthwhile thinking about the longer-term impact on psychiatrists and psychiatric patients: the message that their conditions may be hopeless, thus not worth the effort to treat or to receive treatment, and that death is an acceptable alternative. Such a posture conflicts with the traditional stance of psychiatry as a specialty dedicated to sustaining hope, protecting people from the impulse to end their lives, and helping people find meaning in their existence. The prospect of further spread of psychiatric PAD is indeed reason for concern.

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The social determinants of mental health and disorder: evidence, prevention and recommendations

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People exposed to more unfavourable social circumstances are more vulnerable to poor mental health over their life course, in ways that are often determined by structural factors which generate and perpetuate intergenerational cycles of disadvantage and poor health. Addressing these challenges is an imperative matter of social justice. In this paper we provide a roadmap to address the social determinants that cause mental ill health. Relying as far as possible on high-quality evidence, we first map out the literature that supports a causal link between social determinants and later mental health outcomes. Given the breadth of this topic, we focus on the most pervasive social determinants across the life course, and those that are common across major mental disorders. We draw primarily on the available evidence from the Global North, acknowledging that other global contexts will face both similar and unique sets of social determinants that will require equitable attention. Much of our evidence focuses on mental health in groups who are marginalized, and thus often exposed to a multitude of intersecting social risk factors. These groups include refugees, asylum seekers and displaced persons, as well as ethnoracial minoritized groups; lesbian, gay, bisexual, transgender and queer (LGBTQ+) groups; and those living in poverty. We then introduce a preventive framework for conceptualizing the link between social determinants and mental health and disorder, which can guide much needed primary prevention strategies capable of reducing inequalities and improving population mental health. Following this, we provide a review of the evidence concerning candidate preventive strategies to intervene on social determinants of mental health. These interventions fall broadly within the scope of universal, selected and indicated primary prevention strategies, but we also briefly review important secondary and tertiary strategies to promote recovery in those with existing mental disorders. Finally, we provide seven key recommendations, framed around social justice, which constitute a roadmap for action in research, policy and public health. Adoption of these recommendations would provide an opportunity to advance efforts to intervene on modifiable social determinants that affect population mental health.

Key words: Mental health, mental disorder, social determinants, social risk factors, prevention, marginalized groups, population mental health, social justice

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Social determinants of health represent the most modifiable set of targets for intervention currently available to prevent the onset of mental health problems and disorders, and to promote positive mental health in our populations. Social determinants of mental health encompass the set of structural conditions to which people are exposed across the life course, from conception to death, which affect individual mental health outcomes, and contribute to mental health disparities within and between populations. These structural conditions include factors such as income, employment, socioeconomic status, education, food security, housing, social support, discrimination, childhood adversity, as well as the neighbourhood social and physical conditions in which people live, and the ability to access acceptable and affordable health care. Importantly, our chances of being exposed to protective or harmful social determinants of (mental) health are "shaped by the distribution of money, power and resources at global, national and local levels, which are themselves influenced by policy choices"[1]. Such determinants are therefore not randomly or benignly distributed within or between populations, but are manifested by systems and institutions of power that often produce and reproduce intergenerational inequities in people's opportunities to realize safe, secure, prosperous and healthy lives.

There is now compelling evidence that the risk of developing any mental health condition is inextricably linked to our life circumstances[2], meaning that a higher burden of population-level psychiatric morbidity is disproportionately experienced by those closer to the margins of our societies. Since poor mental health can be the invisible hand that suppresses life chances, including both how long we live[3] and the quality of years lived[4], improving population mental health by designing effective prevention strategies that intervene on modifiable social risk factors should be seen as a central issue of social justice[5].

We stand at a threshold moment not only in understanding the potential causal role of modifiable social determinants in the onset (or exacerbation) of mental health problems, but also in defining our response to them through effective prevention strategies that reduce inequities in the burden of psychiatric morbidity experienced between and within different populations. Arguably, the last two decades have brought about some progress in our biomedical understanding of psychiatric disorders, while investigating the importance of psychosocial factors in causing mental disorder has remained a peripheral focus for scientific discovery and clinical psychiatry. We have expanded our knowledge about the immutable, overlapping (pleiotropic) and polygenic bases of

psychiatric disorders that can help explain why some individuals are more at risk of a diverse array of psychopathologies than others[6]. We have also achieved a better understanding of how complex the neurobiology of different psychiatric conditions is likely to be[7], including depression, psychosis and bipolar disorder. This progress has, however, simultaneously exposed limitations in our ability to translate the acquired knowledge into effective clinical targets to prevent or alleviate symptoms of mental distress. The promise of personalized prediction and treatment remains out of reach in routine clinical practice[8]. Frontline pharmacological treatments for depression, anxiety, psychosis and bipolar disorder have remained largely unchanged since they were first developed in the 20th century[9]; treatment resistance affects 20-60% of our patients[10]; and the pharmaceutical industry has largely withdrawn from psychiatric drug discovery in the last 20 years[11].

These last two decades have simultaneously witnessed at least two seismic transformations in the mental health landscape. First, unprecedented increases in public awareness and advocacy about mental health, well-being and illness, albeit concentrated in the Global North, have raised political pressure on institutions and governments to act to address the global burden of psychiatric morbidity[2]. Such has been the transformation that promoting mental health and well-being is now identified as a specific outcome in the United Nations (UN) Sustainable Development Goals[12], alongside targets to tackle various social determinants of health – including poverty, inequality, gender equality, and social justice – by 2030. The World Health Organization (WHO) also recognizes the urgent need to address how our environments affect mental health. In the recent *World Mental Health Report*[2], T. Ghebreyesus, the WHO Director-General, reaffirmed the Organization's commitment in "transforming the environments that influence our mental health" to promote mental well-being and prevent mental disorder.

Second, longitudinal declines in public stigma and more positive attitudes towards major psychiatric conditions such as depression – particularly in so-called Millennial and Gen Z generations[13,14] – have been paralleled by sustained increases in the number of people seeking help for mental health issues over the last 20 years. In some contexts, this has placed overwhelming pressure on clinical services tasked with providing primary, secondary and tertiary treatment for mental health conditions, with evidence globally that economic investment in mental health service provision continues to fall far short of need for care[2]. For example, in England, a 54% increase in referrals to public mental health services from 2016 to 2022 was accompanied by a mere 10.9% real-terms increase in service funding[15,16], highlighting the growing treatment gap in population mental health. This gap has been reported globally for depression[17] and psychosis[2], and is particularly high in low- and middle-income countries (LMICs)[18].

The increased need for mental health care over the last two decades is not randomly distributed within populations, but follows clearly the social, demographic and economic lines along which experiences of poor mental health and receipt of mental health care are inequitably distributed[2].

Nowhere is this more evident than in the case of children and young people. Given that adolescence represents a critical period of neural, psychological, behavioural and social development, it is perhaps no surprise that so many mental health problems emerge for the first time during this period. A recent systematic review of the pre-pandemic literature estimated that the onset of around one third, half and two thirds of any mental disorder will have already occurred by ages 14, 18 and 25, respectively[19]. In the US, the proportion of university students – typically aged 18-22 years – who reported having been treated for mental health problems has risen from 19% in 2007 to 34% in 2017[20]. A rapid increase in self-reported depressive symptoms amongst younger adolescents in the US since 2012 has also been reported, peaking in 2018 (the last date of available survey data)[21]. These are not isolated findings. Further research from the US[22], Canada[23], Europe[24], France[25], Iceland[26] and Australia[27,28] all suggest that rates of depression, anxiety, self-harm, eating disorders, attention-deficit/hyperactivity disorder (ADHD) and suicide have risen rapidly amongst teenagers since 2010[29], particularly in females[26,27,30,31]. By contrast, there is some evidence that the prevalence of alcohol and drug use disorders[24,32] and behaviours[33] has decreased over this period.

Observed changes in the prevalence of mental health problems in children and young people have been attributed to both period[21] and cohort[22] effects. While the COVID-19 pandemic – a textbook period effect – appears to have had only minimal impact on long-term mental health in the general population[34,35], impacts on children and young people, who have often borne the brunt of restrictive lockdown policies, are more pronounced[25,34,35]. For example, in England, the number of people less than 18 years old accessing public mental health services in the previous 12 months increased by 20.4% between the start of the pandemic and July 2022[15]. These patterns have been observed in several different countries[34,35], and extend to suicidal outcomes, particularly amongst girls[34]. Inequalities in poor mental health following the COVID-19 pandemic have also been reported for women[36-38], low-income households[36], and several groups minoritized by race and ethnicity[38], gender identity and sexual orientation[39], or migrant status[40].

Other shocks (i.e., food, energy and economic crises, global conflicts, racial injustice), in addition to ongoing climate change, also contribute to the inequitable distribution of mental health and disorder in our populations. These shocks affect people's freedom of movement, social connectedness, and levels of isolation and loneliness. They influence people's economic precarity through impacts on employment, income, education, food and housing security. They affect people's agency and autonomy by threat to life, livelihood and civil liberties, whether via experiences of interpersonal, institutional or systematic racism, or displacement through conflict and violence, political instability, or climate-related events. Most inescapably, these acute shocks belie a more chronic, pervasive exposure to negative social determinants which erode people's opportunities to sustain good mental health, recover from poor mental health, and prevent illness in the future. Repeated exposure to these determinants can create cycles of intergenerational disadvantage, which affect individual, familial and area-level inequalities in mental health[2,41].

At this critical juncture, we argue for the need to fully integrate

a social determinants perspective into the biopsychosocial model of mental health and illness. This requires establishing the extent to which various social determinants are causally implicated in producing poor mental health, and generating inequalities in risk for mental disorders. It also involves understanding the mechanisms and pathways through which these outcomes arise. Armed with this knowledge, we will be in a stronger position to fund, develop, test and implement evidence-based prevention strategies tackling the social determinants of mental health that shift the population-level expression of mental disorders. In turn, this can reduce gross inequities in the mental, physical and social outcomes that arise as a result of poor mental health. Such public mental health strategies should sit alongside existing evidence-based strategies in clinical psychiatry that have proved effective in treating individuals.

In this paper, we provide a roadmap towards this ambitious but necessary revolution. We first review the evidence that exists to support a causal association between key social determinants and mental health and disorder. We focus on those determinants which may have broad effects on several major mental disorders globally, and/or which may be highly prevalent in society, and thus have the potential to offer the biggest gains for public mental health prevention. These include social determinants that occur at the individual or family level (including socioeconomic disadvantage, discrimination, isolation and loneliness, early life adversities, childhood traumas), and those in the wider social environment (including neighbourhood disadvantage, social capital, the physical environment, and climate change). Our review pays special attention to inequalities experienced by women; lesbian, gay, bisexual, transgender and queer (LGBTQ+) people; migrants and ethnoracial minoritized groups. Throughout, we cite the strongest quantitative evidence, where available, and acknowledge any gaps in knowledge. One limitation of this approach is that the majority of the evidence we draw from – though by no means all[e.g.,42] – comes from high-income countries (HICs) in the Global North. Redressing the inequitable production of knowledge in this field is beyond the scope of our review, but provides a direct challenge to make global progress on the UN Sustainable Development Goal for mental health[12,43]. Where available, we highlight evidence collected in the Global South, but recognize that different contexts will also face unique social determinants of mental health that require dedicated attention.

We then introduce a preventive framework for conceptualizing how such social determinants affect the expression of mental health and disorder at the population level, and how this understanding can ground and guide prevention strategies to improve public mental health. In this framework, we introduce the fundamental idea of treating whole populations, which should sit alongside prevailing models of individual clinical care in psychiatry. Treatments here, broadly defined, may include universal, selective or indicated primary prevention strategies that intervene on social determinants of health aiming to affect the population-level expression of mental health and illness, as well as secondary and tertiary prevention strategies to help those with existing mental health problems. Using this framework, we then review the current strength of evidence on the efficacy and effectiveness of a (non-exhaustive) set of universal, selective and indicated strategies that intervene on social determinants for the prevention and alleviation of mental distress. In the final section of the paper, drawing together current evidence, we provide a set of seven recommendations for action, as a roadmap for improving population mental health and reducing inequities in mental health and disorder.

SOCIAL DETERMINANTS THAT IMPACT MENTAL HEALTH AND DISORDER: THE EVIDENCE

Social determinants at the individual level

Socioeconomic disadvantage

Socioeconomic disadvantage is a fundamental determinant of mental health outcomes over the life course[44-46]. Strong socioeconomic gradients have been observed for an array of mental health outcomes in HIC[45] and LMIC settings[42]. Socioeconomic disadvantage can be operationalized in several ways, and is a multifaceted construct encompassing different dimensions, including education[47,48], finance[49,50], occupation[51-53], and living standards[54,55]. All these dimensions have been associated with mental health and disorder, and social inequalities in mental health may arise from a series of interrelated structural and cultural processes operating in society.

According to structural explanations, social stratification creates unequal access to resources – such as wealth and knowledge – that help individuals avoid exposure to harmful stressors[46]. Higher levels of wealth and income enable access to key determinants of positive mental health, including adequate and safe housing[55], sufficient food security[54], and effective health care. Income losses appear to have a far greater impact on mental health than income gains[49], with further financial stressors such as income volatility, perceived job insecurity and moving into debt all linked to worsening mental health[50,56,57]. Poor mental health itself can also impact earnings and contribute to financial stress, meaning that the relationship between socioeconomic disadvantage and mental health is likely to be bi-directional[58]. Indeed, while there is a long-standing debate about the so-called "social causation" and "social drift" theories of mental disorders[46], recognizing the bi-directional and cyclical relationship between socioeconomic disadvantage and mental health is likely to be vital for promoting prevention strategies that interrupt the intergenerational transmission of environmental risks for mental disorders[2]. Since socioeconomic disadvantage is both a risk factor for, and a consequence of, mental disorders, establishing key periods over the life course to intervene is a critical step towards effective prevention. We note here the need for stronger causal inference methods to address these challenges in observational studies.

Early life exposure to socioeconomic disadvantage may be particularly harmful for later mental health. For example, in a systematic review of evidence in children and adolescents[59], 52 of 55 studies (mostly from HICs), including 25 longitudinal ones,

reported an inverse association of mental health problems with socioeconomic position. Children growing up in socioeconomic disadvantage were 2-3 times more likely to experience mental health problems than their non-disadvantaged peers, with risk associated with both duration and severity of exposure. A systematic review reported similar associations with respect to ADHD[60]. An inverse relationship between parental income during a child's upbringing and later schizophrenia risk has been also found in Denmark[61,62], independent of parental mental health and education. Birth cohort evidence from the UK also suggests that children growing up or transitioning into poverty are more likely to experience mental health problems by age 11, independent of maternal mental health[63]. Finally, there is also systematic review evidence from LMICs that supports (mostly cross-sectional, but extending to longitudinal) associations between poverty and depression in adulthood[42].

If causal, early life exposure to socioeconomic disadvantage may increase risk of mental health problems through several different mechanisms, based on potential biological, psychological and social pathways[64]. In LMIC settings, a systematic review concluded that education, food insecurity, socioeconomic position and financial stress had more consistent effects on risk for common mental disorders than income and employment[42]. Families lacking financial resources are less likely to have their basic needs met, including adequate nutrition, which prenatally has been shown to increase the risk of some psychiatric disorders, including schizophrenia, later in life (see below)[65]. Ongoing familial socioeconomic disadvantage is also likely to contribute to chronic stress for parents, which may affect parenting behaviours and the stability of family environments, and may also result in fewer longer-term educational and employment opportunities for children. Mental health inequalities according to education level have been seen across the lifespan. Leaving school at a younger age, fewer years in formal education, and having a lower level of education are each associated with poorer future mental health and increased risk of suicide[48,66]. Education is likely to impact mental health through a variety of means, such as determining one's future social status and income, although these associations are likely to be partially due to confounding by early-life factors such as childhood adversity[67].

Early life adversity

There is strong evidence that several early life (defined here as prenatal and perinatal) adversities – including maternal stress, obstetric complications, and malnutrition – can have profound effects on mental health and disorder decades later[68]. These events do not affect all people equally, making them strongly socially determined risk factors for offspring mental health. For example, parental socioeconomic status and experiences of income inequality are associated with adverse birth outcomes[69]. Furthermore, in the US, there is consistent evidence of racial/ethnic disparities in adverse maternal and neonatal outcomes (including preterm birth, low birthweight and infant mortality) and receipt of prenatal care[70], all of which are higher for Black, Hispanic and Indigenous groups than non-Hispanic White and Asian groups. These disparities are hypothesized to arise through structural racism that operates on a number of levels to affect "a woman's knowledge of prenatal care (individual); the amount of support she receives from her family, friends, and community (social); experiences with racism and other social and environmental stressors (social); the way she is treated by her care provider (institutional); and the policies and practices of her insurer (systemic)"[70, p.124].

There is good evidence that exposure to prenatal maternal stressors – including financial stress and relationship difficulties – is associated with increased risk of many (though not all) offspring behavioural and mental health outcomes, including neurocognitive development[71], negative affectivity[71], externalizing and internalizing problems in childhood[71], autistic traits[71], borderline personality disorder[71], anxiety[71], depression[71,72], and psychosis[68]. Nevertheless, this association has not been universally observed. For example, a systematic review on ADHD and autism spectrum disorder found that evidence was limited to low-quality case-control studies, raising doubts about the likelihood of a causal association [73].

Prenatal malnutrition following famine exposure has also been strongly associated with risk of psychotic disorders[65], notwithstanding similar issues around causality. A systematic review also found evidence to support a protective effect of prenatal multivitamin supplementation on autism spectrum disorder[74], but this was restricted to high-quality studies. Surprisingly few studies have examined the association between prenatal nutrition and common mental disorders, with no systematic review available, although some longitudinal evidence exists for childhood mood and behavioural outcomes[75-77], with associations persisting after adjustment for maternal perinatal mental health, prenatal smoking and alcohol use. Early life vitamin D deficiency has also been proposed as an explanation for higher risk of various psychiatric disorders[78], but recent causally-informed evidence does not support this for depression[79-81], schizophrenia[82] and Alzheimer's disease[81].

Understanding the causal mechanisms through which any prenatal exposure may affect offspring mental health remains a critical objective for psychiatric epidemiology. These associations may be particularly vulnerable to unobserved confounding and selection effects, most importantly by maternal mental health and behaviour. Cyclical relationships between poor perinatal mental health, social adversity, maternal stress, maternal behaviour (including alcohol and substance use), maternal care and prenatal nutrition[83] may lead to a sociodevelopmental cascade that increases exposure to adverse child outcomes (all of which have been associated with risk of mental disorders), including early life infections (with a stronger relationship between some infections and psychosis[68] rather than depression[84]), obstetric complications[68,85], altered neurodevelopment[86], childhood adversities[87], and behavioural and mental health difficulties[88]. If proven, this would warrant public mental health strategies focused on improving prenatal maternal, parental and familial conditions as an intervention strategy that could benefit multiple parent-child outcomes.

Childhood adversity

Childhood adversity is an especially well-characterized social determinant of mental ill health. Whilst no consensus definition exists, McLaughlin defines these adversities as "experiences that are likely to require significant adaptation by an average child and that represent a deviation from the expectable environment" [89, p.363]. To date, much research has focused on a "core set" of adversities that includes child maltreatment (i.e., physical, sexual or emotional abuse; neglect; exposure to domestic violence) and household dysfunction (e.g., substance use, mental ill health, or incarceration of a parent or other household member; parental separation or divorce). In a seminal study on these adverse childhood experiences[90], they were found to be associated with a 4- to 12-fold increased risk of depression, suicide attempt and substance abuse. Increasingly, the conceptualization of childhood adversity has expanded to include interpersonal adversities occurring outside of the home environment (e.g., bullying victimization)[91].

Experience of childhood adversity is unfortunately common [89,92,93]. For example, the World Mental Health Surveys estimate that around two in five individuals have experienced at least one form of childhood adversity[94]. These experiences are clustered in patterns that are unequally distributed throughout the population[95]. In particular, greater socioeconomic disadvantage, which can place increased stress on parents and families[96], is one of the clearest and strongest determinants of exposure to childhood adversities[95,97]; recent evidence suggests that this may be mediated by effects on parental mental health[97]. Children who grow up experiencing more family discord[98,99], who are born to adolescent mothers[95], and who grow up in single-parent households[99] are more likely to experience multiple childhood adversities. Moreover, given systemic inequalities in socioeconomic disadvantage, there is also strong evidence that women, people from ethnoracially minoritized backgrounds, and Indigenous populations are more likely to experience multiple childhood adversities[100,101].

Clear and consistent evidence has demonstrated associations between childhood adversity (both prospectively- and retrospectively-measured) and several poor mental health outcomes in childhood, adolescence and adulthood, including general psychopathology, depression, anxiety, self-harm, psychosis and suicide[95,102-105]. If causal, the population-attributable risk proportions (the percentage of disorder that could hypothetically be prevented via removal of the exposure) for childhood adversity are substantial, calculated at 28.2% of all psychiatric disorders amongst children and adolescents[92], and 29.8% amongst adults[94].

This epidemiological evidence strongly suggests that approaches to reduce childhood adversities and their impact are promising routes for reducing the incidence of mental disorders in the population[96]. Importantly, however, there is still much to learn about the complex relationship between childhood adversity and mental disorders. Recent findings from studies pertaining to measurement[91,106] and prediction modelling[107,108] offer important opportunities to support the development and evaluation of policies and interventions to address this widespread societal problem.

Migration

Migrants are exposed to a complex set of social determinants of mental health. This has resulted in a disproportionate burden of some mental health problems, in particular psychotic disorders. Elevated rates of psychotic disorders in migrants were first noted in 1932 by Ødergaard amongst Norwegian migrants to the US[109], and subsequent research has highlighted the consistency of this phenomenon amongst many migrant groups and their descendants[110], including both economic migrants[111] and refugees[112,113]. There is also consistent evidence of a high prevalence of post-traumatic stress disorders (PTSD) amongst refugees and asylum seekers[114].

Whether other psychiatric disorders – including depression, anxiety, non-psychotic bipolar disorder, and substance use disorders – and suicide are elevated amongst migrant groups is less clear, with some evidence suggesting that the rates of these conditions may even be lower among migrants than in the non-migrant majority population[111,115-117]. Most studies specifically concerned with common mental disorders in refugees, asylum seekers or forced migrants generally lack a comparator, but available evidence suggests that the prevalence of depression and anxiety may be higher in these displaced groups than in the general population[114,118].

Several explanations for these potentially divergent results exist. These include the possibility of selection effects, so that people with pre-existing mental health problems do not migrate. These effects are much less likely to exist amongst displaced persons. Elevated psychosis rates amongst both economic and refugee migrants may – *prima facie* – challenge these explanations, but younger age-at-migration has been associated with greater psychosis risk[119], meaning that the influence of positive selection would be weaker amongst those who emigrate at earlier ages.

Other explanations for elevated rates of psychotic disorders in migrants and their descendants, and of several psychiatric disorders in refugees and asylum seekers, include chronic exposure to socioeconomic disadvantage and social adversities before, during and after index migration[120,121]. For example, migrant groups may be exposed to many social, economic, political and environmental conditions that serve as push factors prior to migration and increase risk of mental health problems. These may include poverty, lack of employment opportunities, food insecurity, conflict, violence, and natural disasters[122,123]. The act of migrating also involves displacement and dislocation, which may be traumatic, compromise personal safety, create uncertainty and stress, and involve prolonged separation from family[124-126], and high levels of risk to life or personal safety[124]. For example, between 40 and 90% of asylum seekers report traumatic experiences during migration[118,122,127], including violence, exploitation, and detainment during the asylum-seeking process[128]. Finally, adapting to life in a host country can introduce challenges for migrants and refugees, including high levels of acculturative stress, exclusion from labour markets, precarious employment, housing insecurity, and socioeconomic deprivation[129,130].

There is strong evidence that the post-migratory environment is causally related to mental health problems amongst migrants and

their descendants[131]. While lower rates of mood and anxiety disorders have been noted in migrants compared with the host population[132], rates in children of migrants are similar or elevated compared with the majority population[132,133]. Risk of psychosis also remains elevated in children of migrants, and may persevere into the grandchildren generation[134]. Post-migratory experiences include exposure to discrimination and structural racism[135-139], and high levels of social isolation and exclusion[135,140,141]. It has been theorized that such experiences lead to psychosocial disempowerment[142,143], and there is recent evidence that this pathway may explain inequities in psychosis risk experienced by both migrants and ethnoracial minoritized groups[144]. Most people also migrate with the expectation of finding better opportunities in the host country[145,146], which may potentially affect mental health if they are not met[147]. Migrants also face barriers to high-quality, timely and culturally appropriate psychiatric care[148-150], affecting recovery from and long-term consequences of experiencing mental disorder.

Ethnoracial discrimination

Ethnoracial disparities across various mental disorders have been documented for decades, independent of migrant status, especially in HICs[110]. The patterns of disparities across racial and ethnic categories are complex, with levels of psychological distress and symptoms of common mental disorders higher in minoritized groups than White groups[151], but lower prevalence/incidence of diagnosed depression, anxiety, or substance use disorders in many ethnoracially minoritized groups[152,153]. In contrast, there is more consistent evidence of increased rates of psychotic symptoms *and* disorders in ethnoracial minoritized groups, particularly amongst groups perceived as more socioculturally distant from the racial or ethnic majority population in HICs[144,152]. For those with diagnosed mental disorders, there is strong evidence that many ethnoracial minoritized groups – and particularly people of Black ethnicities – experience more negative pathways into care and psychiatric treatment[154-156], resulting in higher levels of morbidity[157].

Many of these ethnoracial differences in the incidence, course and treatment of mental disorders have been linked with increased exposure to racial discrimination and structural racism among minoritized groups[144]. Socioenvironmental risk factors are thought to be driven by structural racism – i.e., by interconnected, racially inequitable systems (e.g., housing, education, employment, health care, the legal system) that reinforce each other[158] to stigmatize, discriminate and disempower marginalized people[159].

Racial discrimination involves major events such as experiencing interpersonal racism, exclusion from labour markets, and police harassment[159,160]. These experiences extend to racial microaggressions, which are more subtle everyday expressions of discrimination through being slighted, made to feel inferior, stereotyped, and/or invalidated due to race or ethnicity[161,162]. Racial discrimination has been prospectively associated with poorer mental health and distress[163], common mental disorders[164,165], psychotic disorders[166], and risk for conversion to psychosis among those at high risk[167]. Racial discrimination is also identified as a reason why, even among non-poor upwardly mobile Black Americans, the risk of negative health outcomes is higher than for their poor White American counterparts[168].

Structural racism can also increase exposure to other risk factors for mental disorders at the individual level. For example, recent research from the Adolescent Brain Cognitive Development (ABCD) study in the US[169] found that Black children were more likely to be exposed to traumatic events, family conflict and material hardship compared with White children. Black children also had lower brain volumes in key areas associated with mental health problems, including the amygdala, the hippocampus and prefrontal cortex. These race-related disparities were attenuated after adjustment for exposure to childhood adversities. Data from the same study indicated that Black and Hispanic children are more likely to report psychotic-like experiences than White children, and that this is partially accounted for by experiences of racial discrimination[170]. This supports further research from Europe and Brazil showing that elevated rates of psychotic disorders in several ethnoracially minoritized groups are attenuated to the null after accounting for experiences of structural inequalities (socioeconomic disadvantage, poor education, childhood adversity) and psychosocial disempowerment (discrimination, social exclusion)[144]. Further research is now required to identify the biopsychosocial pathways through which stressors associated with experiences of minoritization and discrimination shape mental health outcomes[171].

Inequalities experienced by the LGBTQ+ community

Interest in the social determinants of health and mental health in LGBTQ+ people has surged in recent years. Acceptance and social inclusion of these people have improved consistently over recent decades, rising steadily from the late 1970s to the early 2010s[172], and show signs of increasing further during the current decade[173]. Nonetheless, LGBTQ+ people continue to be exposed to acts of marginalization and moral panics[51,174-176], which can have harmful effects on mental health[51,177,178]. Marginalization occurs through discrimination, stigma, anti-queer and anti-trans policies, bullying/harassment, and other violence occurring at both micro-levels (e.g., microaggressions) and macro-levels (e.g., denial of human rights and health service access)[177,179-183], placing these people at greater risk of social exclusion and loneliness[182]. Minority stress following exposure to these experiences is thought to be a key process in determining mental health outcomes amongst LGBTQ+ people[184-188].

There is substantial evidence to suggest that experiences of prejudice, stigma, discrimination, violence, and assumptions of cisheteronormativity (i.e., the implicit and explicit assumption and building of society which views everyone as cisgender and heterosexual) hold substantial associations with poor mental health and well-being in LGBTQ+ people across the lifespan[178,189-191]. Parental and peer support, the formation of romantic relationships, and navigating the coming-out process, appear to affect some of

the initial mental health outcomes in LGBTQ+ youth[192,193]. For those who are supported in these processes, there is evidence of higher self-esteem and lower depressive symptomatology, compared with people who do not receive such support[193,194]. Similarly, in recent research, navigating homophobia, biphobia and transphobia, as well as feeling unable to talk about their experiences and navigating cis-heteronormativity, all increase the risk of poor mental health, specifically depression, anxiety and suicidality [192,195,196]. There is some evidence that mental health outcomes are worse for LGBTQ+ people who experience poverty, or who are from ethnoracial minoritized backgrounds, highlighting the intersectional ways in which social inequalities affect mental health[187].

Sex-based inequalities

The incidence and prevalence of many psychiatric disorders differ by biological sex. For example, depression and anxiety are approximately twice as common in women than men[197], a pattern that seems reversed in non-affective psychotic disorders (although this is most pronounced for first onset in early adulthood)[198]. Bipolar disorder occurs with more uniformity[198]. The lifetime prevalence of externalizing and substance use disorders is higher in males[197], who are also more likely to die by suicide throughout the world regions[199]. The extent to which these differences are biologically and/or socially determined remains unclear for some conditions, as discussed below.

Several potential drivers for sex differences in the incidence/prevalence of common mental disorders have been proposed, including ascertainment biases, family environment, social norms, social support, hormones and neurotransmitters[200]. Although available research is limited, there is some evidence challenging the notion that these differences are solely biologically determined[200]. First, the magnitude of sex differences in common mental disorders varies substantially between countries[201], which would not be predicted on the basis of biological determinism alone. Second, there is accumulating evidence for the causal role of certain gendered social risk factors[202]. For example, the contexts in which children grow up and are socialized, alongside differences in social and cultural norms and behaviours, are important considerations when trying to understand sex differences in mental health and disorder. Some risk factors are strongly gendered (i.e., intimate partner violence is more commonly experienced by women), and preventive efforts to tackle their causes are required in education, law and wider society[203].

Other conditions, including eating disorders and autism spectrum disorder, have traditionally exhibited more dramatic sex differences in their occurrence, with systematic review evidence that the prevalence of eating disorders is up to four times greater in biological females than males[204], a ratio reversed for autism spectrum disorder[205]. Recent research on this latter condition has investigated the extent to which these sex differences arise from biases in case ascertainment and detection[205-207]. Some evidence suggests that part of the gap could be due to the validity of diagnostic criteria and instruments used to diagnose the disorder, which prioritize symptoms labelled as male-typic (e.g., overt restricted interests) over symptoms labelled as female-typic (e.g., internalizing problems and emotional difficulties)[207,208]. Likewise, some authors have questioned whether eating disorders are likely to be underdiagnosed in biological males[206], partly as a result of gendered social determinants including stigmatization, trauma and perceptions of masculinity.

An important consideration in understanding how inequalities contribute to sex and gender differences in mental health is that most societies are structured in ways that generally privilege cismen over all other genders, with even legal equality being achieved only in a few countries worldwide[209]. Nonetheless, the relationship between gender equality and gendered differences in mental health problems is complex. For example, wider gender gaps in depression have been observed in countries with higher levels of gender equality amongst both adults and adolescents[201,210]. Various theories have been proposed to explain this evidence. For example, women may experience a mismatch between expectations of equality and reality[211], and/or face the burden of multiple roles as their involvement in the labour market increases in ways that are not matched by compensatory increases in men's involvement in domestic, childrearing and other domains[212]. Indeed, in countries with a dual-earner model, where employment, wage earning, and domestic and childcare tasks are shared more equitably between men and women, gender inequality in mental health risks appears to be smaller[213].

Loneliness and social isolation

Interest in loneliness[214,215] and social isolation[43,215] as social determinants of mental health and disorder has burgeoned in the last decade. The distinction between these conditions is important, and has implications for causal pathways, which have not yet been well described, as well as for targeted intervention.

While social isolation is an objective measure of the number of social connections, quantified in terms of social network size and number of meaningful ties[216], loneliness describes the subjective and distressing mismatch between a person's desired and perceived quantity and/or quality of social relationships[217]. It is therefore possible to have a large number of social contacts but still experience feelings of loneliness, or vice versa. Transient experiences of social isolation or loneliness are common after moving house, migration or bereavement, serving as a prompt to form friendships, such that loneliness could be viewed as an evolutionary advantage in this context[218]. However, where chronic loneliness sets in, as indicated by consistent problems with fostering meaningful relationships[219], this is more likely to adversely impact mental health. Estimates of the prevalence of loneliness internationally range from 9 to 14% in adolescents, falling to 3-10% in middle age, and rising again to 5-21% in older adults[220]. Prevalence estimates for social isolation (around 25%) tend to relate to older adults, and derive from low-quality evidence[221].

The majority of studies investigating longitudinal associations between loneliness or social isolation and mental health have focused on depression, reporting a longitudinal (and bi-directional [222-224]) association of loneliness with depression onset[214], severity[225] and recovery[226]. Such research estimates that 11-18% of cases could potentially be prevented if loneliness were eliminated[225], predicated on causality. There is also evidence that loneliness is longitudinally (and bi-directionally[227]) associated with anxiety[214], as well as with suicide attempt[228]. Both social isolation and loneliness are also associated with suicide among men[229]. In children, whose mental health and well-being were a particular concern in periods of social restriction during the COVID-19 pandemic, both loneliness and social isolation are also associated with depression onset[230]. A mediation analysis has found support for a pathway from social isolation to loneliness and subsequent depression and anxiety symptoms[223], though again bi-directionality was observed. Depression itself may also be a mediator of the association between loneliness and suicide attempt[228].

For other mental health outcomes, longitudinal evidence is just emerging. Cross-sectional research has found associations between loneliness and dementia, paranoia and psychotic symptoms[231], but these tell us little about causal pathways. Recent longitudinal evidence is often based on selected and/or small samples, though providing some evidence that loneliness in young adults is longitudinally associated with psychotic-like symptoms (but not vice versa)[232]. For dementia, a systematic review of mostly longitudinal studies reported stronger associations with measures of social engagement and isolation than of loneliness[233].

Such is the interest in addressing loneliness to prevent and reduce the severity of mental health problems[234] that the UK government has issued an international review of evidence gaps with a call for researchers to address them[234]. Particular priorities in relation to mental health are understanding mechanisms, investigating the impact of loneliness and social isolation in marginalized groups, and addressing the lack of rigorous trials of psychological and social interventions to address these key risk factors. Additional gaps related to this field are estimates of the prevalence and correlates of social isolation in groups other than older adults.

Social determinants in the wider social environment

Neighbourhood socioeconomic disadvantage and inequality

Some of the earliest studies in psychiatric epidemiology investigated whether neighbourhood social determinants were associated with the incidence and prevalence of mental disorders[235]. Early cross-sectional studies in high-income settings identified particularly high incidence rates of some severe mental disorders – especially schizophrenia and non-affective psychotic disorders more generally[235-237] – in more urban and socioeconomically disadvantaged neighbourhoods[235,236]. As with individual socioeconomic status (see above), these studies generated considerable debate about the relative contributions of social selection (i.e., downward drift of vulnerable individuals into socially disadvantaged environments) and social causation. This debate continues to date. While there is now consistent evidence that people who are born and raised in more urban and socially disadvantaged neighbourhoods in HICs are at greater risk of non-affective psychotic disorders[238-241], even after adjustment for individual-level measures of socioeconomic status[239-242], other research has suggested that this may be due to intergenerational selection[243], whereby families with greater genetic liability to severe mental disorders are more likely to remain or drift into more disadvantaged neighbourhoods over time.

In the last decade, epidemiological studies that attempt to leverage genetic information to strengthen causal inference from observational data have been published on this issue, with equivocal results. For example, a nationwide longitudinal study of population density and neighbourhood deprivation at age 15 and risk for later schizophrenia (and depression) found that associations were progressively attenuated to the null in analyses restricted to first-degree cousins and siblings[243], who shared, on average, 12.5% and 50% of genes respectively, implying that such associations in unrestricted population samples are due to unmeasured familial confounding. Some additional studies, based on polygenic risk scores (PRS) for schizophrenia, have also found that increased genetic liability predicts living in more densely populated[244], urban[245,246] and disordered[245] areas in adulthood[244] and adolescence[245,246]. By contrast, two studies have found no relationship between PRS for schizophrenia and population density at birth[246,247]. One further study found no evidence that PRS for schizophrenia predicted deprivation in adolescence[245], although another study has shown such a relationship at birth[247]. Of these studies, three went on to test whether genetic liability confounded longitudinal associations of neighbourhood deprivation[245,247] and population density[246]/urbanicity[245] with psychosis risk; all found that these associations persisted after adjustment for measures of genetic liability.

Studies of other mental disorders, including depression, anxiety and bipolar disorder, have generally found less consistent gradients with neighbourhood social disadvantage and urban-rural status[248,249]. Most evidence has been cross-sectional, remains equivocal and is largely based in high-income settings[248,249]. Longitudinal studies of incidence are sparse, and those that have been conducted have shown mixed results. Studies based on treated depression diagnosed in secondary care support an association with urban birth and upbringing[243,250], while no such pattern has been observed in comparable studies of bipolar disorder[251], or in longitudinal population-based samples of depression and anxiety[252,253]. For suicide, there is consistent evidence that risk is elevated in more disadvantaged, socially fragmented rural rather than urban communities[249].

Neighbourhood socioeconomic disadvantage is, of course, a multidimensional construct. Interestingly, a recent systematic review found that one aspect of neighbourhood disadvantage – i.e., perceived or objective levels of crime – was associated with several mental health outcomes, including depression, psychological distress, anxiety and psychosis[254], suggesting that specific aspects of

that disadvantage may represent putative targets for prevention. Nonetheless, the causal nature of this effect remains to be clarified, since the effects of crime were diminished after adjustment for socioeconomic deprivation, and samples where perceived crime and mental health are measured in the same respondents may be prone to both same-source bias and reverse causality.

Another important neighbourhood social determinant, related to absolute socioeconomic deprivation, is socioeconomic inequality. The aforementioned studies typically estimated associations between average levels of neighbourhood socioeconomic disadvantage and mental health. In contrast, studies concerned with inequality seek to understand whether the unequal distribution of resources (typically based on income) within a population, community or neighbourhood is associated with health. Across HICs, there is robust correlational evidence that countries with higher levels of income inequality experience worse population mental health[255]. A recent systematic review on within-country income inequality also found that two thirds of included studies observed statistically significant associations, with the majority (55%) supportive of a relationship between *higher* inequality and *worse* mental health (the so-called "income inequality hypothesis")[256]. A further 12% of studies found evidence that *higher* income inequality was associated with *better* mental health (supportive of the so-called "mixed neighbourhood hypothesis", which purports that the presence of people with higher income levels in a neighbourhood results in universal improvements in living standards, access to resources and health). Studies supportive of the income inequality hypothesis were more common for all outcomes studied, including depression, psychosis and general mental health, and were conducted in both HICs and LMICs[256]: Their findings persisted after control for absolute levels of socioeconomic deprivation.

Although different theories exist on how higher levels of inequality may lead to worse mental health[256], one possible explanation is that highly unequal neighbourhoods erode levels of trust, weaken social ties, and reduce positive reciprocity, leading to greater exposure to stressogenic environments that negatively affect mental health. This raises the possibility that neighbourhood social capital and other related constructs may be important social determinants of mental health, as reviewed in the next section.

Social capital, fragmentation and ethnic density

Social capital encapsulates the nature and stock of shared social resources, relationships and networks available for groups to achieve common goals or outcomes. It encompasses concepts of trust, reciprocity, norms of behaviour, rules for cooperation, collective attitudes, shared language, and the size and structure of informal and formal networks. As such, it is a complex, multidimensional construct, theorized to operate at different levels (i.e., individual, school, workplace, neighbourhood, regional, national); be a property of individuals or groups; and have different conceptual dimensions (e.g., structural/cognitive/relational, bonding/bridging/linking[257]). Given such complexities, it would be surprising if there was a universal effect of social capital on health. Rather, particular dimensions of social capital could be either protective or harmful, dependent on the dimension, level and/or group exposed.

Despite this challenge, a recent umbrella review concluded that higher levels of social capital were generally associated with better mental health outcomes[258], based on a set of systematic reviews that covered psychological distress, depression and anxiety, and behavioural problems and well-being in children. Two reviews from that paper found evidence of a stronger effect of *cognitive* (shared language, values and codes) than *structural* (networks, rules, roles) social capital on common mental disorders[258].

To our knowledge, systematic review evidence on social capital and suicidal outcomes is missing. Most studies in this space are ecological[259-263], with several reporting national[263], regional[261,262] or neighbourhood-level[259] associations between higher levels of social capital (particularly trust) and lower suicide rates. Nonetheless, effect sizes for suicidal outcomes appear modest, and are often limited to – or stronger in – various subgroups, including White men and women[261], non-Hispanic Black groups[262], men alone[262], younger groups[259] or unmarried people[259], or are sometimes not found at all[260]. One of the few longitudinal studies conducted to date reported that higher structural social capital was associated with lower suicide rates in South Korea[264], but further high-quality evidence is required.

A recent scoping review of social capital and psychosis found mixed evidence of an association[257], with considerable heterogeneity in study design, definitions of social capital, assessment instruments, setting, control for confounders, and findings. As with other mental health outcomes, longitudinal evidence is generally missing. Of nine studies, four reported an overall protective effect of higher social capital on psychosis risk, two found null results, and three reported subgroup or nonlinear effects; here, protective effects were restricted to women[265], those with a family history of psychosis[266], or people living in areas with either the lowest or highest levels of social capital[267], especially among ethnoracially minoritized groups.

These subgroup and curvilinear effects may provide important opportunities to triangulate evidence about how exposure to contextual factors in the social environment generates inequalities in mental health between different groups. In the example above, from the ÆSOP study of first-episode psychosis in Southeast London[267], rates of schizophrenia were higher for people living in low or high social capital neighbourhoods, compared with moderate levels. Social capital was estimated in a random sample of residents via a separate cross-sectional survey. Importantly, response bias meant that White residents were over-represented in the survey, biasing estimates of social capital towards those perceived by this group. In areas with high social capital – as disproportionately perceived by White respondents – psychosis rates were only substantially elevated amongst ethnoracial minoritized residents, who may have been excluded from accessing this social capital. Interestingly, this has recently been replicated in longitudinal research from Sweden amongst people with a migrant heritage[268], and similar findings have been observed in other contexts[269].

These findings may provide a mechanistic explanation for observations from a related literature that higher levels of ethnic density – the degree to which one's ethnoracial group is represented in a neighbourhood – are associated with lower levels of psychosis[270]. Such findings also extend to migrants[271]. Ethnic density is theorized to have a protective effect on mental health via increased social capital (particularly bonding social capital) amongst people who share more similar language, norms, codes, customs and cultural backgrounds. These resources may help buffer against social stressors[144,272]. Relatedly, higher rates of psychosis are observed in more socially fragmented neighbourhoods[273], an effect that appears to persist at school level for young people[274]. A systematic review[275] has demonstrated that evidence for a protective ethnic density effect is strongest for psychosis[270,276], and extends to suicide[277-279], but is less consistent or strong for anxiety and depressive disorders. Recent systematic review evidence also suggests that the protective effect of high ethnic density on psychosis risk is more consistent for Black and Latino populations, with mixed findings for Asian ones[270].

Ethnic density and social capital may be particularly important during childhood. For example, one study found evidence that low ethnic density during childhood was associated with later increased psychosis risk[276]. This may be linked to greater social and cultural isolation, or increased exposure to other risk factors for mental health problems, such as bullying[280]. There is also longitudinal evidence that social capital in childhood buffers the impact of earlier childhood adversity on adolescent mental health problems[281]. Recent cross-sectional data from the National Comorbidity Survey (Adolescent Supplement) in the US also suggest that both school-level bonding and perceived neighbourhood social capital are associated with lower risk of mood and anxiety disorders in young people[282].

As with social capital, the relationship between ethnic density and mental health outcomes may be nonlinear[283]. Very high levels of ethnic density (>80%) are indicative of racial segregation[283], and may be related to poorer mental health for Black Americans and Asian Americans in the US[283], as well as for some South Asian groups in the UK[284]. In this latter country, mental well-being was found to be poorest for people living in the most segregated communities, an effect larger for Black participants and independent of ethnic density[285]. In highly segregated neighbourhoods, the buffering effect of high ethnic density may be eroded as exposure to a range of other risk factors for mental health problems increases, including social exclusion, deprivation, discrimination, violence and crime. These social determinants tend to arise as downstream effects of interpersonal, institutional and structural processes and policies that govern patterns of residential organization[286].

Physical environment

Physical environment encompasses the built environment (housing quality, density and type; urban design), exposure to pollution (particularly air and noise pollution), access to green and blue space, and climate change. We consider physical environment as a potential social determinant of mental health because exposure to protective or harmful physical environments is rarely randomly distributed within or between populations. Rather, exposure is influenced by many factors already described in this paper, including socioeconomic position, minoritization, and structural discrimination in policies, institutions and systems that govern (in)equitable access to housing, education, employment and income[287]. Given the high correlation between physical and social environmental adversities, teasing out their causal mechanisms remains a challenge, which has led two systematic reviews conducted in 2007[288] and 2018[289] to conclude that there was a lack of robust research on the role of physical environment in mental health, with a particular paucity of high-quality longitudinal research.

Nonetheless, some evidence supports an association between mental health and specific aspects of the physical environment. For example, longitudinal research suggests that housing regeneration programs are associated with improvements in depression, anxiety and general mental health outcomes[55,288]. Housing disadvantage is also associated with worse mental health in longitudinal research[55], and may lead to increased residential mobility during childhood, which itself has been longitudinally associated with more emotional and behavioural problems[290], depression[290] and psychosis[291] later in life, independent of material disadvantage, education and social adversities. In further longitudinal research, children growing up in poorer built environments experienced more emotional symptoms and conduct problems at age 3 years[292].

Exposure to some air pollutants has been associated with mental health and disorder, including in case-only study designs (i.e., self-controlled case series, case-crossover designs) that control for short-term time invariant confounders[293]. A systematic review of the effects of particulate matter ($PM_{2.5}$ or PM_{10}, i.e. finer than 2.5 or 10 microns in diameter) reported consistent evidence that short- and long-term exposure to $PM_{2.5}$ was associated with increased risk of depression and anxiety, while short-term exposure to PM_{10} was associated with suicide risk[293]. The depression association has since been confirmed in a subsequent review[294], and may extend to other air pollutants, including ozone (O_3) and nitrogen dioxide (NO_2). However, limitations remain, including publication bias, failure to consider multiple pollutants simultaneously, and a predominantly Global North focus (although with exceptions[295]). It also remains unclear whether observed associations are mediated by effects of pollution on physical health, particularly on early life neurodevelopment[296,297]. Systematic review evidence supports a link between prenatal/perinatal exposure to $PM_{2.5}$ and risk of autism spectrum disorder in offspring[298]. Findings for other mental health outcomes remain sparse, although there is emerging evidence of a relationship between nitrogen oxides and psychosis[299,300].

Evidence on the association of green and blue space with mental health is predominantly based on heterogeneous measures, unrepresentative samples, and cross-sectional study designs, resulting in mixed findings[301-304]. Overall, there are currently insufficient high-quality data to support this association.

Interest is growing in the role that climate change may have on mental health. Various mechanisms may be involved, from increased anxiety or depression arising from existential concerns for the future, to exposure to social adversities arising as a result of climate change, including job loss, housing insecurity, displacement, food insecurity and conflict. While high-quality direct evidence of an impact of climate change on mental health remains missing, our review highlights how social adversities that may occur following climate change could exacerbate mental health inequalities.

A PREVENTIVE FRAMEWORK FOR POPULATION MENTAL HEALTH

Preventive approaches are paramount to enable meaningful progress in reducing the prevalence and impact of social determinants that negatively affect population mental health. Prevention in psychiatry encompasses the mitigation or removal of risk modifying factors and the enhancement of protective factors linked to mental disorders[305]. Here, the goal is to lower the incidence, prevalence and recurrence of mental disorders, and the burden placed upon individuals, their families and wider society[306]. Given the huge direct and indirect costs of mental disorders to individuals and to society[307], there are strong ethical and economic cases for prevention in psychiatry[308]. However, there are also costs to prevention, some of them paradoxical, which we consider below.

Prevention strategies are best grounded in a thorough understanding of the epidemiological characteristics of the relevant condition, and a working – although not necessarily perfect – model of causation[309]. We recognize that screening, early detection, and diagnostic testing are essential aspects of an effective prevention strategy for mental ill health[310]. While other reviews have considered these clinical tools in great detail[311,312], we restrict our review of such tools to those that explicitly aim to intervene on social determinants of mental ill health.

Frameworks for prevention

The WHO recognizes three levels of prevention: primary, secondary and tertiary (see Table 1). Whilst the latter two prevention levels are critical for reducing the burden of mental disorders through early intervention (secondary prevention) and ongoing management (tertiary prevention), action regarding social determinants falls mainly within the domain of primary prevention. Therefore, although we briefly overview evidence from all three levels in the following section, we devote most of our attention to primary prevention.

Primary prevention focuses on preventing the onset of mental disorders. This level of prevention includes universal, selective and indicated strategies, with interventions classified on the basis of the risk of individuals or sub-populations to develop a mental disorder.

Universal prevention strategies focus on entire populations, agnostic to risk status. Classic examples include fluoridation of drinking water to prevent dental caries, or folic acid fortification in flour to reduce neural tube defects during embryogenesis[313]. In a mental health context, examples may include teaching school children about emotions and mental health, or the introduction of a universal basic income, which aim to prevent mental disorders in addition to potentially bringing wider benefits to society. However, the potential benefits of any population-centred approach need to be tempered by the fact that modifiable risk factors are usually distributed unequally. Some people are at high risk, whereas most have a lower baseline risk of developing a disorder. In other terms, most of the burden of mental disorder in the population comes not from the small proportion of people at the highest risk, but rather from the far larger proportion of people with moderate or slightly above-average risk. The use of universal preventive interventions, therefore, has unequal costs and benefits in different individuals.

G. Rose, a British epidemiologist, considered the implications of this[309]. He noted that, when we study disease incidence in a single

Table 1 World Health Organization's classification of preventive approaches for mental disorders (adapted from Fusar-Poli et al[312])

Public health framework	US Institute of Medicine
Primary prevention aims at preventing the new onset (incidence) of one or more mental disorders, or of suicidal ideation.	
	Universal prevention targets the general public, or a whole population that has not been identified on the basis of increased risk.
	Selective prevention targets individuals or subgroups of the population whose risk of developing a mental disorder is significantly higher than average, as evidenced by biological, psychological or social risk factors.
	Indicated prevention targets high-risk people who are identified as having minimal but detectable signs or symptoms foreshadowing mental disorder, or biological markers indicating predisposition for mental disorders, but who do not meet diagnostic criteria for disorder at that time.
Secondary prevention aims to lower the prevalence of established cases of the disorder or illness in the population (prevalence) through early identification and treatment of diagnosable diseases.	
Tertiary prevention includes interventions that reduce disability, enhance rehabilitation and prevent relapses or recurrences of the illness.	

population, we see determinants – genetic or environmental – of the position of individuals within the risk distribution. However, this can leave us blind to huge differences in risk and disease incidence that may exist between populations, even though the individual determinants may be similar in both. These differences between populations, summarized by the population mean of a normally distributed risk factor, can be due to factors that are distinct from those that determine individual risk within those populations; individual risk can be understood only within that wider context. The crux of Rose's argument is that more cases of a disorder may be prevented by focusing on shifting the population mean (or other measure of central tendency) to make the whole distribution of the sicker population's risk profile look more like the healthier's one, rather than by targeting the minority at very high risk in the population (see Figure 1). The "prevention paradox" is the potential downside of this strategy; while the prevention may come with some costs for all – even if only a matter of inconvenience – most individuals will receive little to no benefit from the intervention, even though the benefits for the population as a whole may be large[314].

Much of Rose's work considered physical health, particularly cardiovascular disease, but he believed that the same principles would apply to mental disorders. As an example, Polek et al[315] showed the implications of a normally distributed risk factor (e.g., mental distress) for the occurrence of suicidal thoughts and non-suicidal self-injury in a sample of adolescents and young adults. While those with very high distress values (three standard deviations above the mean) are at highest relative risk, the majority of these outcomes occur in those at medium risk – one or two standard deviations above the mean. If the whole population distribution could be shifted to the left, then more occurrences of suicidal thoughts and non-suicidal self-injury would be prevented than using a strategy focused on the few at highest risk[315]. The full implications of this approach are yet to be explored throughout preventive psychiatry, but there is clear evidence that this is likely to be a fruitful area for important public mental health concerns, including common mental disorders[316,317] and suicidality[315,318]. The implications are increasingly discussed[310,319], but may only be fully appreciated when large-scale prevention studies focusing on common risk factors for multiple outcomes include measures of mental health routinely.

Although a strong proponent of universal approaches, Rose acknowledged that an effective prevention strategy should also encompass selective and indicated approaches[320]. Selective prevention strategies target individuals or sub-populations who have higher risk than the general population for onset of mental disorder. This risk may be assessed using a biopsychosocial model, through the evaluation of biological, psychological or social risk factors for mental ill health in individuals or subgroups of the population. Intervening in this way, particularly if early in development, may serve to interrupt some of the pathways that lead from risk factors to mental disorder. Indicated prevention refers

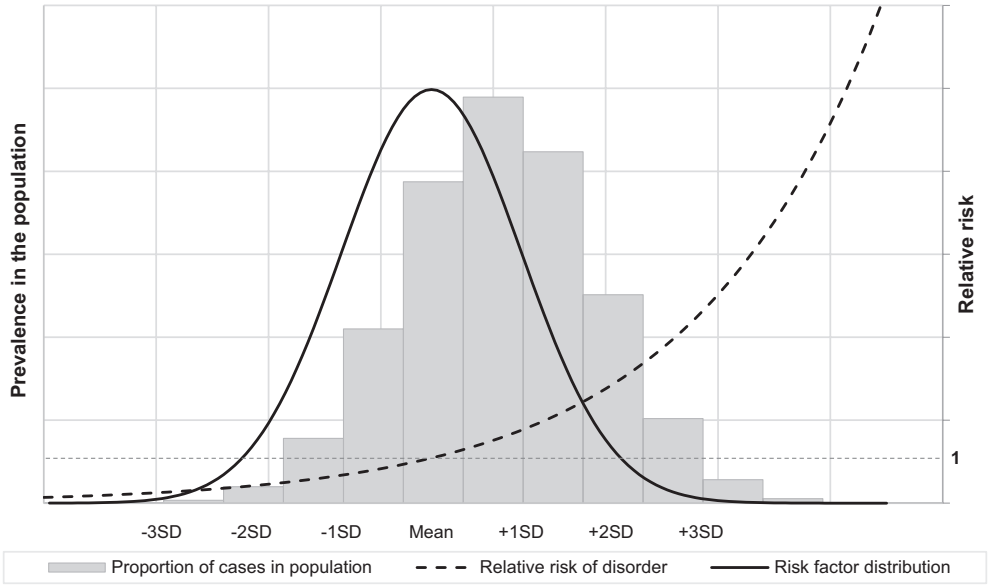

Figure 1 Hypothetical relationship between a normally distributed risk factor, relative risk of mental disorder and the proportion of cases in the general population. A risk factor for mental disorder is normally distributed in the population with a hypothetical mean and standard deviation, SD (bell curve indicated by solid black line). That risk factor is associated with a hypothetical relative risk of mental disorder, indicated by the dashed black exponential curve. For convenience, we set the relative risk to be 1 (grey dashed horizontal line) at the mean level of exposure to that risk factor. The hypothetical proportion of cases that arise in the population are indicated by the grey bars. Under these assumptions, most cases of disorder in the population will occur for those only exposed to moderate levels of the risk factor (from the mean to +2 SD above the mean). Fewer cases will be generated by the small proportion of the population beyond +3 SD above the mean, even though they are at substantially greater relative risk. Thus, following G. Rose's argument[309], more cases of disorder in a population may be prevented by intervening at lower levels of exposure in the general population than by targeting high-risk groups. This hypothetical argument has been confirmed in psychiatry (see, for example, Polek et al[315]).

to interventions designed for high-risk populations who are already identified as having symptomatology of mental disorder, but whose symptoms are sub-threshold for diagnosis.

Importantly, different levels of prevention may be additive, such that an individual may at once be the target of multiple levels of prevention strategies. This is perhaps demonstrated most clearly in schools, where so-called "multi-tiered systems of support" offer a gradated approach to student mental health, whereby all students receive universal interventions, and a smaller proportion are offered selective and/or indicated interventions, depending on risk status[321]. Such approaches can be adapted depending on context[322].

Prioritizing primary prevention

As we argue throughout this paper, social determinants represent some of the most modifiable intervention targets in a field where the development of new treatments for established disorders has largely stagnated. In contrast to other areas of medicine in which preventive approaches have established strong roots, approaches to prevention in psychiatry are inequitably prioritized, with the majority of available resources devoted to secondary (and tertiary) treatment of existing mental disorders (and their consequences), rather than preventing the onset of new disorders[323]. The dearth of action on primary prevention in mental health has been recast as one of the grand challenges in global mental health[324], and very likely hinders progress in reducing the incidence, prevalence and burden of mental disorders that afflict society[319].

PREVENTION STRATEGIES THAT ADDRESS SOCIAL DETERMINANTS: THE EVIDENCE

In this section, we use the preventive framework introduced above to review evidence for the efficacy of prevention strategies that target some of the major social determinants of mental health outlined earlier. We principally focus on primary prevention strategies, including universal, selective and indicated approaches. We also briefly review important secondary and tertiary prevention strategies that aim to promote recovery in those with established conditions. We focus on prevention strategies where we believe evidence is strongest (summarized in Figure 2), based on systematic reviews, randomized controlled trials (RCTs) or quasi-experimental evidence, where available. Additionally, we highlight areas where the evidence base is weaker, equivocal or absent. We also draw the readers' attention to reviews and reports of prevention strategies that aim to promote mental health and reduce mental distress and disorder[312,325-327].

We believe that the strategies that are particularly crucial for effective public mental health promotion and prevention are those which target social determinants in the early life course, beginning prenatally and extending into infancy, childhood and adolescence. There are several reasons to support this: a) 50% of all mental health conditions begin by age 18[19]; b) many of the antecedents of mental disorders begin early in life; c) preventing the onset of these problems earlier provides the best opportunity to interrupt intergenerational transmission of cyclical relationships between social determinants and mental health problems; d) the incidence and prevalence of mental health problems and disorders amongst children and young people is increasing, making this an imperative matter of social justice.

Universal prevention strategies

Parenting interventions

Parents play a crucial role in the emotional and behavioural development of a child. Consequently, many programs have been developed to enhance positive aspects of the parents' influence. Proactive and positive parenting techniques increase parent-child attachment and build self-esteem and confidence, which reduce behavioural problems[328,329]. The most common parenting programs are group-based, which may be a cost-effective method of reaching their goals, and last 8-12 weeks, with 1-2 hour sessions weekly[328,329].

Evidence consistently supports the efficacy of these programs in improving child mental health. For example, a systematic review of 24 intervention trials of short-term group-based parenting programs for children under 4 years old found that the programs had beneficial effects on overall child mental health and behaviour, as well as on parent-child interaction[329]. There is further systematic review evidence that two of the most common parenting interventions – the *Triple P* program[330] and the *Incredible Years* program[331] – reduce disruptive behaviour in this age group. The effects of parenting interventions may be more pronounced for externalizing than internalizing symptoms[329], although there is also strong systematic review evidence from RCTs supporting beneficial effects for the latter[332]. A remarkable finding from one review was that the estimated number needed to prevent one case of adolescent anxiety was only 10, a number which is much smaller than that for many common medical interventions[332]. With that in mind, it is perhaps not surprising that cost-benefit analyses of common parenting programs demonstrate cost savings[330].

A recent trial described a short (four 90 min sessions) perinatal parenting intervention that focused on sharing and understanding parenting roles in a co-parenting model[333]. The intervention aimed to reduce parenting stress to improve child outcomes. When the child was aged 1 year, parents in the intervention arm rated their offspring as having lower negative emotionality and lower externalizing symptoms, although these effects did not extend to age 2 years, 20 months after the program conclusion.

There is also evidence from a review of 48 trials that parenting interventions lead to benefits for parents as well as children, including reductions in parental depression, anxiety, stress, anger and guilt, and increases in confidence and relationship satisfaction[328]. Perhaps as a consequence, studies of the *Triple P* parenting program have also shown that participation is associated with reductions in child abuse and maltreatment[330]. From a global

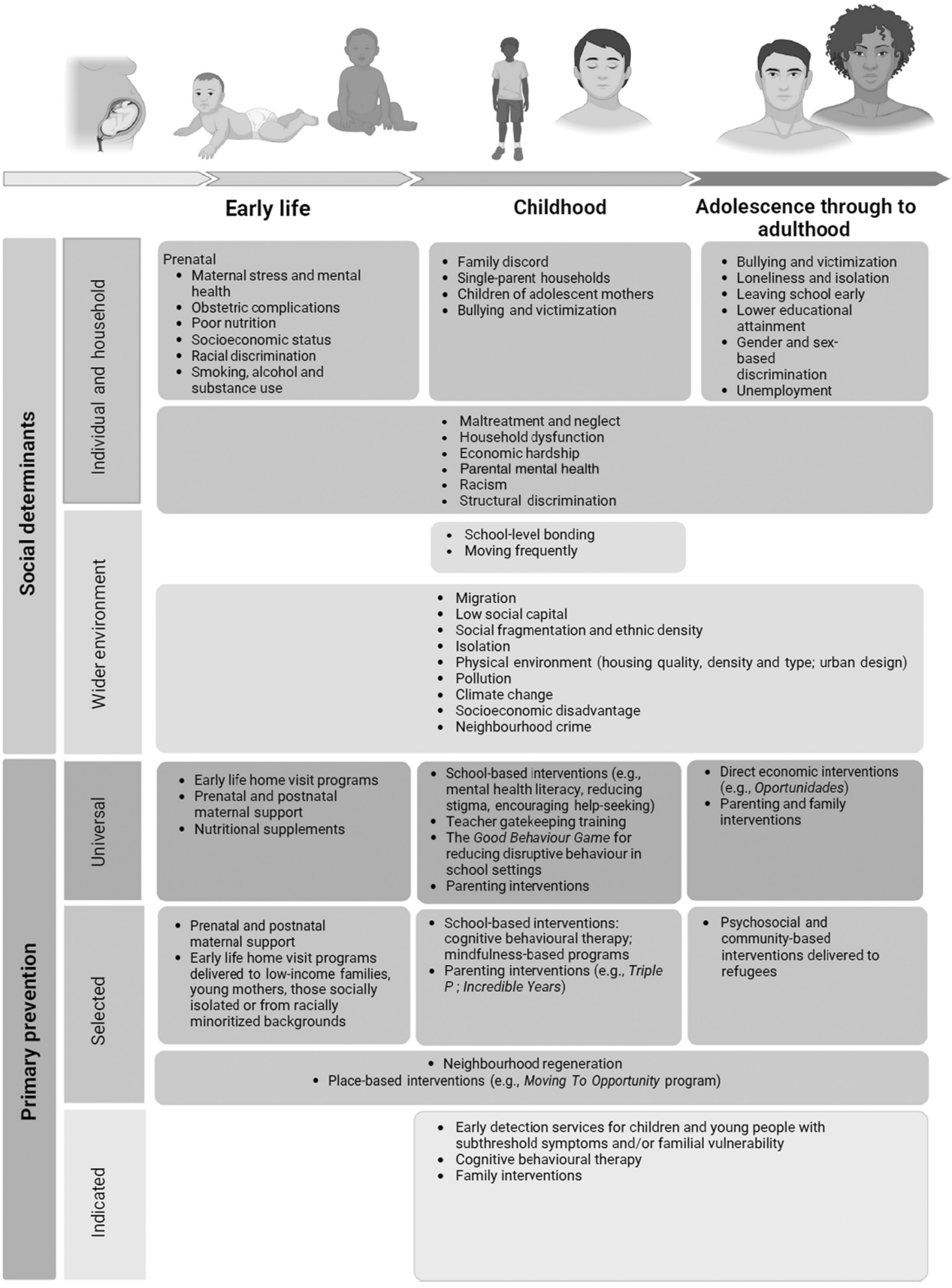

Figure 2 Summary of the social determinants of mental health and disorder and of the main primary prevention strategies

perspective, it is reassuring to see that parenting programs implemented in HICs have similar positive outcomes in lower-income settings such as sub-Saharan Africa[334].

Several key questions remain about optimizing parenting interventions, including whether effects persist in the absence of the intervention over the long term (observed by one[332] but not other reviews[328,335]), the ideal age to intervene (with evidence of beneficial effects associated with interventions in both childhood[331] and adolescence[332,336]), and whether they should be deployed universally or to selective populations (bigger effect size of parenting interventions have been found for high-risk families[332]). Another set of related early-life interventions – home visits during pregnancy – have been deployed as more selective prevention strategies, reviewed later.

School-based mental health programs

Schools are potentially optimal settings for public health practitioners to provide universal mental health promotion and prevention. Numerous such programs have been designed for school children, and may be adapted to offer nested selective and indicated interventions.

Many school-based programs focus on mental health literacy, with the aim of educating youth about mental health, reducing stigma related to mental disorders, and encouraging help-seeking behaviour[337]. A recent systematic review of RCTs showed that these programs increase mental health literacy and reduce stigma, although there is a lack of evidence on whether these effects persist over the long term[337]. Whether they increase help-seeking behaviour remains unclear[338].

School-based interventions that focus on reducing disruptive behaviour have existed for many decades. A 2011 umbrella review concluded that these programs are effective in reducing externalizing problems[339]. The *Good Behaviour Game*, for example, was developed in 1969, and is a team-based activity designed to reward children for pro-social behaviour and discourage disruptive behaviour[340]. RCTs have shown that the *Good Behaviour Game* is effective in reducing conduct problems in children[340]. Although the primary focus is on behavioural regulation, the program also supports emotional regulation. A recent Australian trial showed that the program also decreased internalizing symptoms[341]. Remarkably, one study followed up students at age 21/22 who had participated in the program in school when aged 6 years, and found that participants were less likely to report suicidal thoughts and attempts compared with controls[342].

There are several school-based programs that specifically focus on prevention of depression and anxiety. A 2017 systematic review (updated in 2021) summarized evidence from 90 intervention studies[343,344]. The majority of interventions were based on 8-12 sessions of 45-90 min of cognitive behavioural therapy (CBT), modified for the classroom[344]. The review clearly showed that these programs were effective in reducing symptoms of depression and anxiety, though effect sizes were generally small[343,344]. Although such programs are often delivered universally, effect sizes for depression were larger for trials that targeted higher-risk student populations (i.e., selective and indicated approaches)[343,344]. Notably, while effect sizes for preventing depression and anxiety were relatively small, they persisted in long-term follow-up[343,344]. Furthermore, the authors of the 2017 review point out that even small effects can have big impacts on prevention from a population perspective[344], aligning with Rose's argument. Relevantly, a 2016 review estimated that universal prevention programs of depression and anxiety delivered in schools (mostly CBT-based) prevented 50% of cases of a diagnosable internalizing disorder in the following 6 to 9 months[345].

Recently, several mindfulness-based programs have been developed and trialled for school-aged children[346]. Mindfulness approaches encourage people to intensely focus on the present moment, in order to calm physiological responses and reduce stress. A 2022 systematic review of 66 RCTs found that mindfulness programs for children are successful in reducing anxiety/stress (analyzed as a combined outcome) and depressive symptoms[346], although effect sizes tended to be small and were limited to selective rather than universal samples. Trials in universal samples found no evidence of improvements in mental health, despite small improvements in behavioural outcomes, executive function and attention. Further, there were no positive effects in studies that included follow-up beyond program conclusion[346].

Another group of school-based mental health programs focus specifically on suicide prevention. These programs tend to take three forms: a) awareness and education initiatives, which seek to inform students about suicidal behaviour to reduce stigma and increase likelihood of help-seeking behaviour; b) gatekeeper training, which seeks to teach students or teachers to identify signs of suicidality, and refer students to appropriate services; and c) screening programs, which seek to identify risk factors for suicide or suicidal thoughts, with the aim of referring people who screen positive for further assessment and/or treatment[347,348]. Several reviews have concluded that these programs are successful in reducing suicidal thoughts, including 12 months after program completion [347,349]. The most recent review concluded that similar effects are seen for suicide attempts, with some evidence that these effects may last for up to 20 years[348].

As with many school-based interventions, suicide prevention programs are most successful when they are multi-faceted[347]. One excellent example is the *Saving and Empowering Young Lives in Europe (SEYLE)* program, a suicide prevention RCT implemented in 168 schools across 10 countries[350]. The intervention included training teachers and school staff to be gatekeepers, delivering a mental health and suicide literacy program for students, and screening for high-risk students. At 12-month follow-up, participants in intervention schools were 50% less likely to have experienced suicidal thoughts and suicide attempts in the previous two weeks compared with students from control schools[350].

Several reviews have highlighted that little evidence exists on cost-effectiveness of school-based programs in prevention of mental health problems[337,344]. One review on prevention of depression and anxiety in schools estimated that the number needed to prevent one case per 100 children was 70 students[345], while the authors

of the *SEYLE* trial concluded that the program could prevent one suicide attempt for every 167 students who participated in the program[350]. Depending on the resources required for these programs, these prevented outcomes could represent important cost savings. Nevertheless, rigorous economic evaluations are needed, particularly those that take a long-term perspective. An additional limitation of research on school-based interventions is that few studies have included functional assessment; a recent commentary argued that measuring function may better reflect the success, or lack thereof, of programs whose aim is to allow children to flourish[351].

Finally, it should be noted that the overwhelming majority of studies in this area are from HICs, although available evidence suggests that schools are also a suitable setting to deliver mental health promotion interventions in LMICs[322]. On the other hand, rates of school enrollment vary dramatically between countries, and it cannot be excluded that school-based programs inadvertently exacerbate mental health inequalities for those unable to access basic education. Moreover, recent concern has been raised that some aspects of school-based mental health interventions could increase levels of distress amongst some young people[352]. This requires further investigation so that safety can be fully balanced alongside demonstration of efficacy.

Interventions that address loneliness

The evidence base is weak for preventive interventions that address loneliness, in order to prevent onset of mental health problems, or to reduce severity or improve prognosis of pre-existing mental disorders. Such interventions might be best situated among universal approaches, given that the stigma of loneliness dissuades uptake of targeted interventions, but in reality they may need to straddle universal, selective and indicated approaches. Built environment interventions to address loneliness and mental health, whilst showing promise in terms of acceptability, have no evidence of effectiveness[353]. Systematic reviews of trials of interventions addressing loneliness do not include mental health impacts. Consequently, we need investment in evaluations that encompass both physical and mental health[354].

Selective prevention strategies

Direct economic interventions

Given the demonstrably strong links between poverty, socioeconomic disadvantage and poor mental health reviewed earlier, selective interventions that improve people's socioeconomic position could be crucial policy levers to improve population mental health. Although economic inequality primarily affects the health of the poorest, it is also linked to worse mental health of the whole population[256,355]. This suggests that interventions that reduce inequality by targeting selective or indicated groups could even have universal mental health benefits. There is already evidence that policies driven by progressive welfare economics are associated with fewer mental health inequalities according to socioeconomic circumstances[356,357]. A recent systematic review of 136 studies found that increases in individual and household income improved mental health and well-being, while decreases had the opposite effect[49]. These effects were strongest when individuals were lifted out of poverty.

This evidence has added to debate on whether guaranteed incomes or cash transfers have beneficial effects on mental health. From 1974 to 1979, a guaranteed annual income experiment in rural Manitoba, Canada, ensured that families met at least 60% of what Statistics Canada considered the cut-off to be designated as a low-income family. Evaluations later showed a statistically significant reduction in hospitalizations during the program, primarily related to mental health, and this effect persisted for at least 6 years after program completion[358].

Much of the research on the potential benefits of cash transfer programs have focused on child and adolescent mental health. For example, a recent systematic review found causal evidence that adolescent mental health (specifically, internalizing problems) improved when their families were lifted from poverty[359], and a review of child benefit programs introduced in Canada since 1945 showed that they had positive effects on child mental health and behaviour[360].

It should be noted, however, that the success of cash transfer programs may vary according to economic context, gender, implementation of program, and local culture[361]. For example, the aforementioned systematic review on changes in income and mental health found stronger effects of poverty alleviation programs on mental health in LMICs[49], and other reviews have found similar positive effects for cash transfer programs in these contexts in adults[362] and children[359,361]. These effects may be long-lasting. For example, a cash transfer program in Kenya showed that, 4 years after program implementation, youth whose families participated in the program had significantly fewer depressive symptoms[363]. Similar findings may also extend to low-income settings in HICs. For example, a natural experiment in the US investigated the role of income supplementation on child mental health following the opening of a casino on American Indian reserve land[364]. It demonstrated that children who were lifted out of poverty had statistically significant reductions in symptoms of conduct and oppositional defiant disorders compared with those who remained in poverty, falling to levels seen amongst children never exposed to poverty in the same region[364].

Some cash transfer programs include mandatory conditions for recipients. *Oportunidades*, one of the first conditional cash transfer programs, was implemented in Mexico, and supplemented participants' income by 20-30% on the conditions that children were enrolled in school, and that family members took part in preventive medicine programs and attended health-related presentations. For families who enrolled when their child was less than 2 years old, children had fewer behavioural problems when aged 8-10 years compared with children who were enrolled in the program 18 months later[365].

Critics of conditional cash transfer programs have pointed out

that they are highly paternalistic in nature, exacerbate gender-based inequalities, and do not solve structural problems that lead to long-term poverty[366]. Indeed, one systematic review found that placing conditions on monetary interventions may have detrimental effects on adolescent mental health in some sub-populations, in particular girls, for whom conditional cash transfers may add to existing pressures including household duties and caring responsibilities[359].

Early-life home visit programs

As evidence has accumulated supporting the effects of perinatal stress on brain development[367], public health practitioners have focused more attention on supporting healthy development early in life. Home visitation programs for pregnant or post-partum mothers, their partners, and their children have often been delivered to selected populations at risk of experiencing considerable social disadvantage, adversity and negative health outcomes. These groups have often included low-income families, and mothers who are young, unmarried, socially isolated or from ethnoracial minoritized backgrounds[368].

Home visitation programs vary in delivered activities, but the general aim is to improve the home environment for the new child. These programs often include aspects of social support for new parents, education about child development, informal training about positive parenting techniques (and avoidance of negative parenting behaviours), and facilitation of mother-child interaction. This is important because different parenting practices have been consistently associated with levels of child aggression, delinquency and socioemotional functioning, with authoritarian (e.g., harsh) parenting styles leading to poorer child outcomes than authoritative (e.g., affection balanced with discipline) approaches[369]. A systematic review of 34 RCTs and quasi-experimental studies that investigated the effect of home visitation programs found that they resulted in improvements in the home environment, particularly in studies that used robust measures of parenting behaviours[368].

Some notable RCTs in the US have examined perinatal monthly home visit interventions by nurses. For example, in a trial conducted in Memphis, TN, women received nurse visits during pregnancy, immediately post-partum, and several times until the child's second birthday, while the control group received usual perinatal care[370]. At age 6 years, children of mothers who received the nurse visits had fewer behavioural problems and were less likely to be aggressive. In another trial in rural New York state, women at higher risk of mental health difficulties due to their social position were randomized to receive nurse home visits until the child's second birthday or treatment as usual[371]. At age 15 years, children of mothers who received nurse visits drank less alcohol and were less likely to be involved in criminal activity compared with children in the control arm; this intervention was also highly cost-effective, with a return on investment realized by the time the child reached age 4 years. This intervention continued to exhibit marked dividends into adolescence, through reduced welfare and justice system involvement[372]. A similar intervention study in Australia, that also included monthly nurse home visits for the first two years of the child's life, showed that children of mothers who received nurse visits had overall lower scores on the Strengths and Difficulties Questionnaire, indicating fewer emotional and behavioural problems[373]. Interestingly, the same study showed positive outcomes for parents across a wide range of domains, including less hostility, less parent-child conflict, higher well-being and quality of life, and increased self-efficacy. Whether such interventions would show the same effect if implemented universally remains unclear.

Neighbourhood interventions

The neighbourhood may offer an effective level at which to prevent mental disorders and promote mental health. Nonetheless, designing, testing and implementing interventions which seek to modify social or physical environments in order to improve public health is notoriously difficult. For this reason, most research to date remains observational[353,374].

The classic example of an RCT to lift people out of neighbourhood poverty is *Moving To Opportunity*, conducted in five US cities, in which families in high-poverty neighbourhoods were randomized to receive housing vouchers to move to low-poverty neighbourhoods[375]. At 3-year follow-up, there was evidence of reduced distress/anxiety symptoms amongst parents in the intervention arm, and reduced depressive/anxiety symptoms in children, though these results were restricted to boys and younger children (8-13 years)[375]. Nonetheless, later follow-ups have found differential effects on adolescent mental health, including higher risk of conduct disorder, PTSD and depression in boys, and lower risk of conduct disorder in girls in the intervention arm[376-378]. The reasons for this are likely to be multifaceted, but may include sex-specific differences in interactions with new social environments, including the social skills required to navigate more affluent environments, or the consequences of increased residential and school moves on social integration and support[378]. Such issues further highlight the potential unintended harms that may result from some forms of intervention that attempt to lift people out of poverty.

Neighbourhood regeneration programs[379] have been rarely tested. One exception is a cluster randomized trial in Philadelphia[380], which reported lower depressive symptoms and improved self-worth amongst residents in intervention settings where a greening initiative focused on improving the physical quality of the built environment by planting trees, removing litter, and landscaping vacant land in urban settings. A recent review of interventions to promote housing affordability and stability found no evidence of improved mental health outcomes in selective populations (particularly homeless and Veteran groups)[381].

The paucity of evidence for neighbourhood interventions reflects the complexity of delivering such interventions and their possible unintended consequences, despite evidence that neighbourhood social disadvantage, fragmentation and social capital are significantly associated with mental health.

Public mental health interventions for specific populations

Several minoritized groups are at increased risk of developing mental health problems and disorders, so selective interventions in these groups may be particularly effective in reducing mental health inequalities at the population level. One clear example is providing interventions to refugee groups who are vulnerable to worse mental health. There is systematic review evidence from RCTs that providing psychosocial interventions to refugees is effective in reducing PTSD symptoms[382]. Encouragingly, brief individual[383] or group-based[384,385] psychological and behavioural interventions appear to reduce depressive and internalizing symptoms in refugees, including children[386] and adolescents[384], though these may not be sustained in the long-term post-intervention[385], and some evidence is of low quality[386]. A recent systematic review also found evidence that community-based interventions which provided refugees with greater bridging and linking social capital (i.e., building ties with others in the community, helping them navigate new structures, systems and institutions) may be most effective in reducing mental health symptoms in this population[387]. Nonetheless, the variable quality and small number of studies included in these reviews requires this promising evidence base to be strengthened.

Selective interventions in ethnoracial minoritized groups have also been investigated. In many contexts, the intersectionality with socioeconomic disadvantage means that interventions targeted at low-income parents, families or neighbourhoods are sometimes implicitly selected on a high proportion of people from ethnoracial minoritized backgrounds[371]. Generally, evidence suggests that these interventions are effective in benefiting mental health across different ethnic groups, including the aforementioned *Incredible Years* parenting intervention in both European[388] and North American[389] settings. While these studies lend some support to the effectiveness of culturally-agnostic interventions, there is also evidence that culturally-adapted mental health interventions offer more benefits in some ethnoracial minoritized groups over non-adapted treatments or treatment-as-usual[390,391]. Further, given that experiences of discrimination and stigma operate at various levels as barriers to mental health help-seeking, understanding how cultural and structural factors intersect to produce mental health inequalities in ethnoracial minoritized groups remains a critical prerequisite to developing effective selective interventions that reduce these experiences and promote mental health[392].

There is also emerging evidence that selective interventions for sexual and gender minority groups can be effective in improving mental health outcomes[393]. These include policy-level interventions, family interventions, and provision of coordinated mental health services, with evidence of beneficial effects on mental health, substance use and bullying victimization amongst minoritized youth[393]. Others have highlighted the importance of building up cultural competence amongst health care professionals as a vital intervention to reducing mental health inequities for LGBTQ+ people[187]. Nonetheless, as for other minoritized groups, barriers around mistrust of health care providers represent a further obstacle (and target) for improving timely access to preventive mental health care and support.

Indicated prevention strategies

Indicated strategies to prevent the onset of mental disorders typically seek to identify high-risk individuals on the basis of emerging sub-threshold psychopathology or family history of psychiatric illness with an associated decline in functioning. The delivery of indicated prevention has principally focused on youth-oriented mental health care provision to prevent transition to disorder. This ranges from specialist secondary care (e.g., early detection services for psychosis) through to disorder-agnostic youth mental services that adopt clinical staging models to provide care according to illness stage. Most recently, these models are being repositioned as broad-spectrum integrated primary care services for youth mental health that deliver indicated prevention in a variety of innovative ways, and in a variety of contexts, including digitally, in educational settings, workplaces, the community, and clinical spaces[311]. They offer various interventions to indicated populations, ranging from clinical therapy to peer advocacy and psychosocial interventions to promote resilience, improve mental health literacy or improve social support. Only some of these interventions aim to explicitly tackle social determinants of mental health (social support, loneliness, bullying), usually as part of a multidisciplinary approach.

Just as the pattern of risk for mental disorders is socially inequitable, so too is the likelihood of receiving clinical care that is delivered in a timely, appropriate and proportionate manner according to need[187,396]. This is a global challenge driven by various issues in different settings, including stigma, health literacy, cultural norms, system capacity and economic development. Because indicated prevention strategies predominantly originated from clinical systems of care, identification and inclusion of high-risk populations is subject to similar barriers and inequities. For example, there is evidence that people from socioeconomically disadvantaged, migrant and ethnoracial minoritized backgrounds are under-represented in services for early detection of psychosis[397-399], as well as in child and adolescent mental health services[400]. These biases may be compounded by the instruments used to identify high-risk individuals, which are often developed[394,401] and tested[402] in unrepresentative, help-seeking samples. These inequalities mean that those already exposed to substantial disadvantage are least likely to receive indicated prevention, and less likely to take part in research that informs us about what works for whom, making this an imperative matter of social justice[403].

Furthermore, as currently configured, indicated prevention strategies are unlikely to substantially reduce the incidence and prevalence of mental disorders, because they currently lack sufficient population coverage to do so. For example, studies in England[398] and Australia[399] have shown that only 4-22% of people diagnosed with first-episode psychosis in services for early intervention in psychosis had prior contact with early detection services before illness onset. This calls for broader-based transdiagnostic indicated prevention solutions which could be integrated into community

and school settings, as recently evidenced and advocated by McGorry et al[311], explicitly addressing social determinants of mental health.

Secondary and tertiary prevention strategies

In this section, we present a brief overview of existing social interventions that aim to optimize various aspects of recovery in people with established mental disorders.

Social prescribing

Social prescribing, primarily adopted by primary care physicians, connects individuals with established mental disorders to sources of social support within local communities[404]. Examples include volunteering, befriending, and hobby groups[405]. Despite its popularity, the evidence base lags behind practice, with studies currently lacking methodological rigour[406,407]. Although positive effects on various mental health outcomes have been observed in systematic reviews[404,408-410], the quality of evidence is generally low[408-411], and restricted to uncontrolled samples[408,409,411] or selective subgroups[410]. There is also initial evidence that minoritized groups are under-represented in social prescribing[412]; factors such as finance, language and cultural barriers may pose issues around access and engagement.

Vocational interventions

Given the cyclical relationship between socioeconomic disadvantage and mental health, secondary and tertiary interventions that help people return to work or education should be considered an important component of public mental health policies. One such example is *Individual Placement and Support (IPS)*, where an employment specialist supports an individual with mental health problems to seek competitive employment. *IPS* has been consistently demonstrated to be superior over other forms of vocational interventions to help individuals with severe mental illnesses obtain and maintain competitive employment[413-415]. These findings hold across geographical locations and across high- and low-resource settings[413], though success and uptake may depend on motivation and self-efficacy in job seeking, which may introduce additional barriers for those already exposed to greater structural and systemic disadvantage[416-418]. While these interventions may benefit people with other mental health outcomes, they appear most effective for severe mental disorders[419].

Family interventions

It is well known that family interventions can help reduce risk of relapse for people with psychosis[420,421]. They also appear to reduce depression and suicidal ideation in young people[422,423], though these effects could be restricted to older adolescents and may be affected by risk of bias concerns[424]. Secondary and tertiary family interventions can also lead to reductions in parental stress and depression, and improvements in parenting behaviours[422,425], which may be particularly relevant to interrupting intergenerational transmission of familial risks for mental health problems[424]. These effects also extend to LMICs, with 65% of interventions being delivered by non-specialist workers[425,426].

Trauma-informed interventions

Traumatic events contribute substantially to mental health inequalities, as we highlighted earlier. Given this, models of trauma-informed care have gained traction in secondary prevention, and may be particularly pertinent to recovery for specific groups, including victims of intimate partner violence, ethnoracial minoritized groups, and refugees and asylum seekers with established mental disorders. To date, the most commonly adopted and evaluated approaches include eye movement desensitization and reprocessing (EMDR) and trauma-focused CBT[427,428]. Despite this, a recent systematic review[429], which largely focused on interpersonal traumas in women, found inconsistent evidence that trauma-informed interventions improve a range of psychological outcomes, including symptoms of PTSD, anxiety and depression. The authors attributed this to inadequate study designs, also observed by other reviews[430,431], and called for broader trauma types and outcomes to be rigorously evaluated. For children and young people exposed to trauma, systematic reviews show moderate effects for EMDR and trauma-focused CBT – but not conventional CBT[428] – in the treatment of PTSD[428,432]. Meta-analytic evidence also demonstrates moderate effectiveness of trauma interventions in reducing symptoms of PTSD, depression and anxiety for displaced persons in HICs[382] and LMICs[433]. Greatest effects were found for trauma-focused CBT, particularly with extensive cultural adaptations[434].

RECOMMENDATIONS FOR ACTION

In this paper we have highlighted the social gradients in the incidence and prevalence of psychological distress and mental disorders within and between populations. This evidence consistently shows that those exposed to adverse social determinants of health – whether through poverty, discrimination, trauma or exclusion – are most likely to experience poor mental health over their lifetime, as well as downstream physical health, social and economic sequalae that can perpetuate cycles of intergenerational inequality in health and social outcomes. We have also shown how these inequalities arise through a broader set of structural processes and policies that disadvantage minoritized and marginalized individuals and communities through experiences of interpersonal, institutional and systemic discrimination. These experiences prevent equitable access to adequate education, employment, housing, social support and health care, which subsequently increase exposure to stressful life events and risk of poor mental health.

What, then, can and should be done? We argue that primary prevention should be prioritized to address and remove social inequities in order to prevent the onset of mental disorder and lower the burden of psychiatric morbidity in the population. There are at least three compelling reasons for this case. First, equality is central to human rights[435], and so efforts to reduce social inequities that affect population mental health are a matter of social justice. Second, since many psychiatric disorders exhibit such social gradients, universal, selective or indicated primary prevention strategies would not only promote more equitable mental health, but also achieve substantial gains in improving the mental health of whole populations. Finally, while recognizing the vitality of secondary and tertiary prevention in treatment, recovery and relapse prevention for people with existing mental disorders, primary prevention needs to be integrated into equitable and accessible whole-population care systems. Here, parity of investment in effective primary prevention would represent a win-win-win for individuals, populations and health care systems, both in LMIC contexts, where secondary and tertiary mental health care services are often extremely limited, and in HIC contexts, where need for care has outstripped capacity[41].

In this concluding section, we identify seven recommendations for action (see Table 2), which provide a roadmap for mental health professionals, policy makers and researchers to improve population mental health and reduce inequities in mental health problems by prioritizing intervention on social determinants.

Table 2 Overview of recommendations for action to intervene on social determinants to improve population mental health and reduce inequities in mental health problems

1. **Make social justice central to all public mental health interventions.** Mental health problems are inequitably distributed between and within populations, principally arising from systemic structural inequalities. Making social justice core to all public mental health interventions and policies would reduce these inequities.
2. **Invest in interventions that pay off in multiple domains.** Few social determinants solely affect mental health. Investing in interventions that target key social determinants will improve physical, mental and social outcomes for individuals and communities. Intervention programs should routinely measure mental health alongside these other outcomes.
3. **Invest in interventions that target critical windows of the life course to interrupt intergenerational transmission of mental health inequalities.** Providing good-quality and accessible parental and familial support early in life can interrupt the intergenerational transmission of mental health inequalities within families or communities.
4. **Prioritize interventions that focus on poverty alleviation.** Any comprehensive public health approach to reduce the burden of poor mental health must include efforts to reduce poverty. Poverty is inextricably linked to most social determinants of mental health, and could be considered a root cause.
5. **Strengthen causal inference in research on social determinants of mental health and primary prevention.** Most research on social determinants of mental health is observational, often subject to selection and confounding bias. Stronger causal inference methods are needed, as well as larger, interdisciplinary observational and experimental studies in representative and adequately powered samples to accelerate progress of knowledge and develop effective primary interventions.
6. **Establish inclusive longitudinal population mental health monitoring.** Many countries struggle to accurately estimate psychiatric morbidity in their populations, which inhibits both clinical and public mental health provision. Samples are often unrepresentative. Reliable, inclusive and precise longitudinal monitoring of population mental health is the essential basis for effective prevention.
7. **Ensure parity between primary, secondary and tertiary prevention in mental health.** Investing sufficiently in primary prevention to stop the onset of mental disorders prevents suffering, improves quality of life and societal outcomes, and reduces demand for secondary and tertiary prevention.

1. Make social justice central to all public mental health interventions

Social justice is concerned with the fair (equitable) distribution of wealth, power, opportunities and privileges within society. No society is perfectly just. To a greater or lesser extent, different societies will have differing levels of fairness in access to the economic, social and political means that allow individuals or groups to determine and realize their preferred goals and outcomes. The equitable (fair, just) distribution of resources is closely related, but not always identical to the equal (balanced, proportionate) distribution of resources. For example, on average, older adults (of working age) tend to have higher incomes than younger adults, holding all other variables constant, as a result of accumulated knowledge and experience; income is thus surely unequally distributed by age, but we may choose not to consider this inequitable.

Accordingly, not all differences in mental health are, *per se*, inequitable. Men are more prone to develop schizophrenia than women[198], potentially due to biological differences[436], but this difference is likely not to be a matter of social justice. By contrast, while the elevated prevalence of depression in women may also be partly biologically determined[437], there is strong evidence that it may also result from greater exposure to interpersonal violence, childhood trauma or other gendered social or psychological factors [200,437], making interventions to prevent these inequitable experiences a remedial matter of social justice.

We consider that most social differences in the onset and maintenance of mental health problems arise from inequitable exposure to structural disadvantage, thus requiring the principles of social justice to be embedded at the heart of all public mental health policy efforts to prevent mental disorders. It has been argued that "the job of justice in its most pressing role demands a permanent vigilance and attention to social and economic determinants that compound and reinforce insufficiencies in a number of dimensions of well-being"[5, p.78]. Logically, then, this requires public mental health, and public policy more broadly, to ensure that all prevention strategies explicitly redress social, economic, political and environmental insufficiencies that both increase the risk of mental disorders and inhibit people's recovery from them. Prevention strategies and policies that embed social justice theory from their conception are most likely to be effective in reducing social inequities in mental disorders, and in shifting the entire population distribution of risk. This approach requires careful theoretical and empirical consideration of various issues, including what suf-

ficient conditions would look like, and which social determinants should be prioritized from the perspective of social justice. These issues will vary over time and between different contexts. For example, while poverty alleviation is a global goal likely to improve mental health universally[359], it may be a more imperative matter of social justice in LMICs, where a much higher proportion of the population live in poverty.

Finally, the need for social justice applies not only to the strategies and policies to address social determinants of health, but also to the research that supports them. Our review has focused on the disproportionate body of evidence from HICs in the Global North. While we have highlighted evidence from LMICs where we have identified it, and while many determinants are likely to be similar, others may be different[2]. Social justice requires both accelerated investment into further high-quality research on the most effective prevention strategies for social determinants in LMICs, and strategies to counteract the inequitable reproduction of knowledge concentrated on the Global North that reviews unavoidably perpetuate.

2. Invest in interventions that pay off in multiple domains

Most, if not all, of the social determinants discussed in this paper are associated with adverse outcomes that extend beyond the realm of mental health. As an example, experience of childhood adversity – a risk factor strongly associated with a range of negative mental health outcomes – is also associated with a host of poor physical health[103], social[438], and educational/occupational[439] outcomes. In a second example, whole communities are often exposed to highly intersectional, cyclical patterns of social disadvantage[2,138,374], meaning that successive generations of families may face limited choices in navigating social determinants of health, including socioeconomic disadvantage, social exclusion, discrimination, trauma, and hostile environments, which simultaneously contribute to poor physical health, mental health, and social outcomes[41,45]. However, despite substantial evidence supporting such multi-finality, progress in addressing social determinants and their associated consequences has been slow, due in part to the pervasive siloed thinking amongst researchers, practitioners and policy makers.

Greater cross-sector collaboration and more inclusive outcome measures may help advance prevention efforts, particularly where these include approaches aimed at whole populations. At present, many promising interventions that target social determinants are not assessed in terms of mental health effects, which represents a lost opportunity to learn about their potential individual-, community-, and society-level impacts[440]. For example, there are a wide range of innovative approaches being implemented within the education, social care and criminal justice sectors that may be beneficial for mental health but are not currently recognized as such due to an absence of formalized measurement of mental health outcomes. One exemplar approach is that of the *Uptown Hub* in New York[441], which provides a community-based service for youth at risk of involvement with the judicial system. The service offers a range of support to young people between the ages of 14 and 24 years, including engagement and retention in work or education, recreational involvement, peer and psychological support to foster resilience, as well as other well-being activities to promote good mental and physical health. Evaluation of such programs is now required to carefully quantify and measure the range of direct and indirect outcomes that they could achieve.

In light of these considerations, we recommend that mental health be measured as a standard outcome in the evaluation of any policy, programme or intervention targeting social determinants. Although this requires additional data collection in the context of evaluations that may have quite separate aims, including mental health alongside other outcomes is becoming increasingly feasible with innovations such as computerized adaptive testing[442], passive sensing technology, and administrative record linkage[443]. Furthermore, the value of such information would greatly enhance our understanding of which approaches are most effective for addressing social determinants, and which could facilitate real progress in improving population health in parallel with other social outcomes (e.g., crime, education, employment, welfare).

3. Invest in interventions that target critical windows of the life course to interrupt intergenerational transmission of mental health inequalities

Although the majority of mental disorders manifest during adolescence[19], they are often rooted much earlier in development. A life course perspective can help us understand how exposure to various social determinants – that operate from before birth throughout life – affects one's chances of experiencing poor (or good) mental health[444], or how it may perpetuate these outcomes through intergenerational transmission within families or communities[445]. By taking a life course approach, we can potentially develop effective interventions that interrupt the intergenerational transmission of accumulated adversities during critical windows of vulnerability[446].

Given the importance of the prenatal period in shaping mental, physical and cognitive trajectories, providing good-quality and accessible parental and familial support early in life is essential to affect this process[367]. Earlier, we presented evidence of positive outcomes following early-life home visitation programs for pregnant and post-partum mothers, with benefits extending into childhood and adolescence, and huge cost savings[371,373]. These interventions are particularly effective in selective groups. Ensuring that young families have sufficient financial support to alleviate stress and meet their needs, including adequate food and housing security, also warrants targeting direct economic interventions at selective groups during critical periods of child development. Stable, secure relationships, particularly in the early years of life, appear fundamental to buffer against life stressors, meaning that family-based interventions hold enormous potential for mental health prevention and breaking intergeneration cycles of disadvantage.

Interventions that support stable, secure and cohesive commu-

nities in the wider social environment may also help buffer children from the impact of social adversity on mental health[281]. For young people, educational settings are likely to be particularly relevant environments in which to implement interventions that promote life-long mental health. For example, schools can nurture socioemotional, academic and cognitive skills, which can bolster against future disadvantages (e.g., unemployment). This could lead to improved educational attainment and increased socioeconomic status to disrupt intergenerational cycles of exposure to some social adversities that increase risk of mental health problems. Further, the onset of many mental health problems occurs during the transition from adolescence to adulthood, a point at which the stakes are high for achieving socio-developmental milestones. Preventing onset in this period could have a profound impact on future social and economic trajectories[447].

We have also seen how some neighbourhood environments can act as reservoirs for structural racism and discrimination that increases the likelihood of exposure to individual-level stressors[448]. Systemic underinvestment, disenfranchisement and lack of opportunities in such neighbourhoods restrict upward social mobility, and so these experiences – including deleterious mental health outcomes – become highly intractable, intergenerational and systemic forms of disadvantage and oppression. Effective public mental health interventions must create opportunities to break these cycles of exposure within our communities, with evidence that this may be particularly important early in life[449].

4. Prioritize interventions that focus on poverty alleviation

Any comprehensive public health approach to reducing the burden of poor mental health must include a focus on poverty alleviation. Poverty is inextricably linked to most social determinants of mental health, and could be considered a root cause. It is incumbent on all stakeholders in the public health sphere to advocate for poverty alleviation in order to mitigate its deleterious, multi-final effects. In addition to improving population mental health, reducing poverty would make major contributions towards improving population physical health, reducing societal inequalities, and reducing barriers to social justice, thus connecting with other recommendations we outline here.

Poverty has particularly pernicious effects early in life, with consequences that stretch across the life course. Children who grow up in poverty tend to live dramatically different lives compared with those who do not. This begins with their immediate environment, as children in poverty are more likely to be living in crowded and/or poor-quality housing, and to be exposed to food insecurity and pollution[450]. Poverty also has strong effects on their parents, as the stress of living in poverty affects parental well-being, and introduces conflicts that negatively influence parenting behaviours and the strength of the parent-child relationship[450,451]. Worse, poverty is strongly and consistently linked with child maltreatment and neglect[451]. Children living in poverty are more likely to be exposed to violence, either in their homes or in the communities where they live[450].

The adversity faced by children in poverty leaves them less prepared for school, as they rate lower on numerous aspects of readiness at school entry age, including social and behavioural skills, language development, and cognitive abilities[452,453]. This results in a socio-developmental cascade with long-lasting impacts, as children who grow up in low-income families are less likely to achieve academically through all levels of schooling, and are more likely to leave school early, or with lower qualifications[452,454]. Although they are more likely to enter the labour market early, they have lower incomes throughout adulthood[454]. Beyond educational and economic outcomes, living in poverty also influences the social lives of those experiencing it. Low income also limits individuals' capacity to engage in social, leisure and civic activities, leaving them less able to mitigate stressful experiences via larger social networks and increased social support and capital[455].

Given the numerous pathways through which poverty influences social determinants of mental health, only some of which are mentioned here, efforts to alleviate poverty should result in mental health benefits. Any public health campaign to improve population mental health that does not address poverty will be unlikely to meet its goal.

5. Strengthen causal inference in research on social determinants of mental health and primary prevention

We have sought to identify the strongest evidence regarding those social factors that contribute most substantially to population-level mental health and disorder, and single out which public health interventions are most likely to prevent adverse mental health. While high-quality RCT and/or longitudinal evidence is available in some domains, there is still much to learn about the causal pathways between social determinants and mental health.

One common and emergent theme in our review is the extent to which these associations arise from non-causal mechanisms such as genetic selection or unobserved confounding. Effective prevention strategies that target social determinants will only improve population mental health if those determinants induce a change in the outcome under study (i.e., they have a causal effect on the outcome). Proponents of biological determinism argue that nearly all socially-constructed "exposures" result from the selection of people with greater genetic vulnerabilities to mental disorders into more adverse social environments[456]. Thus, under this paradigm, social adversities are – like mental ill health – seen as just another consequence of genetic influences. However, while genetic selection may contribute to social patterns of disease occurrence[457], neither genetic nor environmental factors alone will be sufficient or necessary in the aetiology of mental disorders. More research is required to understand the myriad of causal sets that lead to psychiatric disorder, and their relative impacts at the population level. Here, we propose that modern causal inference methods[458] should become *de rigueur* when using observational data to investigate the social determinants of mental health. Further, these methods are only as strong as the underlying measures, samples and assumptions upon which they are predicated, so ac-

celerating the use of longitudinal, well-characterized and epidemiological representative samples – and synthesizing expertise and data from across academia, psychiatry and industry – should be a priority to make substantial progress in identifying the social causes on which to intervene.

Our review also raises the need to avoid social reductionism. Many social factors – operating from proximal to distal ranges – are likely to contribute to cyclical disadvantage, structural discrimination and mental health. We may worry less about which specific cause (e.g., which type of abuse or neglect, which domain of deprivation or inequality) is *the* determinant of risk, but rather focus on identifying the causal structure through which risk manifests itself, and across which holistic interventions are required. Adopting a causal architecture framework[459] and grounding our research in theoretical models of causation would accelerate understanding of how, where and when to intervene effectively.

Finally, many systematic reviews of interventions in this paper were caveated by observations around low quality, small samples and heterogeneous methodologies, while very few RCTs of complex social interventions have been attempted. Arguably, the funding landscape around these issues needs transformation. Many small, low-quality observational studies hamper the synthesis of reliable evidence on what works for whom[460]. Larger, ambitious, interdisciplinary and multisectoral collaborations that attempt to tackle a big idea through the triangulation of high-quality evidence, including experimental paradigms – although more difficult, costly and risky – could help transform our understanding of primary prevention strategies that improve population health across multiple domains.

6. Establish inclusive longitudinal population mental health monitoring

Psychiatry has a long-held fascination with the determinants of mental health across disorders and dimensions that still rely upon phenomenological interpretation. This is true for both clinical psychiatry and psychiatric epidemiology. But the cornerstone of both approaches is the need to count. Accurately monitoring the incidence and prevalence of mental disorders, as well as the distribution of underlying symptomatology, in the population over time, serves at least two crucial purposes. First, it establishes the basic need for clinical treatment in a population, upon which appropriate resourcing can be set for secondary and tertiary prevention. Second, it allows empirical quantification of the potential gains in population mental health that could be achieved through the effective deployment of universal, selective and indicated primary prevention strategies.

Many countries struggle with basic monitoring of the burden of psychiatric morbidities in their populations[461], which inhibits both clinical and public mental health provision. In LMIC settings, the reasons for this may be self-evident, since limited resources may mean political prioritization of other vital issues. Recent reviews have highlighted the evidence gap in incidence and prevalence estimates of psychiatric disorders between HIC and LMIC settings[462]. In HIC settings, the lack of routine data on psychiatric morbidity in the population is sometimes surprising. In England, for example, while the National Health System collects routine mental health service contact data for planning purposes, it is difficult to obtain reliable estimates of incidence and prevalence from help-seeking samples that often lack validated assessment data about psychopathology. Even in countries with well-established disease registries, such as Denmark, Sweden or Finland, incidence is based on contact with secondary mental health care services, and may therefore be less useful for some psychiatric conditions, including depression and anxiety. Prevalence estimates from survey data, while more population-based, are often drawn from smaller samples, which limits inferences that can be made about psychiatric morbidity in different subgroups. Finally, all methods of population mental health monitoring will suffer to a greater or lesser extent from unrepresentative sampling, whether due to biases in case detection or help-seeking.

In order to respond effectively across primary, secondary and tertiary levels of prevention, modern paradigms for reliable, inclusive and precise longitudinal monitoring of population mental health at scale are needed. In the context of social determinants, it is particularly vital that these include representative and well-powered samples from socially disadvantaged and minoritized backgrounds. In many contexts this could be achieved by better routine recording of mental health data and the use of harmonized data management platforms that harness technological advances in data security and linkage with clinical and population health data, of which some examples already exist[463].

7. Ensure parity between primary, secondary and tertiary prevention in mental health

The need for primary prevention in mental health should be examined closely by policy makers worldwide. The advantages of this prevention are evident in terms of improving quality of life, social functioning and workforce participation, and reducing suicides. Such approaches have been outlined in this paper, and encompass creating environments where people (particularly members of marginalized groups) know where to access early support after an adverse life event or when facing chronic difficulties, have opportunities for social connectedness, and are supported to function optimally in their work, family and social roles. As an overarching principle, it is also important to address the reduced uptake of interventions among socially disadvantaged groups[464]. Beyond this, the ultimate societal ambition is to achieve primordial prevention, i.e. to prevent the emergence of risk factors for mental disorders and suicidality. Responsibility for this lies outside the remit of public health, and relies on societal systems that engender the socioeconomic and cultural conditions that promote mental health and well-being in a population.

There are also strong reasons why investment in primary prevention of mental ill health should have parity with that in secondary and tertiary prevention. The social determinants we have outlined above generally contribute to the onset, severity and

prognosis of mental disorders. Therefore, any efforts to arrest the progression of mental disorders (implemented as secondary and tertiary prevention) will falter where the conditions needed for primary prevention do not exist.

CONCLUSIONS

In this review, we have highlighted the major social determinants that generate and sustain intergenerational inequalities in risk and maintenance of mental health problems and disorders. Although stronger causal evidence is required for some determinants, we have shown that a variety of primary prevention strategies to alleviate social inequalities, which often have their origins in early life, can be effective in reducing the population burden of potentially life-long mental health problems that will typically emerge in adolescence.

Various forms of discrimination and minoritization, including structural racism, are likely to exacerbate intergenerational social inequalities in mental health. We have outlined seven recommendations aligned around social justice that policy makers, practitioners and clinicians are invited to adopt to advance efforts to intervene on modifiable social determinants that place populations in peril of poor mental health.

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Addressing social determinants of mental health: a new era for prevention interventions

Kirkbride et al[1] provide a comprehensive overview of the social determinants of mental health. Their paper reviews the evidence for the causal influence of those determinants on population mental health and demonstrates the potential for prevention interventions that address those determinants across the life course. They argue convincingly that we stand at the threshold of a new era in prevention interventions for mental health globally – namely, those that focus on the social determinants of mental health.

Among the many contributions of their paper, several aspects stand out. First, the authors place a strong emphasis on a social justice framework when characterizing social determinants. As they point out, these are fundamentally a product of inequitable social and economic systems, which concentrate power and privilege in the hands of a few. Inequities in the distribution of mental health in populations are a product of experiences of exclusion and discrimination brought about by fundamentally unjust social systems. Second, the authors provide compelling evidence of causal links between social determinants and mental health outcomes, at both the individual and the wider social levels. These are documented with a strong emphasis on marginalized groups, which are frequently exposed to intersecting social determinants. Third, their review of the observational and intervention research strongly emphasizes a life course approach, demonstrating how early exposure to adversity carries lifelong mental health consequences, and why early intervention is so important. Fourth, they carefully document the evidence for social interventions that span the continuum of universal, selective and indicated prevention. Finally, their review demonstrates the modifiability of many social determinants, and the need to integrate a social determinants framework into existing, largely individually focused clinical treatments.

There are three key areas for future development of research on social determinants of mental health, which Kirkbride et al mention, but are worth highlighting here. The first is the need for more longitudinal observational research. Currently there is limited evidence on causal pathways linking social determinants to the mental health outcomes of populations. A recent study commissioned by the Wellcome Trust involves landscaping of longitudinal mental health datasets around the world and is a key step forward in advancing the field[2]. This study has compiled more than 3,000 longitudinal datasets from 146 countries, improving their accessibility and opening possibilities for further analysis and enrichment.

The second area for future development is the evaluation of prevention interventions that address the social determinants of mental health. Three key steps are necessary if we are to prevent mental illness by addressing its social determinants. First, we need to build more robust theoretical models, mapping out the pathways by which social interventions yield mental health improvements. These may include distal socioeconomic mechanisms (for example, the mediating role of income instability in the association between economic recessions and the incidence of anxiety disorders) and more proximal neuropsychological mechanisms (such as the mediating role of self-regulation in the relationship between multi-dimensional poverty and adolescent depression). Second, we need to design studies that can test these mechanisms, for example by conducting randomized controlled trials that include analysis of key mediators in our hypothesized causal models. In order to demonstrate that a mediator is a causal factor, there must be a temporal relationship between that mediator and the outcome, a dose-response association, evidence that no third variable causes changes in the mediator and the outcome, robust experimental research and a strong theoretical framework[3]. Third, it is vitally important that we share data across diverse settings, because context really does matter when it comes to addressing social determinants. For example, specific experiences of multidimensional poverty or humanitarian emergencies brought about by climate change will vary substantially by context and will require diverse measurement and intervention approaches. There are also likely to be diverse mediators which may serve as targets for interventions. All of this requires an inter-disciplinary effort, bringing together economists, epidemiologists, mental health specialists, neuroscientists and people with lived experience, to develop shared approaches to these complex challenges.

As an example of this effort, in the *Improving adolescent mental health by reducing the impact of poverty (ALIVE)* study, we are designing and evaluating a selective prevention intervention to reduce the incidence of depression and anxiety among adolescents living in urban poverty in Colombia, Nepal and South Africa[4]. Our hypothesis is that multi-dimensional poverty increases risk for depression and anxiety among adolescents both directly and through its negative impact on self-regulation. By self-regulation we mean the capacity to set goals and maintain goal-directed behaviour, despite emotionally salient and challenging environments[5]. Our four-arm pilot trial includes an economic intervention (cash transfers, financial literacy, negotiation skills, and information about returns to education); an intervention designed to strengthen self-regulation; an intervention that combines economic and self-regulation components; and a control arm. The study includes detailed cultural adaptation and validation of key measures, and strong involvement of adolescents in the design and delivery of the research in each country site.

The third key area for future development is research on the social determinants of mental health in low- and middle-income countries (LMICs). As Kirkbride et al point out, most of the evidence on the social determinants of mental health (including observational and intervention research) originates from the Global North. It is vital that this trend is reversed. Most of the world's poor and vulnerable populations live in LMICs. The world's children and adolescents are concentrated in these countries (90% of the world's 1.2 billion adolescents live in LMICs[6]), making the

argument for early life course interventions even more cogent. Although LMICs are highly diverse, they share a heightened vulnerability to looming climate change, conflict, and food insecurity. If we are to take seriously Kirkbride et al's call for a social justice approach to the social determinants of mental health, and develop population level interventions that have the potential to globally prevent mental health conditions such as depression, anxiety and psychosis, it is essential that greater research funding and policy attention is allocated to LMICs.

Kirkbride et al's paper is a landmark contribution that signals a growing community of practice across low-, middle- and high-income countries. Crucial for the future of this field is more robust engagement with policy makers and implementers in national governments and international aid agencies – such as multilateral development banks – to facilitate partnerships in funding, scaling up and evaluating the population level impact of interventions that address the social determinants of mental health.

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Challenges in implementing interventions to address the social determinants of mental health

It is easy to agree with Kirkbride et al[1] that a causal link exists between social factors and later mental health. Indeed, when the term "social factors" is defined as broadly as it is in their paper to include biological exposures due to the physical environment, we know from population genetics that social factors (i.e., the environment) are the most important causes (i.e., heritability is less than 50%) of most mental disorders[2]. Furthermore, as genetic disorders cannot be prevented other than through lifestyle changes, it is easy to agree that broadly-defined social determinants are the most modifiable causes of mental disorders[3].

Much more interesting issues are those involving complexities in the implementation of interventions. To this point, even though broadly-defined social determinants (i.e., the environment) are more modifiable than other (i.e., genetic) determinants of mental health, this broad statement provides little guidance for action. It is important to appreciate in this regard that when "social factors" are defined as broadly as they are here, any policy is an "intervention". This means that the fields of macroeconomics, community psychology, and health care policy, as well as all policy decisions regarding such things as housing, preschool education programs, foster care and community policing, become of psychiatric interest. But these policies influence much more than mental health. And mental health is seldom a major consideration of policy makers in these areas. Even if it was, the population-level effects of these policies on mental health are largely unknown. And the complexities involved in providing even rough estimates of these effects are daunting.

Other complexities exist in designing interventions even in situations where causal effects are clear and where there are no competing interests across outcome domains. Indeed, there is often a trade-off between population optimality with respect to a point estimate and to a variance of the desired outcome. To illustrate, consider the question of where to build the next firehouse in a large metropolitan area where risk of a fire varies across neighborhoods (e.g., poor neighborhoods with older construction at higher risk), individual-level risk of death when a fire occurs also varies across neighborhoods (higher in neighborhoods with older construction), and expected number of deaths when a fire occurs varies in a different way across neighborhoods (e.g., higher expected number of deaths in high-rise buildings with many residents and exclusive egress via elevators than in smaller low-rise buildings). Given these and other inputs, operations research models can determine the optimal location for building the next firehouse to minimize overall population loss of life. However, the optimal location from that perspective might increase inequality of risk, which means that quite a different location would be selected if the goal was to equalize risk of death rather than to minimize loss of life. How do we decide which location to choose? The answer is anything but clear when competing considerations exist and resources are constrained.

Similarly difficult decisions are made every day on a smaller scale by practicing psychiatrists as they decide how to allocate their fixed clinical resources. These decisions are made in the context of higher-level decisions about allocation of health care resources (e.g., to community prevention vs. treatment). And these health care system-level decisions, in turn, are made in the context of even higher-level government decisions about the organization and financing of health care and the relative allocation of public resources across multiple sectors. Decisions at lower levels are inevitably constrained by prior decisions made at higher levels.

What are psychiatrists to do in the face of this complexity? Most psychiatrists focus on optimizing the resources available to them in their practice. Other psychiatrists consider social determinants of health in clinical decision-making[4]. And, at the extreme, some few psychiatrists change profession and become health care administrators or politicians to increase their impact on population

mental health with higher-level decisions.

There is a need to focus on intervention opportunities for social determinants of mental health that are within the reach of psychiatrists in their own practices and local health care systems. For example, the *Moving to Opportunity* housing experiment discussed by Kirkbride et al was a massive ($100M+) macro policy intervention funded by the US Government's Department of Housing and Urban Development and carried out by an interdisciplinary team led by welfare economists, not by psychiatrists[5]. Other macro interventions shown to influence population mental health in cities and states are highlighted by the Results First Clearinghouse Network (RFCN)[6], a network of nine clearinghouses aggregating evidence about community-level interventions of diverse sorts found to work in the US; and by the Institute of Health Equity (IHE) of University College London[7], which has implemented and evaluated a wide range of coordinated area-level universal, selected and indicated interventions designed to advance six policy objectives[8]: give every child the best start in life; enable all children, young people and adults to maximize their capabilities and have control over their lives; create fair employment and good work for all; ensure a healthy standard of living for all; create and develop healthy and sustainable places and communities; and strengthen the role and impact of ill-health prevention.

But all the above programmes require deep buy-in by city, county and state governments, substantial coordination across sectors, and implementation of coordinated series of interventions designed to address the fact that social disadvantage is usually over-determined. Although psychiatrists could help achieve this buy-in to such interventions by participating in organized lobbying efforts, their perspective will inevitably take a back seat to those of other more powerful lobbying groups.

However, there are other interventions that individual psychiatrists could implement right now on their own by taking social factors into consideration in their practices and making use of local resources to help foster the wrap-around services that are often needed by disadvantaged patients[4]. In addition, groups of psychiatrists working in local health care systems could be instrumental in having their systems implement a mix of universal, selected and indicated interventions on social determinants of mental health that could have profound effects on population physical and mental health. A good guide in this respect is provided by the OASIS framework[9], developed by the VA Boston Health Care System, which outlines the potential mechanisms by which health care-based social need interventions can improve health outcomes.

Nonetheless, there is a need to distinguish the various levels of intervention on social determinants of mental health, and to more clearly identify and promote those that are within the reach of psychiatrists in their own practices.

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Revitalizing the role of social determinants in mental health

Amidst long arcs of the pendulum between attention to psychosocial and neurobiological factors in mental health, substantive progress now depends on these two approaches being seen as complementary and synergistic rather than contradictory. From this launchpad, Kirkbride et al's paper[1] is an impressive, high-level and up-to-date overview regarding the role of social determinants in mental health and disorders. Perhaps most helpfully, it highlights a series of complexities worth reflecting on as the field moves towards a more sophisticated understanding of the interpenetrating effects of social determinants, and to generating and actioning relevant interventions.

A first challenge is the false dichotomy between primary and secondary/tertiary prevention strategies. Primary prevention can be a powerful route to addressing social determinants, but is often not the only one. As a result, primary and secondary approaches ought to be seen as interdependent instead of oppositional[2]. Delivery of effective primary prevention schemes should result in reduced need for secondary/tertiary prevention (albeit perhaps staggered or delayed), yet there will still be a need for clinical and service innovations to better address breakthrough cases and suffering. For example, a sizable proportion of young people presenting to community-based early intervention services appear to have more complex needs than might have initially been anticipated or planned for[3]. Despite the best of intentions, some youth may even be underserved in such settings, underscoring the urgency behind having a full suite of options across the entire continuum of care, and smooth pathways between the various layers of a mental health system[4].

Second, psychiatry has historically become tangled – and at times knotted – around the question of whether poor mental health influences social circumstances or vice versa[5]. However, Kirkbride et al argue that, even without a granular accounting of each mechanistic link in complex causal chains, we now understand a fair bit regarding how to potentially break relevant feedback loops. Direct genetic and neurobiological factors, identified in impressive and rigorous studies, are at present mostly unmalleable and thus far account for only a small proportion of the population-attributable risk fraction across a range of mental health conditions. In contrast,

putative social interventions or policy levers aimed at sensitive periods of development (to which biology undoubtedly contributes) certainly exist, and can at the very least be conceptualized and tested[6], for a number of reasonably well-established social determinants – ranging from early years programs to neighborhood regeneration all the way through to indicated prevention strategies in clinical settings. And since so many of the social determinants are held in common across mental and even physical health conditions, interventions based on these variables are likely to have a slew of benefits. This is a critical corollary to Rose's prevention paradox: although the force required to shift the population curve may be intimidating compared to an approach that focuses on high-risk groups alone, the former may nonetheless have outsized and favourable ripple effects on both mental health as well as other aspects of health and well-being.

Kirkbride et al's paper compellingly suggests that this should be a central rationale for renewing the attention given to social determinants across primary and secondary prevention paradigms. Nowhere is this better illustrated than in their depiction of poverty, its cascading effects across the life course, and how intervention strategies that push poverty alleviation to the sidelines may therefore be destined for failure. There is little question, then, that those interested in addressing social determinants of mental health must appreciate not only individual risk factors, but the underlying causal structures through which risk manifests.

The wide-ranging ways in which inequality and poverty exert their direct and indirect effects also means that discrete interventions cannot be considered in isolation. Rather, they accentuate the need for social determinants of mental health to be addressed by coordinated interventions across layers of causal structure (including individual, interpersonal, institutional and structural) that are also purposefully designed to reach across policy domains. In the case of mental health, there is a porous boundary between preventive interventions and social/educational policy, such that the lens should be one of integrated public policy and not just health policy. Indeed, given the disability and indirect costs associated with mental health problems and disorders, their onset during youth and their persistence if untreated, a "whole of government" approach akin to that taken during other crises may be indicated and even necessary.

Finally, Kirkbride et al allude not just to the need for further investment in interventions and population health monitoring, but also to ongoing investigations regarding their effects. In part this is because interventions are not without risk and may have unintended consequences, including iatrogenic ones[7]. And, even when beneficial, potential interventions should be seen in their social context and recognized as having limits. For example, although specific migration exposures are widely acknowledged to be risk factors for psychosis, making reactive policy changes (such as eliminating immigration) based on this would be untenable as well as discriminatory. Instead, the key question is how public policy can benefit from dialogue between theorists, empiricists and policy practitioners to – among other things – appreciate that immigration may represent a proxy for underlying exposures and stressors; posit potential mechanisms across biological, psychological and social levels of causation; and then plan and test interventions that reduce risk, promote integration, and advance implementation. The optimal strategies will likely involve capturing diverse and patient-oriented outcomes, discerning the structures through which social conditions and outcomes emerge and are interwoven, and perceiving the widespread benefits of inclusive and equity-oriented policies.

More than anything, Kirkbride et al's depiction of the current state-of-the-art represents a call for creativity and investment to address the social determinants of mental health. If inequality harms[8], then the current chasms between demonstrated need, the required multi-sectoral engagement, and concerted action on social factors affecting the mental health of individuals, communities and populations is deeply unsettling. It is also one of a range of contemporary dilemmas that – like climate change and diminishing economic opportunities – will particularly affect young people, the future of any society. Whether due to recent crises that have temporarily prevented new solutions from being born, or the longer-term hollowing out of government expertise and capacity[9], the energy to catalyze integrative approaches to such a far-reaching challenge seems to have come to a lull. It now demands sustained renewal and revitalization.

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The need to bring community, policy makers and researchers to the table in prevention programs

Kirkbride et al's outstanding paper[1] updates recommendations from the perspective of social determinants of health to mitigate the onset of mental disorders and lay out a roadmap for an effective prevention plan. They explain that the maldistribution of essential social determinants is not random, is shaped by policy and by those in power, and could reproduce intergenerational inequities

in people's opportunities. They refer to the saliency of "a threshold moment" to actualize our response, given societal demands to tackle the global burden of psychiatric morbidity. They underline the shift of focus from the internal individual-level factors to the environmental conditions that impact mental health and well-being, particularly in children, adolescents and younger ages.

The authors' analysis leads to several new significant insights. Their preventive framework to enhance children's mental health and prevent psychopathology offers a rich array of primary and secondary interventions with proven evidence for rapid implementation. They identify gaps and inconsistencies in intervention results that require further evaluation, and studies that lack scientific rigor. With a strong anchor on equity, their seven recommendations make a compelling claim for investing in primary prevention.

This important contribution offers a blueprint for preventive actions. However, the authors acknowledge the limitations of prevention strategies to significantly reduce the incidence and prevalence of mental disorders, since there is a shortage of population coverage and it is highly challenging to implement interventions to alter social or physical environments. Preventive interventions may fail to solve the structural problems that generate them in the first place. Some studies may not stratify the diverse groups to examine if the average effect differs by population subgroups of age, sex, region and ethnicity.

Partly missing from the review is an adequate attention to the possible unintended harmful effects of prevention interventions, some of which may have consequences that are the opposite of those desired[2]. These unintended consequences – such as stigmatization of children or frustration of teachers who participate in a school mental health promotion program – are hard to anticipate, identify and observe[3]. Recent work suggests the need to consider possible physical, psychosocial, economic, cultural and environmental harms of prevention interventions, especially when they do not align with the target community's norms, values and preferences[4]. For example, work using mediation analysis[5] found that boys in families receiving a housing voucher in the *Moving to Opportunities* intervention showed an elevated risk of mood and externalizing disorders. Similarly, other research points to how primary prevention interventions can aggravate disparities and social inequities, particularly when they lack cultural humility in their approaches for minoritized populations[6]. Having the perspective of those involved in the program can be critical to optimize the impacts of the prevention interventions and minimize their unintended consequences.

Specific framing is one of the tricky features of this contribution. Certain review areas may sound like putting the onus on individuals, replicating a narrative that the problems are theirs rather than at the institutional or societal levels. Subtly, this message may convey disempowerment, implying that we researchers can tell these groups how to solve their problems rather than co-create with them the solutions. Considering racial or minoritized groups as the inheritors of the problems, and framing appropriately the preventive interventions (i.e., acknowledging the role that society as a whole has had in generating the problems) can revert the liability. Sometimes we phrase race questions as biological or behavioral flaws or equate race with racism in our interpretation of findings[7].

A more extensive review of the system- and institution-level preventive interventions would call attention to policies and regulations to prevent the onset of mental illness and psychological distress. Addressing structural determinants, as in income support provided by the *Earned Income Tax Credit*, and changing legislation which promotes unpredictable and precarious work schedules for parents in low-paying jobs, are examples of the broad potential impact of policy levers in reducing the adverse mental health harms to young children and decreasing the psychological distress to families. Public policies play a role in onset of and recovery from mental illness. An example is the analysis of the impact of health insurance expansions in Oregon, which demonstrated a decrease in the depression rate[8], although physical health outcomes did not improve in the first two years.

Kirkbride et al focus on positive and enrichment approaches to the neighborhood, such as neighborhood regeneration programs. This section is one of their review's most thoughtful and provocative components. It lends itself to collaborating with the community and policy makers to co-create a program of how, given the context and resources, mental health prevention should best be prioritized. In deciding which alternatives should be selected, the community voice must be central to the discussions. This can help researchers to anticipate unintended consequences and align with what matters most to that community. On the other hand, it can avoid that policy makers view the feasibility and sustainability of such prevention programs as challenging to sell to their electorate.

The authors are practical in recommending that we give precedence to interventions that might influence multiple domains, such as intervening in the prenatal period or in childhood in order to orient mental, physical and cognitive trajectories. However, policy makers must also play a significant role, since their ranking of what needs to be prioritized and invested in might differ from our theoretical models of causation and reparation. Community-research-policy partnerships[9] might be the best avenue to build and implement the preventive agenda. Because not all social determinants equally affect or impact onset, progression or recovery of mental health problems, which might depend on the population and its characteristics, some preliminary work and convening might be needed to bring the different partners to agree on a plan of action and on the desired outcomes.

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Advancing quantitative evaluation of social determinants of mental health and intervention effects: the need for community risk assessments

Kirkbride et al[1] provide a comprehensive, rigorous and thoughtful overview of the literature on social determinants of mental health, focusing on evidence for both causal effects of determinants and effectiveness of interventions. They also put forward a series of recommendations, focusing on how to prioritize prevention and intervention that attends to social justice and poverty alleviation with more rigorous study designs and greater data surveillance. I would like to add one additional recommendation: the need for community risk assessments.

The literature mostly reports risk ratios and beta values in cohort studies and intervention trials, from which conclusions can be drawn about relative magnitudes of risk elevation and reduction. Yet these measures largely do not provide information on which causes are most important, or which interventions are likely to be most effective, at the community level. Community risk assessments provide context- and community-specific information to set priorities, to be realistic about which interventions are worth the effort to implement, and to identify gaps where new, or more effective and scalable, interventions need to be developed.

The quantification of community risk has a long history[2-5], yet its application remains limited, especially in psychiatric epidemiology. What makes community risk assessments useful is that they combine prevalence and effect size, and make transparent assumptions that are often unacknowledged in more standard relative measures.

Across communities with low or high prevalence of exposure, the risk ratio or beta from a regression model may be similar: for instance, those who are exposed have twice the risk of the outcome compared to those unexposed. However, the public health impact of exposure may vary tremendously across the scenarios, and is captured in the population prevalence difference, the expected cases in the exposed, the population attributable fraction, and the number needed to harm. In a rare exposure scenario, for example, we could prevent just less than 10% of cases even if we perfectly implemented an intervention that removed 100% of the exposure. In a common exposure scenario, instead, almost half of cases could be prevented if we eliminated all the exposure.

Highlighting public health impact in our quantification of associations between exposure and outcome would push us as a field towards prioritizing intervention development for common exposures, including many of the social determinants of health reviewed by Kirkbride et al. Interventions with small relative effect sizes will have more impact for common exposures than interventions with large relative effect sizes for rare exposures. For example, Kirkbride et al cite a systematic review of the association between socioeconomic status and child/adolescent mental health[6], which reported that the disorder prevalence difference between individuals with high and low socioeconomic status ranged from 8.9% and 13.2%, respectively, in the lower bound, to 15.9% and 33.4%, respectively, in the upper bound. While the risk ratios in lower and upper bound are similar, the public health implications are remarkably different. We can estimate that eliminating poverty would reduce ~10% of disorder in the lower bound scenarios, and ~20% – twice as many – in the upper bound. Considering interventions to reduce childhood/adolescent poverty, such as cash transfers, which have a meta-analyzed odds ratio of 0.72 for adolescent internalizing conditions[7], we can then model the anticipated impact of their scaling in terms of potential public health impact, given the anticipated population attributable proportion.

Greater attention to assessment of community impact of exposures will also provide more rigor to our framing of interventions. Among Kirkbride et al's recommendations is to strengthen causal inference in research on social determinants of health. Commonly used estimates often make heroic counterfactual/potential outcome assumptions that cloud interpretation. For example, a risk ratio from a cohort study comparing depression incidence among those who are in poverty and those who are not compares two scenarios: the potential depression outcome if the entire population were in poverty versus the potential depression outcome if poverty were eliminated. While valuable for etiologic identification and elaboration, such measures are not directly relevant for public health, because an intervention to eliminate all poverty is unfortunately more of a thought experiment than a reality. Instead, targeted intervention effects that incorporate community risk[8] allow one to estimate the proportion of the outcome that could be prevented if we were able to reduce exposure by a specific amount. We might frame a question around estimating what proportion of depression cases could feasibly be prevented if poverty were shifted by the estimated amount.

This type of exercise, landscaping the total community impact of exposure, and addressing the potential impact of interventions within that landscape, can bring together epidemiology and implementation science. As Kirkbride et al (and others[9]) note, the scalability of interventions that we know to work is a major barrier to improving community mental health. Assessment of community impact can provide additional analytic scaffolding to such statements.

A common critique to community risk assessments is that they are context-specific and will change based on location and time, but that is precisely the point. In the real world, we assess risk and implement interventions within specific contexts. Community risk assessments also clarify that our understanding of effect sizes and intervention effects, including relative measures, are anchored in time; what would be a high impact at one time point may not be as high at another time point, as prevalence and risk factors shift.

We know that the generalizability of exposure and intervention effects across time and place is an important component of public health science, yet discussions of these concepts are often relegated to a few sentences at the end of our papers. Community risk assessments provide a way to integrate knowledge about the specifics of

contexts into our science. There may be contexts across the world where we do not have sufficient information about exposure or outcome prevalence to reliably estimate community risk; in those circumstances, it is prudent to conduct foundational epidemiological surveillance before attempting to implement specific interventions, to minimize unintended consequences and squandered resources.

While community risk assessments are of great value, like all measures they can also be misused and misunderstood. Further, risk factors are often synergistic, thus measures such as population attributable fraction sum well beyond 100%. Yet, the inclusion of community risk assessments would make synergy across risk factors more transparent; by only reporting relative measures of interaction (e.g., interaction betas, stratified risk and odds ratios), their synergistic impact on population mental health remains obscured.

In summary, Kirkbride et al provide a tremendous service to the field with their extensive and thorough review. It is incumbent on all of us, as scholars and researchers, to develop interventions that address social determinants of health at multiple levels, through a social justice approach. Such efforts will be aided by acknowledging differences in exposure and intervention effects across contexts, and quantitatively modeling them with the readily tools developed in epidemiology. We are only as effective as the numbers that we produce. In addition to rigorous study design, we should reliably assess community risk to maximally affect change.

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The changing nature of work in the 21st century as a social determinant of mental health

An extensive literature has documented the association of psychosocial work stressors – e.g., job strain, effort-reward imbalance, organizational injustice, long working hours, job insecurity, shift work, workplace harassment and bullying – with mental health problems[1-4]. However, the implications for population mental health of the changing nature of work in the 21st century have not been sufficiently highlighted.

The classical job strain model captures job task-related exposures (e.g., the combination of excessive psychological demands with lack of autonomy), but does not speak to the broader picture of what has been happening in the workplace during the era of globalization, automation, and the rise of alternate forms of work (e.g., casual and part-time work). Three trends are exemplary in this respect: digital enforcement, just-in-time scheduling, and workplace fissuring. Each of these trends represents a potential social determinant of mental health at the population level.

Digital surveillance has become widespread across workplaces in some countries, whether in the form of tracking devices worn by employees in Amazon warehouses ("fulfillment centers") to meet their daily quotas, or the monitoring software installed on the desktop computers of remote employees during the pandemic.

One of the most intensely surveilled occupations in the US is trucking, which employs about 3 million drivers. Truck drivers are already at high risk of mental health problems, due to the excessive hours of work, lack of sleep, and social isolation[5]. Since the deregulation of the US trucking industry in the 1980s, they have also had to contend with the burden of low wages, due to a shift in compensation from salaried work to piece rate compensation. Truck drivers are paid for miles driven, not for the hours they spend on the road stuck in congested traffic or the hours waiting for their cargo to be loaded/unloaded. As a result of the switch to piece rate compensation, truckers' wages dropped by 44% between 1977 and 1995[5].

In order to make a living, drivers have been forced to spend longer hours on the road, which increases the risk of accidents. In response, lawmakers in 1997 mandated the installation of electronic logging devices on all trucks. These devices have helped to enforce "hours of service" regulations in the trucking industry, which dictate that truckers may drive no more than eleven hours a day, after which they must take a mandatory rest break. However, despite the industry-wide improvement in compliance with hours of service limits, the introduction of digital enforcement paradoxically increased the rate of crashes, because drivers responded by speeding to make up for lost productivity[6].

In terms of worker autonomy, the same time-logging devices are bundled with other capabilities which enable employers to monitor driver performance in areas such as fuel usage, frequency of changing lanes, and adherence to travel routes. This has nothing to do with compliance with safety regulations, but is all about extracting efficiency and maximizing productivity.

The concept of just-in-time scheduling originally began as a management strategy in the manufacturing sector to align the delivery of raw-material supplies with production schedules. Subsequently it spread to the retail and service industry, where employers use it to manage labor costs by scheduling employees based on fluctuating consumer demand. For example, if a store manager believes that his/her shop will be unusually busy ahead of a national holiday, he/she can update scheduling on the fly and ask additional employees to come in.

Under just-in-time scheduling, workers typically receive their

schedules on short notice, and may have their shifts changed or canceled at the last minute. Employers may put workers on call with no guarantee that there will be work available for them. According to the American Time Use Survey, an estimated 45% of wage and salary workers over the age of 15 are given their schedules less than a month in advance, while 20% are told about their schedules less than one week in advance[7].

In addition to making it difficult to arrange childcare, attend school, or hold a second job, irregular work hours also result in income volatility for hourly wage workers. Variable work hours in turn jeopardize access to many safety net programs (e.g., food assistance programs in the US) which require a minimum number of hours of work per week. A study in South Korea found that workers with unpredictable work hours had a significantly increased risk of depressive symptoms[8].

A third example of the changing nature of work is workplace fissuring, which refers to the management practice of outsourcing parts of the organization which are not viewed as "core competencies" of the firm[9]. For example, most cleaners, laundry workers and kitchen staff in the hotel industry are not employees of the brand-name hotels, but are "independent contractors" hired by third party companies. Customer service departments of major corporations have been spun off to third party companies, which in turn hire an army of independent contractors to perform the work. The independent contractor is responsible for purchasing the assets required to perform the work (home office equipment such as a computer, headsets and a dedicated phoneline), and must pay for the costs of training to become a customer service representative for the brand name corporation, as well as pay a monthly fee to use the digital platform that connects him/her to customers.

At the same time, the independent contractor classification means that the worker receives none of the benefits of being a salaried employee, such as a pension or health insurance. These workers are typically paid for the time they spend responding to customer calls, not for the hours waiting for customers to call in. An estimated 1 in 5 people in the US workforce are engaged in the fissured workforce – including hotel and hospitality, telephone operators, home health care, janitors, security guards, and fast food restaurants.

The consideration of working conditions as a social determinant opens up the possibility for an expanded set of structural interventions to promote population mental health, e.g., changing laws to protect the rights, welfare and safety of employees. It forces the question: what is the role of corporations and employers in generating mental ill-health, and what is the potential for work-based interventions, policies and regulations to promote mental health? Businesses (and shareholders) profit from wringing maximum productivity out of workers through low pay, long work hours, unpredictable schedules, digital surveillance, and shifting the costs of doing business on to workers. Consumers also benefit from lower prices, but, in many cases, consumers are also workers being exploited by the same system.

It is time for us to consider the changing nature of work in the 21st century as a significant social determinant of mental health, and to make a substantial effort to develop interventions addressing it.

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Some priorities in targeting social determinants to achieve prevention of mental disorders

Kirkbride et al[1] provide convincing evidence of a causal relationship between social determinants and poorer mental health outcomes. The extent, complexity and prevalence of these determinants could lead to hopelessness at the prospect of addressing the inequalities and inequities involved. However, the authors instil hope and optimism by providing examples of interventions delivered at the family, school, neighbourhood or societal level that have been effective in primary prevention. They then offer seven key recommendations for action by mental health professionals, policy makers and researchers to prevent or reduce mental health problems that arise from social determinants. All these recommendations warrant further discussion. However, I will focus on two: the need to prioritize interventions providing positive outcomes across multiple domains, and the demand to utilize the causal architecture approach in psychiatric epidemiology.

Kirkbride et al propose that mental health outcomes should be evaluated in any policy, programme or intervention targeting social determinants. This would be a highly informative and beneficial endeavour. However, while achievable, it would require a significant shift in how research is conducted, and would involve establishing and maintaining relationships and collaborations across multiple disciplines, faculties and departments. The benefits would be reciprocal, as the functional outcomes of education, employment, housing and diversion from the criminal justice system are likely to be very meaningful from the viewpoint of several stakeholders. This action would also entail that mental health clinicians and researchers have a role in advocacy at a government level, as any policy that affects the key social determinants will

have a knock-on effect on mental health at a population level.

However, clinicians are already overburdened with the high prevalence of mental disorders, and academics need to be continuously productive in a highly competitive environment for grants and fellowships. The benefits of this approach would take years to realize and can be challenging to evaluate directly. Therefore, those time-consuming endeavours of across-discipline collaborations and advocacy would need to be acknowledged by the authorities and institutions that award grants and promotions, as some are already doing.

Kirkbride et al call for the causal architecture approach to be used in psychiatric epidemiology, as this would lead to an understanding of the pathways between one or more exposures and the disease/disorder. This approach could result in the identification of modifiable risk factors and inform where interventions should be targeted. The mechanisms by which social determinants contribute to the aetiology of mental disorders are likely to be complex and could also differ amongst individuals. For example, in the case of childhood adversity and trauma, the experience itself of being the victim of abuse or adversity could lead to subsequent mental health problems, but, additionally, the manner by which individuals are supported (or not supported) by their family and loved ones, as well as by the legal or medical system, could also be involved in the pathway[2]. Another example of a likely complex relationship is that between low income and poor mental health, since socioeconomic differentials as well as psychological perceptions and self-esteem, in addition to an absolute lack of material resources, may lead to a higher risk of experiencing a mental disorder[3].

Another key aspect of the causal architecture approach is that the sampling should be from a representative population. As the authors rightly point out, there is a relative lack of research in lower- and middle-income countries, despite these countries representing over 80% of the world's population[4]. There have been recent endeavours to undertake methodologically robust epidemiological studies in the Global South. In one such study, the incidence of untreated psychotic disorders was found to be three times higher in Northern Trinidad compared to both the Kancheepuram district in India and Ibadan in Nigeria[5]. The incidence rate observed in Northern Trinidad (59.1 per 100,000) would have ranked as the third highest if considered in a previous meta-analysis including 44 estimates of the international incidence of psychotic disorders[6]. Both substance use and levels of community violence and crime have increased markedly in Trinidad in recent years. This suggests that there are settings in which the potential for primary prevention of psychotic disorders by targeting social determinants could be particularly high.

It is also worth considering the proportion of mental disorders that interventions targeting social determinants could prevent. Population attributable fractions have been estimated to be nearly 38% for childhood adversity and just under 10% for cannabis use in schizophrenia, and to be 13.4% for childhood sexual abuse in depression[7]. This is in keeping with the call by Kirkbride et al for social determinants to be fully integrated into the bio-psycho-social model of mental health and illness. It also highlights that primary prevention strategies aimed at social determinants could reduce the incidence of mental disorders but not eradicate them. Considering this, while Kirkbride et al focus on primary prevention, social determinants could also inform improvements and advancements in secondary prevention.

To ensure an equitable allocation of resources, a secondary prevention strategy could be the determination of resourcing and funding of services on the basis of the geographic prevalence of social determinants, such as social deprivation, fragmentation and rates of migrants and minority ethnic groups. Indeed, it has been demonstrated that the incidence of psychotic disorders can be reliably predicted based on the prevalence of social determinants in geographically defined areas resulting from census data[8]. Yet, the majority of mental health services continue to be funded on a *per capita* basis. There are also inequalities and inequities for certain groups in accessing treatments; for example, individuals from racial and minority ethnic groups are less likely to be referred to or receive psychological interventions in the UK[9]. This unequal distribution of resources and these barriers to accessing services need to be addressed alongside the efforts for primary prevention.

The call to action by Kirkbride et al is ambitious, but its goals are achievable. It can help to address the underlying inequalities and inequities within our societies that contribute to the development of mental health problems and may sustain them across further generations.

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Deconstructing the social determinants of mental health

Social factors have an important impact on the onset of and recovery from mental illness[1]. Where individuals live, how they live and what factors impinge on their living, including their access to nutrition, to housing, to recreation, as well as their pattern of interactions with other people around them, have consequences and relevance for their emotions and behaviours.

The fact that humans are social beings implies that, for most people, well-being depends on the totality of the social environment

in which they live. It is useful and informative that research has sought to disaggregate the components of that environment and focus attention on specific aspects. But the reality is that not one social factor can exert its impact on health, including mental health, without the influence of several other factors. Indeed, in poor or low-resourced communities, where the living context is marked by multiple deprivations and interconnected social, physical and mental health problems, as well as by the intergenerational transmission of those syndemics[2], the particular role of a given social factor in the onset or course of a mental health condition is difficult to isolate clearly. An acknowledgement of this conceptual complexity is therefore necessary, although the practical necessity of focusing on particular aspects as if they were operating in isolation is understandable.

As highlighted in the paper by Kirkbride et al[1], the available body of knowledge suggests that the link between social factors and mental illness is rarely direct, even when factors as easily understood as poverty and economic disadvantage are those of interest. Furthermore, much of the evidence exploring the relationships of social factors with mental health has been provided by studies conducted in the Global North. Widening our exploration to diverse social, economic and cultural settings is likely to deepen our understating. Even though there is now a growing interest in the topic in the Global South[3], studies with a focus on the social determinants of mental health from low- and middle-income countries need to be pursued more vigorously.

Social factors exist and manifest within cultural and traditional milieus. For example, while the relationship between gender equality and the gender-patterning of the distribution of some mental disorders is complex, culture may be an important driver of this complexity. Actually, the traditional and cultural position of women is relevant to whether gender inequality will be an important determinant of the distribution of some mental disorders. Cultural variations also exist in the way that families are composed, in the social position of the young and the elderly, and in the organization of and power distribution within households.

The fact that some of these social factors are also undergoing rapid changes in many countries, especially in low- and middle-income ones, introduces another layer of complexity to the relationship between social factors and health in general, and mental health in particular. In many countries, the traditional composition of families is changing from extended to nuclear, and so is the status of the elderly. Some of these changes are being driven by economic pressures as well as by unrelenting, and sometimes unplanned, urbanization. In these contexts, the urban drift of the young is leaving many elderly persons behind in towns and villages, increasing their risk of isolation and loneliness[4]. For such elderly persons, rural living is no longer a haven of serenity and peace, but rather a source of neglect and alienation.

The interpretation of the links between social factors and mental illness is further complicated by differences between objective and subjective assessments. In fact, the ambiguity of the findings concerning the link between low income and common mental disorders may be due to the fact that relative rather than absolute poverty is a predictor of mental illness when other factors are taken into account[5]. A similar caveat is required when interpreting the association between subjective or relative social status and mental health[6]. Indeed, one could argue that this is the basis of the paradoxical finding, in a number of population surveys, of a lower prevalence of mental disorders in poorer than in richer countries. The meaning attached to a social factor or circumstance by an individual can be presumed to, at least in part, determine what coping and adaptation mechanisms will be available and deployed to meet adversities and other challenges to mental health.

Social factors are as important to the causation of mental disorders as they are to the recovery from them. The immediate source of support in times of ill health is often the family. The composition and size of a household are culturally determined, and are relevant to the immediacy of the availability of support to an individual when in need. In some communities, the relevant social network may also include non-family groups such as those available in places of worship and markets[7]. It is possible that these social groups pose challenges to an individual's mental health just as they may be available to provide various forms of instrumental and emotional support to help mitigate the effects of adversities. Whether the risks posed by a particular social network to the mental health of an individual outweigh the potential benefits may be related to the complex interplay of a variety of social and cultural factors.

What is the role of the understanding of social determinants of mental illness for planning of evidence-based interventions? Our understanding of the neurobiology of psychiatric conditions remains limited, in spite of the great strides in the study of the brain. Preventing or treating mental disorders continues to rely on blunt biopsychosocial tools that are limited in their capacity to deliver contextualized approaches. It is therefore evident that, as we seek to have a broader and deeper understanding of social determinants of mental health[8], an important focus must be the need to design interventions that include context-informed social prescribing. That should also be a good fit for comprehensive mental health promotion and prevention strategies[9].

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Effectiveness and cost-effectiveness of online recorded recovery narratives in improving quality of life for people with non-psychotic mental health problems: a pragmatic randomized controlled trial

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Narratives describing first-hand experiences of recovery from mental health problems are widely available. Emerging evidence suggests that engaging with mental health recovery narratives can benefit people experiencing mental health problems, but no randomized controlled trial has been conducted as yet. We developed the Narrative Experiences Online (NEON) Intervention, a web application providing self-guided and recommender systems access to a collection of recorded mental health recovery narratives (n=659). We investigated whether NEON Intervention access benefited adults experiencing non-psychotic mental health problems by conducting a pragmatic parallel-group randomized trial, with usual care as control condition. The primary endpoint was quality of life at week 52 assessed by the Manchester Short Assessment (MANSA). Secondary outcomes were psychological distress, hope, self-efficacy, and meaning in life at week 52. Between March 9, 2020 and March 26, 2021, we recruited 1,023 participants from across England (the target based on power analysis was 994), of whom 827 (80.8%) identified as White British, 811 (79.3%) were female, 586 (57.3%) were employed, and 272 (26.6%) were unemployed. Their mean age was 38.4±13.6 years. Mood and/or anxiety disorders (N=626, 61.2%) and stress-related disorders (N=152, 14.9%) were the most common mental health problems. At week 52, our intention-to-treat analysis found a significant baseline-adjusted difference of 0.13 (95% CI: 0.01-0.26, p=0.041) in the MANSA score between the intervention and control groups, corresponding to a mean change of 1.56 scale points per participant, which indicates that the intervention increased quality of life. We also detected a significant baseline-adjusted difference of 0.22 (95% CI: 0.05-0.40, p=0.014) between the groups in the score on the "presence of meaning" subscale of the Meaning in Life Questionnaire, corresponding to a mean change of 1.1 scale points per participant. We found an incremental gain of 0.0142 quality-adjusted life years (QALYs) (95% credible interval: 0.0059 to 0.0226) and a £178 incremental increase in cost (95% credible interval: –£154 to £455) per participant, generating an incremental cost-effectiveness ratio of £12,526 per QALY compared with usual care. This was lower than the £20,000 per QALY threshold used by the National Health Service in England, indicating that the intervention would be a cost-effective use of health service resources. In the subgroup analysis including participants who had used specialist mental health services at baseline, the intervention both reduced cost (–£98, 95% credible interval: –£606 to £309) and improved QALYs (0.0165, 95% credible interval: 0.0057 to 0.0273) per participant as compared to usual care. We conclude that the NEON Intervention is an effective and cost-effective new intervention for people experiencing non-psychotic mental health problems.

Key words: NEON Intervention, recovery narrative, non-psychotic mental health problems, digital health intervention, quality of life, meaning in life, lived experience narrative

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Recorded narratives describing personal experiences of mental health problems have been widely used in health care and community settings[1], including in professional training[2] and as a resource in psychotherapy sessions[3]. They have been a central component of national campaigns to reduce mental health stigma[4], where they have been used as a scalable mechanism to create a perception of social contact with people who have experienced mental health problems[5].

Recorded recovery narratives (RRNs) are a specific category of mental health narratives which describe recovery from mental health problems[6]. They are widely available to the public[7], either individually or in collections curated around a common theme, such as books intended to create hope by presenting narratives describing psychosis recovery[8]. They have been widely used to promote mental health recovery[9]. Narrators have described creating hope in others as a motivation for publishing their recovery narrative[10]. However, whilst the benefits to narrators of sharing a narrative are well established[11], the benefits to narrative recipients are under-

investigated.

Through a six-year research program (2017-2023), the Narrative Experiences Online (NEON) study has investigated whether access to an online RRN collection can benefit people currently experiencing mental health problems and their informal carers. This has included developing and evaluating the NEON Intervention, a web-based digital health intervention which provides access to a collection of 659 RRNs[12].

The program theory for the NEON Intervention is the NEON Impact model, which was developed from systematic review, interview and experimental evidence[13-16]. In this model, the expected benefit of receiving RRNs is enhanced quality of life through increases in hope, connectedness, empowerment, meaning in life, initiation of help-seeking behaviours, and emulation of helpful narrator behaviours. Possible harms include emotional burden from encountering difficult experiences described in RRNs, and emulation of harmful narrator behaviours. As we developed the NEON Intervention, we selected safety strategies to manage known harms, supported by lived experience and academic advice[12].

Here we report on a pragmatic parallel-group randomized controlled trial of the NEON Intervention across England, which aimed to explore whether receiving online RRNs, in addition to usual care, benefits people with experience of non-psychotic mental health problems. The primary objective of the trial was to evaluate the effectiveness of the NEON Intervention in improving quality of life, as compared to usual care only. Secondary objectives were: a) to evaluate the effectiveness of the NEON Intervention in improving hope, empowerment and meaning in life, and in reducing psychological distress, as compared to usual care; b) to assess the cost-effectiveness of the NEON Intervention compared to usual care, from a health and social care provider perspective; c) to determine whether effectiveness and cost-effectiveness varied according to prior health service usage; and d) to understand how the intervention was used.

Participants were randomly assigned to receive immediate (intervention group) or 52-week delayed (control group) intervention access, were not masked to treatment allocation due to the nature of the intervention, and continued to receive their usual care. The primary objective and the secondary objectives a) and b) were assessed at 52-week follow-up, and their measures were baseline-adjusted.

METHODS

Study overview

We obtained ethical approval for the trial from the Leicester Central Research Ethics Committee (19/EM/0326), and approval for managing the NEON Collection from the West London and Gene Therapy Advisory Committee Research Ethics Committee (18/LO/0991).

The trial was prospectively registered (ISRCTN63197153). A Trial Management Group and an independent Programme Steering Committee provided oversight. All trial procedures and the NEON Intervention were delivered through a web application validated by a feasibility study with mental health service users[12].

The chief investigator (MS), the senior statistician (CR) and the trial statistician (CN) were blinded to treatment allocation. MS and CR remained blind until trial analysis work was completed and approved. The trial protocol[17], the statistical analysis plan[18], the NEON Intervention development and delivery cost[19], and the baseline participant characteristics[20,21] have been previously reported.

Reporting of the results of the trial follows the Consolidated Standards of Reporting Trials (CONSORT) 2010[22] and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022[23] statements.

Participants

Inclusion criteria, ascertained by an online eligibility-checking interface (see below), were: experience of mental health problems in the last five years, experience of mental health-related distress in the last six months, resident in England, aged 18+ years, capable of accessing or being supported to access the Internet, able to understand written and spoken English, and capable of providing online informed consent. Participants who reported psychosis experience in the previous five years, defined as being diagnosed with psychosis or having experiences that they or others would call psychotic, were excluded. Experience of mental health distress in the last six months was evaluated using three items from the Threshold Assessment Grid[24], all as related to current experience of mental health problems.

In order to maximize external validity, since digital health interventions can extend mental health service provision to people not engaged with health services, we recruited participants who had or had not used mental health services to date. Participants were recruited through mental health services by clinical support officers, and publicly through a broad range of community engagement and social media activities led by the central study team [20]. All recruitment advertising and messaging followed ethical principles approved by the Ethics Committee[25]. All participants continued to receive their usual care, ranging from no treatment through to treatment by secondary or tertiary mental health services.

Clinical outcomes and service usage assessments

The primary outcome was quality of life, assessed through the Manchester Short Assessment (MANSA)[26] at baseline, week 1, week 12, and week 52 (primary endpoint). The MANSA score is the mean of 12 subjective items assessed on a scale from 1 (low quality of life) to 7.

Four clinical secondary outcome measures were completed at baseline and week 52. Hope was assessed using the Herth Hope Index[27], a 12-item measure with sum score ranging from 12 (low hope) to 48. Meaning in life was assessed through the Meaning in

Life Questionnaire[28], a 10-item measure producing two mean subscale scores ("presence of meaning" and "search for meaning"), each ranging from 1 (low) to 7. Self-efficacy was evaluated through the Mental Health Confidence Scale[29], a 16-item measure with sum score ranging from 16 (low self-efficacy) to 96. Psychological distress was assessed using the Clinical Outcomes in Routine Evaluation 10 (CORE-10)[30], a 10-item measure capturing relevant aspects of symptomatology, with sum score ranging from 0 (low distress) to 40.

Data for the economic analysis were obtained at baseline and week 52. They consisted of health status data collected through the EQ-5D-5L[31,32], and health service use data obtained through an abridged Client Service Receipt Inventory (CSRI)[33]. Collection forms, ranges and psychometric properties have been previously described[20].

The trial had a target sample of 994, which was selected to provide 90% power to detect a minimal clinically important effect size (Cohen's d) of 0.25 on the mean item score for MANSA, allowing for 40% attrition.

Procedures

Registration and baseline data collection

All recruitment approaches directed potential participants to a website where their eligibility was established through an online self-report questionnaire. If eligible, an electronic participant information sheet was provided, and participants consented by checking a box on an online consent form and then validating an email address. Optionally, a mobile telephone number could be supplied, which was subsequently used by the study team to send messages to encourage engagement with the NEON Intervention.

Participants who confirmed their email address were asked to create an account by providing a password. They completed online forms to collect baseline demographic/clinical items and measures[17] and were then randomized. This process could be completed in multiple sessions to avoid fatigue. Due to concerns about digital exclusion[34], the website was designed to work on most personal computers and mobile devices, including communal computers such as those found in public libraries. A management procedure approved by the Trial Management Group and the Programme Steering Committee enabled auditable decisions to suspend repeat registration accounts.

Randomization

Randomization was through permuted blocks with randomly varying block length (2,4,6), with a 1:1 allocation ratio and no stratification. The automated randomization system embedded in the NEON web application was approved by the supervising trial unit. A randomization list was generated by an independent statistician using the Stata RALLOC package[35,36]. Intervention group users were given immediate NEON Intervention access. Control group users gained access to the NEON Intervention after completing primary endpoint questionnaires.

Follow-up and usage data collection

At weeks 1 and 12 after randomization, all participants were prompted by email and on next login to complete web-based questionnaires collecting MANSA responses, and to quantify the number of recovery narratives accessed outside of the NEON Intervention since baseline. At week 52 after randomization, all participants were prompted to complete web-based questionnaires for primary outcome, secondary outcomes, and economic data, and to specify the number of narratives accessed outside of the NEON Intervention since baseline. Data collection reminders were sent by email, text, and phone call. Due to concerns about primary endpoint questionnaire completion rates, the trial was amended to allow a £20 voucher to be claimed for completion of the 52-week questionnaires[21].

Lateness intervals allowed for questionnaires were 8 days for week 1, 32 days for week 12, and 91 days for week 52. The 52-week lateness interval was adjusted from the protocol (31 days) due to reports that post-pandemic changes such as workplace return were disrupting questionnaire completion[19]. The trial closed to follow-up on September 22, 2022. Data on usage of the NEON Intervention were logged, including details of every narrative request and associated narrative feedback, and interactions with safety features.

National regulation for England indicates that only serious adverse events (SAEs) should be monitored in trials not concerning medicinal products[37]. Possible SAEs were reported through web-based forms for logged-in participants or without login to allow third party reporting. They were also identified retrospectively through hospital use reported on the 52-week CSRI form. Reports detailing possible SAEs were examined and actioned by the Chief Investigator.

The NEON Intervention

The NEON Intervention is a web-based interface providing access to the NEON Collection of recorded recovery narratives. The trial opened with 348 narratives, and (per protocol) narratives were added during the trial period, with 659 narratives available when the final randomized participant reached the primary endpoint. Narratives comprised video, audio, images and text. Every narrative was assessed for inclusion by researchers. All included narratives were characterized using the 77-item researcher-rated Inventory of the Characteristics of Recovery Stories (INCRESE)[38].

The central feature of the NEON Intervention is a homepage providing four narrative access mechanisms, each selected using a button labeled with indicative text. The "Match me to a story" and "Get me a random story" buttons both select a narrative not previously accessed. The former invokes the automated recommender system; the latter uses a random number generator. The "Browse

stories" button allows the selection of a narrative using demographic and content categories derived from INCRESE items. The "My stories" button allows return access to narratives previously rated as hope-inspiring or bookmarked by the participant.

After viewing a narrative, participants were asked to rate its immediate impact by responding to up to five validated narrative feedback questions[12]. To maximize response rates, there was one mandatory question on how hopeful the narrative left the participant feeling, with four available responses: "less hopeful than before"; "no change"; "a bit more hopeful"; "much more hopeful".

All intervention pages also include buttons to access intervention information ("Welcome", "About NEON"), to access a guidance page ("I'm upset"), and to rapidly leave the NEON Intervention ("Get me out of here"). Until completing the primary endpoint questionnaires, control group users received access to a simplified homepage excluding narrative access mechanisms.

Before their first access, participants were presented with orienting information and asked to complete an updatable personal profile, where they could identify narrative formats (e.g., text) and content (e.g., self-harm or violence) that they wished to avoid. To familiarize them with the system, participants were shown a first narrative identified empirically as being hope-promoting for feasibility study participants[12], not requiring any content warnings, and conforming to participant format preferences (e.g., a video narrative for participants wishing to avoid text). They were then asked for narrative feedback.

The automated recommender system utilized personal profiles, INCRESE characteristics, and narrative feedback ratings. It was trained with feasibility study usage data[12]. INCRESE characteristics were used to identify narratives similar to those rated positively by the participant (content-based recommendation) using a k-nearest neighbor (kNN) filtering algorithm[39]. Participant profiles were used to identify other similar participant profiles, and then to identify narratives rated positively by these latter participants (collaborative recommendation) using singular value decomposition (SVD) and SVD++ filtering algorithms[39]. The narrative with the highest estimated rating was selected from a combined list.

We used multiple approaches to encourage engagement, whilst considering the need of enabling participants to self-manage engagement. From trial start, engagement messages were sent to participants with intervention access, both by email and text message. Some messages linked directly to exemplar narratives. During the trial, we added functionality to encourage engagement. This consisted of anonymized participant testimonials, "badges" (graphical symbols received on meeting thresholds such as 10 narrative requests), and a system for capturing personal reflections on impactful narratives.

Trial analyses

The economic analysis was conducted in Stata version 16.1 (StataCorp LLC). All other analyses were conducted in R version 4.1.2 (R Foundation, 64-bit implementation). The statistical significance level was two-sided 5%. Analysis used a prospectively-modified intention-to-treat sample which excluded accounts suspended due to repeat registration[18].

Clinical outcomes analysis

The analysis of primary and secondary outcomes used a linear regression model of outcome at week 52 adjusting for baseline. Multiple imputation was used to impute all missing baseline and clinical outcomes using the MI package[40], assuming that data were "missing at random" (MAR). Fifty datasets were generated, and parameters from each individual analysis were combined using Rubin's rules.

To examine differential effects on clinical outcomes, the primary analysis was repeated to include an interaction term between treatment and three demographic items: gender, ethnicity, and (for prior health service usage) use of specialist care mental health services. Baseline clinical outcomes data collected during times of national lockdown were compared with those collected outside of lockdown, using t-tests. With MANSA data collected at weeks 1, 12 and 52, a mixed effect model using random effects for intercept parameters and days of measurement from baseline was fitted, and adopted to examine interactions with periods coded as within national lockdown. Both analyses used dates documented in the statistical analysis plan[18].

We examined the sensitivity of our findings to protocol deviations by conducting a complete case analysis as well as per-protocol analyses excluding repeat registration cases where the intervention group account was retained; randomized in error participants; participants who completed week-52 outcome assessments late; and control group participants who obtained NEON Intervention access due to a technology error. We examined the sensitivity of our findings to missingness by conducting a complete case analysis with significant predictors for missingness added as covariates, and multiple imputation using a pattern mixture model to assess robustness with plausible departures from MAR[41].

Health economic analysis

A within-trial cost-effectiveness analysis compared the cost and quality-adjusted life years (QALYs) gained for both study arms from the perspective of the National Health Service (NHS) in England. Downstream health care resource use was calculated for both arms using CSRI data combined with UK-based unit costs. EQ-5D-5L responses collected at baseline and at week 52 were converted to EQ-5D-3L utility values (UK tariff)[42], as required by the National Institute for Health and Care Excellence (NICE)[43], using an established mapping method[44]. QALYs were calculated from per-participant utility values, assuming a linear relationship between the time points[45]. Mean total cost (log-link and Gamma family) and QALYs (identity-link and Gaussian family) were estimated for each arm using generalized linear models and recycled predictions adjusting for trial allocation and baseline characteristics (age, gender, MANSA total score), baseline EQ-5D-3L utility,

and baseline cost (cost regression only)[45]. Multiple imputation was used for missing data (assumption: MAR).

The main outcome was the incremental cost-effectiveness ratio (ICER), calculated as the ratio of incremental costs to incremental QALYs. Uncertainty was handled by bootstrapping with 2,000 replications. Cost-effectiveness was determined against thresholds of £20,000 and £30,000 per QALY gained[43]. Sensitivity analyses were performed to assess robustness of base-case results, incorporating a range of assumptions on intervention delivery cost, QALY derivation and health service resource cost. In one sensitivity analysis, missing data were imputed using a pattern mixture model to assess robustness with plausible departures from MAR[41]. In a preplanned subgroup analysis, an ICER was calculated for lifetime specialist care mental health service users only.

RESULTS

Participant flow

Trial recruitment took place between March 9, 2020 and March 26, 2021. During this period, a total of 2,096 people were eligible for the trial, of whom 1,123 (54%) completed the registration process. The most common reasons for non-participation were not requesting a consent form after receiving the participant information sheet (N=835), and not validating an email address after completing the consent form (N=138). One hundred repeat registration accounts were suspended. The remaining 1,023 accounts formed the modified intent-to-treat sample. There were more participants in the control (N=516) than in the intervention (N=507) arm, due to imbalance in account suspensions. Seven control group participants received early access to the NEON Intervention due to a technology error. The error was rectified, and NEON Intervention access was suspended until follow-up at week 52 for these participants.

Of the 507 intervention arm participants, 473 (82.1%) accessed at least one narrative and are identified as having received the intervention. Withdrawals were 17 in the intervention and 4 in the control arm. Missing quality of life data at week 52 were 273 (54.0%) in the intervention and 185 (35.9%) in the control arm. The participant flow is shown in Figure 1.

Baseline demographic and clinical characteristics

Baseline demographic and clinical characteristics were similar across treatment groups (see Table 1). All regions in England and all levels of educational attainment were represented. Mean age was 38.4±13.6 years. Of the 1,023 participants, 910 (89.9%) were White, 827 (80.8%) were White British, 811 (79.3%) were female, 794 (77.6%) lived with others, 586 (57.3%) were employed, and 272 (26.6%) were unemployed. The most common primary mental health problems experienced in the month before registration were mood and/or anxiety disorders (N=626, 61.2%) and stress-related disorders (N=152, 14.9%). Specialist care mental health services had been accessed by 614 participants (60.0%), and primary care mental health services by 949 participants (92.8%).

Baseline data collected through assessment instruments were similar across treatment groups (see Table 2). Baseline MANSA data were provided by 444 participants (39.1%) during a national lockdown period, and by 579 participants (60.9%) outside of a national lockdown period. There was no evidence that national lockdown influenced baseline quality of life (difference: 0.00, 95% CI: –0.11 to 0.12, p=0.94) or any secondary outcomes at baseline.

Effectiveness data

All participants in the modified intent-to-treat sample (N=1,023) were included in the primary analysis.

At week 52, we found a significant baseline-adjusted difference in the MANSA score between the intervention and control groups (0.13, 95% CI: 0.01-0.26, p=0.041), indicating that the NEON Intervention increased quality of life. There are 12 items in the MANSA; hence this equates to a mean change of 1.56 scale points per participant. This finding was sensitive to small departures from MAR, since it became insignificant if people in the intervention arm with missing data had a reduction of more than 1% in their MANSA score compared with individuals who had observed data. There were no significant baseline-adjusted differences in the MANSA score at week 12 (0.06, 95% CI: –0.05 to 0.16, p=0.30) and week 1 (0.05, 95% CI: –0.04 to 0.13, p=0.26) (see Table 3).

We also found a significant baseline-adjusted difference in meaning in life (presence of meaning subscale) at week 52 (0.22, 95% CI: 0.05-0.40, p=0.014), indicating that the NEON Intervention increased the presence of meaning in life. This equates to a mean change of 1.1 scale points per participant. There were no significant differences in other secondary outcomes (see Table 3).

The primary analysis was repeated to examine interaction effects between clinical outcomes and three demographic items: gender, ethnicity, and (for prior health service usage) use of specialist care mental health services. For CORE-10, there was evidence of differential effectiveness by gender (p=0.004). For meaning in life (presence of meaning subscale), there was evidence of differential effectiveness by ethnicity (p=0.02). There was no evidence for differential effectiveness by lifetime specialist service use (see Table 4).

To collect evidence for the nature of the interaction, we calculated baseline-adjusted differences for those pairings with a significant differential effect. For gender, we found a significant difference in CORE-10 score when comparing intervention arm with control arm females (–1.74, 95% CI: –2.98 to –0.49, p=0.006), providing evidence that the NEON Intervention reduced psychological distress for females. There was no significant change when comparing intervention arm to control arm males (2.55, 95% CI: –0.43 to 5.53, p=0.09).

For ethnicity, we found a significant increase in meaning in life (presence of meaning subscale) when comparing White British participants in the intervention vs. control arms (0.34, 95% CI: 0.12-0.56, p=0.003), but no significant change for minority ethnic

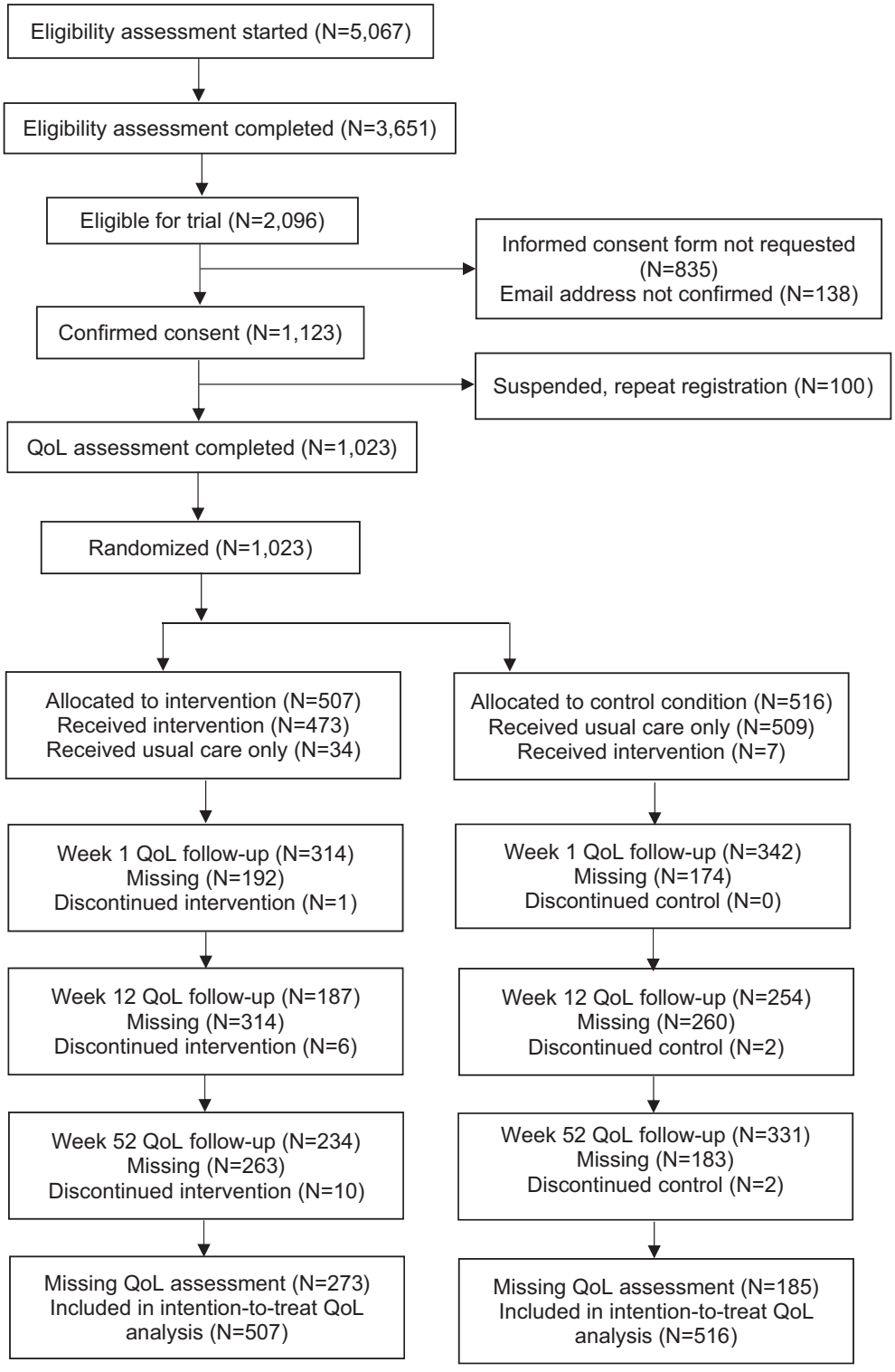

Figure 1 CONSORT diagram. QoL – quality of life

participants (–0.30, 95% CI: –0.89 to 0.28, p=0.30).

When we examined the sensitivity of our findings to protocol deviations by conducting a complete case analysis (N=565), we found an identical baseline-adjusted MANSA difference at week 52 for all protocol deviations examined individually and collectively. Hence we conclude that our MANSA findings are not sensitive to protocol deviations. When we adjusted our complete case analysis for predictors of missingness, the baseline-adjusted difference in meaning in life (presence of meaning subscale) was lower, but still positive and significant (0.22, 95% CI: 0.0057-0.42, p=0.04).

Table 1 Baseline demographic and clinical characteristics of participants

	Intervention (N=507)	Control (N=516)	Total (N=1,023)
Gender, N (%)			
Female	387 (76.3)	424 (82.2)	811 (79.3)
Male	103 (20.3)	81 (15.7)	184 (18.0)
Other	11 (2.2)	7 (1.4)	18 (1.8)
Age (years), mean±SD	38.6±13.5	38.2±13.6	38.4±13.6
Ethnicity, N (%)			
White	441 (87.0)	469 (90.9)	910 (89.9)
White British	391 (77.1)	436 (84.5)	827 (80.8)
Mixed/Multiple ethnic background	19 (0.04)	8 (0.02)	27 (0.03)
Asian	30 (0.06)	17 (0.03)	47 (0.05)
Black/African/Caribbean	10 (0.02)	14 (0.03)	24 (0.02)
Region of current residence, N (%)			
East of England	31 (6.1)	30 (5.8)	61 (6.0)
London	111 (21.9)	99 (19.2)	210 (20.5)
Midlands	104 (20.5)	99 (19.2)	203 (19.8)
North East and Yorkshire	50 (9.9)	52 (10.1)	102 (10.0)
North West	45 (8.9)	53 (10.3)	98 (9.6)
South East	101 (19.9)	113 (21.9)	214 (20.9)
South West	59 (11.6)	66 (12.8)	125 (12.2)
Education, highest qualification, N (%)			
No qualification	18 (3.6)	12 (2.3)	30 (2.9)
Secondary education	55 (10.8)	61 (11.8)	116 (11.3)
Vocational qualification	161 (31.8)	166 (32.2)	327 (32.0)
Degree level qualification	165 (32.5)	184 (35.7)	349 (34.1)
Higher degree level qualification	102 (20.1)	89 (17.2)	191 (18.7)
Mental health service use, N (%)			
Ever used primary care mental health services	470 (92.7)	479 (92.8)	949 (92.8)
Ever used specialist care mental health services	303 (59.8)	311 (60.3)	614 (60.0)
Main mental health problem in the last month, N (%)			
Mood and/or anxiety disorders	314 (61.9)	312 (60.5)	626 (61.2)
Stress-related disorders	72 (14.2)	80 (15.5)	152 (14.9)
Personality disorders	66 (13.0)	57 (11.0)	123 (12.0)
Eating disorders	18 (3.6)	27 (5.2)	45 (4.4)
Neurodevelopmental disorders	–	–	12 (1.2)
Substance-related disorders	–	–	8 (0.8)
Other (less than 5 participants) or unspecified	37 (7.3)	40 (7.8)	57 (5.5)
Residential status, N (%)			
Alone	123 (24.3)	106 (20.5)	229 (22.4)
With others	384 (75.7)	410 (79.5)	794 (77.6)
Occupation, N (%)			
Employed	280 (55.2)	306 (59.3)	586 (57.3)
Sheltered employment	–	–	6 (0.6)

Table 1 Baseline demographic and clinical characteristics of participants (*continued*)

	Intervention (N=507)	Control (N=516)	Total (N=1,023)
Training and education	51 (10.1)	55 (10.7)	106 (10.4)
Unemployed	144 (28.4)	128 (24.8)	272 (26.6)
Retired	30 (5.9)	23 (4.5)	53 (5.2)

Cells with less than 5 participants appear with a "–" sign. The total for some items does not correspond to the N for the overall sample due to some missing data.

In our mixed effects model, there was no evidence that national lockdown influenced MANSA data collected at any follow-up.

Cost-effectiveness data

Total cost data were available for 191 (37.7%) intervention arm and 291 (56.4%) control arm participants. Total QALY data were available for 187 (36.9%) intervention arm and 282 (54.7%) control arm participants. All analyses hereafter used multiple imputation if data were missing.

In the adjusted base-case analysis, total mean cost per participant at week 52 was £1,960 for the intervention arm and £1,782 for the control arm. Therefore, the NEON Intervention increased costs by £178 per participant (95% credible interval: –£154 to £455). Total mean QALYs at week 52 were 0.5770 for the intervention arm and 0.5628 for the control arm. Therefore, the NEON Intervention increased QALYs by 0.0142 per participant (95% credible interval: 0.0059 to 0.0226) (see Table 5).

The ICER was £12,526 per QALY gained, which was less than the selected cost-effectiveness thresholds (£20,000; £30,000), indicating that the NEON Intervention would be a cost-effective use of health service resources (see Table 5).

The ICER was lower than £30,000 in all but one sensitivity analysis (cost of intervention, worst case). When the costs of delivering the NEON Intervention were omitted, the incremental cost between intervention and control was –£170 (95% credible interval: –£507 to £108), indicating that intervention arm membership reduced non-NEON health service resource use.

Figure 2 reports the cost-effectiveness acceptability curve illustrating probability of cost-effectiveness at different threshold values. The probabilities of cost-effectiveness were 71.2% (£20,000 per QALY gained) and 88.2% (£30,000 per QALY gained).

The base-case analysis assumed that all data were missing at random. Sensitivity analysis indicated that, if data were not missing at random, the NEON Intervention would no longer be cost-effective against the £30,000 per QALY threshold if people in the intervention arm with missing data have a reduction of more than 2.3% in their total QALYs gained, compared with individuals who have observed data.

Service usage

We conducted a subgroup analysis including all participants who had used specialist care mental health services at baseline. For this subgroup, the per-participant incremental cost was negative between intervention and control (–£98, 95% credible interval: –£606 to £309), and there was a per-participant QALY gain (0.0165, 95% credible interval: 0.0057 to 0.0273). Hence, the NEON Intervention was classified as dominating usual care for this subgroup, i.e. both reducing costs and improving QALYs.

Table 2 Results of baseline assessments

	Intervention (N=507)	Control (N=516)	Total (N=1,023)
Manchester Short Assessment (MANSA) score, mean±SD	3.8 (0.9)	3.8 (0.9)	3.8 (0.9)
Missing, N (%)	0 (0)	0 (0)	0 (0)
Clinical Outcomes in Routine Evaluation 10 (CORE-10) score, mean±SD	21.7 (7.2)	21.6 (7.3)	21.6 (7.3)
Missing, N (%)	9 (1.8)	10 (1.9)	19 (1.9)
Herth Hope Index score, mean±SD	28.9 (6.6)	28.9 (7.1)	28.9 (6.9)
Missing, N (%)	10 (2.0)	10 (1.9)	20 (2.0)
Mental Health Confidence Scale, mean±SD	51.7 (13.8)	51.5 (14.5)	51.6 (14.2)
Missing, N (%)	9 (1.8)	11 (2.1)	20 (2.0)
Meaning in Life Questionnaire, "presence of meaning" subscale score, mean±SD	3.4 (1.4)	3.4 (1.5)	3.4 (1.5)
Meaning in Life Questionnaire, "search for meaning" subscale score, mean±SD	4.7 (1.5)	4.7 (1.4)	4.7 (1.4)
Missing (for entire questionnaire), N (%)	10 (2.0)	12 (2.3)	22 (2.2)
EQ5D-3L score, median (interquartile range)	0.6 (0.4-0.8)	0.6 (0.4-0.7)	0.6 (0.4-0.8)
Missing, N (%)	11 (2.2)	12 (2.3)	23 (2.2)

Table 3 Primary analysis of effectiveness of intervention vs. usual care

	Baseline-adjusted difference (95% CI)	p
Manchester Short Assessment (MANSA) score (week 52)	0.13 (0.01-0.26)	**0.041**
MANSA score (week 12)	0.06 (–0.05 to 0.16)	0.30
MANSA score (week 1)	0.05 (–0.04 to 0.13)	0.26
Clinical Outcomes in Routine Evaluation 10 (CORE-10) score (week 52)	–0.72 (–1.74 to 2.41)	0.17
Herth Hope Index score (week 52)	0.45 (–0.56 to 1.46)	0.39
Mental Health Confidence Scale score (week 52)	1.40 (–0.83 to 3.63)	0.22
Meaning in Life Questionnaire, "presence of meaning" subscale score (week 52)	0.22 (0.05-0.40)	**0.014**
Meaning in Life Questionnaire, "search for meaning" subscale score (week 52)	0.05 (–0.13 to 0.23)	0.59

Significant findings are highlighted in bold

Intervention usage

A total of 10 (1%) intervention arm participants requested technical support to access the intervention. For those intervention arm participants who received the intervention (i.e., accessed at least one narrative), the median number of narrative requests was 3 (interquartile range: 1-7, minimum: 1, maximum: 107). In total, 327 (69%) of these participants provided at least one narrative feedback item. Of the 2,908 intervention arm narrative requests, 1,559 (54%) received a feedback item on hope. Of these, 168 (11%) indicated that the participant was less hopeful than before accessing the narrative, 544 (35%) that he/she was a bit more hopeful, 175 (11%) that he/she was much more hopeful, and 672 (43%) that there was no change.

Non-NEON narrative usage

Recovery narratives are publicly available on a substantial scale. So, we used a questionnaire to collect information on access to recovery narratives not provided through the NEON Intervention. At week 52, 316 (31%) participants had accessed at least one narrative outside of the NEON Intervention since baseline, comprising 172 (33%) control group and 144 (29%) intervention group participants. Those accessing more narratives through the NEON Intervention also accessed more narratives through other non-NEON routes (Kruskal-Wallis test: p<0.001 for each follow-up time).

Safety analysis

There was one SAE related to trial participation in the intervention arm, which was associated with a recovery story triggering substantial distress. This was an expected harm detailed in the NEON Impact model and on the participant information sheet. The participant discontinued use of the NEON Intervention. There were no related SAEs in the control arm.

DISCUSSION

This study demonstrates that the NEON Intervention is effective in increasing quality of life for people experiencing non-psychotic mental health problems, as assessed after 52 weeks of access. Our intention-to-treat analysis found a significant baseline-adjusted difference of 0.13 (95% CI: 0.01-0.26, p=0.041) in the MANSA score between the intervention and control groups, corresponding to a mean change of 1.56 scale points per participant.

It proved to be feasible for most participants to use the NEON Intervention independently of the study team, with only a very small number of users (1%) requiring technical support to access the platform. This capacity for independent usage of the intervention suggests the feasibility of scaling it up. Hence, the relatively small increase in quality of life at the individual level is likely to produce a substantial mental health impact if the NEON Intervention is provided at population level.

Table 4 Interaction effects between clinical outcomes (at week 52) and some pre-identified variables (p values)

	Lifetime specialist services use	Gender	Ethnicity
Manchester Short Assessment (MANSA) score	0.10	0.45	0.80
Clinical Outcomes in Routine Evaluation 10 (CORE-10) score	0.25	**0.004**	0.73
Herth Hope Index score	0.56	0.89	0.09
Mental Health Confidence Scale score	0.31	0.27	0.72
Meaning in Life Questionnaire, "presence of meaning" subscale score	0.70	0.96	**0.02**
Meaning in Life Questionnaire, "search for meaning" subscale score	0.28	0.39	0.99

Significant findings are highlighted in bold

Table 5 Base-case economic analyses and sensitivity analyses

	Cost			QALYs			ICER
	Intervention	Control	Incremental	Intervention	Control	Incremental	
Base-case analyses							
Adjusted base-case analysis	£1,960	£1,782	£178 (–£154 to £455)	0.5770	0.5628	0.0142 (0.0059 to 0.0226)	**£12,526**
Unadjusted base-case analysis	£2,373	£3,472	–£1,099 (–£2,494 to £19)	0.5652	0.5744	–0.0091 (–0.0369 to 0.0196)	£120,547
Sensitivity analyses							
Cost of intervention, best case	£1,895	£1,774	£122 (–£205 to £399)	0.5781	0.5630	0.0151 (0.0069 to 0.0234)	**£8,057**
Cost of intervention, worst case	£2,232	£1,740	£492 (£155 to £770)	0.5784	0.5633	0.0151 (0.0068 to 0.0233)	£32,582
Cost of intervention, no fixed cost	£1,830	£1,802	£28 (–£301 to £306)	0.5771	0.5637	0.0134 (0.0050 to 0.0215)	**£2,102**
Cost of intervention, zero cost	£1,629	£1,799	–£170 (–£507 to £108)	0.5774	0.5626	0.0148 (0.0063 to 0.0233)	**Dominant**
QALY generalized linear model, Poisson family	£1,974	£1,780	£194 (–£136 to £471)	0.5793	0.5619	0.0175 (0.0086 to 0.0258)	**£11,123**
Cost of non-mental health inpatient stay, per day payment	£1,954	£1,745	£209 (–£126 to £489)	0.5787	0.5640	0.0147 (0.0062 to 0.0228)	**£14,253**
Cost of non-mental health inpatient stay, zero cost	£1,863	£1,595	£268 (–£53 to £531)	0.5767	0.5637	0.0130 (0.0049 to 0.0213)	**£20,635**
Multiple imputation, omitting baseline variables	£1,735	£1,759	–£24 (–£377 to £264)	0.5703	0.5638	0.0066 (–0.0020 to 0.0150)	**Dominant**
Complete case analysis	£1,758	£1,706	£52 (–£574 to £609)	0.5753	0.5711	0.0042 (–0.0122 to 0.0210)	**£12,573**

Credible intervals for incremental outcomes are reported in parentheses. QALY – quality-adjusted life year, ICER – incremental cost-effectiveness ratio. ICERs indicating cost-effectiveness at a threshold of £30,000 are highlighted in bold. "Dominant" indicates that the ICER is negative.

Our study also demonstrates that the NEON Intervention is cost-effective from the perspective of health commissioning. The ICER was £12,526 per QALY gained, which was less than the selected cost-effectiveness thresholds (£20,000; £30,000). For the subgroup of participants who had previously used specialist care mental health services, the per-participant incremental cost was negative between intervention and control, and there was a per-participant QALY gain, so that the intervention was classified as dominating usual care, i.e. both reducing costs and improving QALYs. The intervention is likely to be even more cost-effective in a population-level implementation scenario, because the resources required to deliver it in practice will be mostly quasi-fixed costs, al-

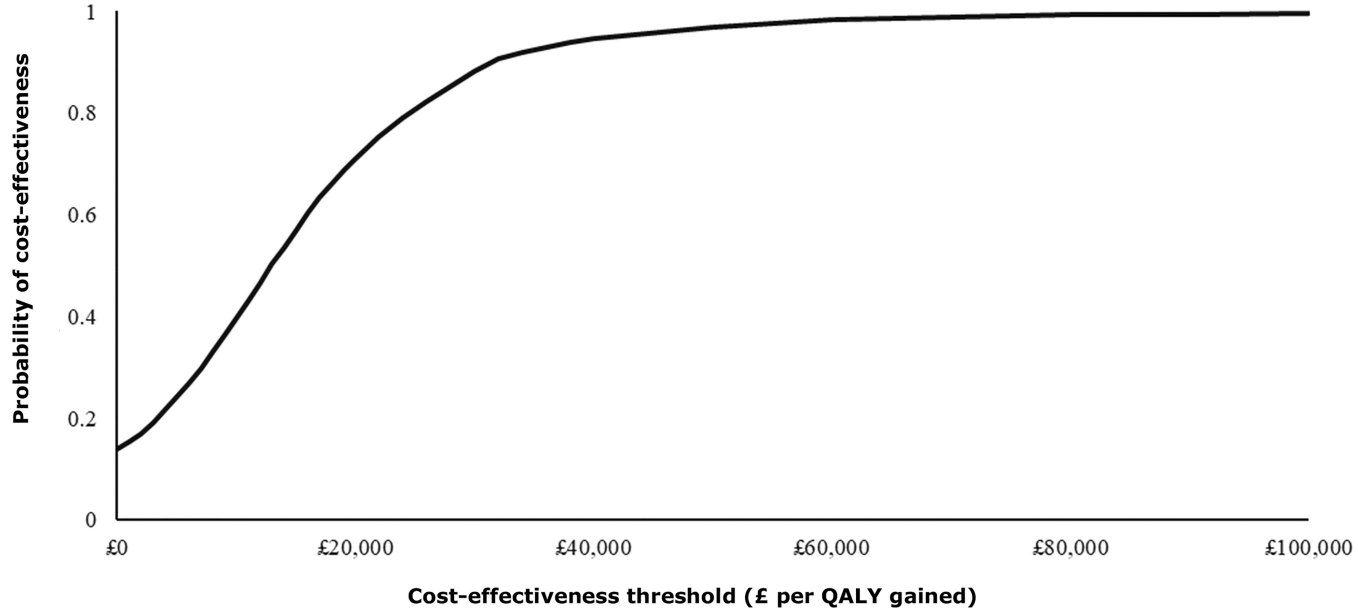

Figure 2 Cost-effectiveness acceptability curve (adjusted base-case analysis). QALY – quality-adjusted life year

lowing the cost components to be apportioned across increasing numbers of users.

Whilst assembling our narrative collection for use in the trial took a substantial effort from the study team, several participants decided, in turn, to offer their narrative to the NEON Collection, inspired by their trial experiences. Therefore, population-scale deployment of the intervention may lead to a virtuous circle of narrative donation, with each donation increasing the diversity of mental health experiences present in the collection. This is important, since the NEON Impact model positions connection with a narrative as a mechanism, and the likelihood of connection is enhanced by greater narrative diversity in the collection[47].

The potential for easy scalability is a critically important characteristic of the NEON Intervention, in the light of the ongoing mental health treatment gap[48]. A survey of psychiatric leaders in 57 countries suggested that the increased delivery of treatment in non-psychiatric settings and an increased availability of a range of interventions are both important strategies for supporting help-seeking around mental health whilst reducing the treatment gap[49]. The NEON Intervention only requires a computer or smartphone and Internet access, and hence it may have a role to play in the delivery of these strategies, particularly as the rapidly increasing availability of mobile and networking technologies will make the delivery of digital health interventions ever more practical in lowest resource settings[50]. Modifications of the intervention to enable success in these settings might be considered, such as enabling accessibility on low-specification (and hence low-cost) phones or networks. Different cultures can influence adoption of digital health interventions[51] and hence cultural adaptation of the NEON Intervention should be considered to enhance adoption[52].

Our study had some limitations. We recruited a convenience sample, which was largely female. RRNs are widely available to the public, and hence access by the control group was possible and did occur, though our findings demonstrate that greater NEON Intervention narrative access was associated with greater public recovery narrative access, suggesting that NEON Intervention use led to public recovery narrative use. Some data were imputed, and our findings are sensitive to our missing data assumptions. Our recruitment period was during the COVID-19 pandemic, and the limitations imposed by this period may have increased the influence of digital exclusion, such as ability to access public computers. Most of our follow-up period may have been influenced by these factors as well.

There was little evidence for safety concerns from our trial, as the one SAE related to trial participation was resolved through discontinuation of the intervention. However, our approach to safety data collection was limited, as our national regulator only allowed monitoring of SAEs, and hence we did not monitor for adverse events not classified as serious, and our approach to safety monitoring required active report of possible SAEs. Since important safety concerns can be identified through the inspection of non-serious or not actively reported adverse events[53], we cannot draw a definitive conclusion on intervention safety from our trial, and ongoing monitoring of safety is indicated with more widespread availability.

From our findings, we conclude that the NEON Intervention is a low-intensity self-management intervention which has demonstrated effectiveness and cost-effectiveness for people with non-psychotic mental health problems in an England-wide trial. Implementation at a population level is indicated, with appropriate monitoring for safety of usage. Evaluation of integration of the intervention in mental health services as an adjunct to usual clinical practice can be recommended. The next steps include refinement for use in other linguistic and cultural settings, and extension to other clinical populations, and we are actively supporting a range of international follow-on studies.

A future integration of these initiatives into a single multi-language and multi-disorder online intervention would be an innovative approach to addressing the multimorbidity challenges of increasingly diverse national populations.

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The definition of treatment resistance in anxiety disorders: a Delphi method-based consensus guideline

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Anxiety disorders are very prevalent and often persistent mental disorders, with a considerable rate of treatment resistance which requires regulatory clinical trials of innovative therapeutic interventions. However, an explicit definition of treatment-resistant anxiety disorders (TR-AD) informing such trials is currently lacking. We used a Delphi method-based consensus approach to provide internationally agreed, consistent and clinically useful operational criteria for TR-AD in adults. Following a summary of the current state of knowledge based on international guidelines and an available systematic review, a survey of free-text responses to a 29-item questionnaire on relevant aspects of TR-AD, and an online consensus meeting, a panel of 36 multidisciplinary international experts and stakeholders voted anonymously on written statements in three survey rounds. Consensus was defined as ≥75% of the panel agreeing with a statement. The panel agreed on a set of 14 recommendations for the definition of TR-AD, providing detailed operational criteria for resistance to pharmacological and/or psychotherapeutic treatment, as well as a potential staging model. The panel also evaluated further aspects regarding epidemiological subgroups, comorbidities and biographical factors, the terminology of TR-AD vs. "difficult-to-treat" anxiety disorders, preferences and attitudes of persons with these disorders, and future research directions. This Delphi method-based consensus on operational criteria for TR-AD is expected to serve as a systematic, consistent and practical clinical guideline to aid in designing future mechanistic studies and facilitate clinical trials for regulatory purposes. This effort could ultimately lead to the development of more effective evidence-based stepped-care treatment algorithms for patients with anxiety disorders.

Key words: Anxiety disorders, treatment resistance, consensus guideline, operational criteria, panic disorder, agoraphobia, generalized anxiety disorder, social anxiety disorder, evidence-based care

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Anxiety disorders – including specific phobias, social anxiety disorder, panic disorder, agoraphobia, generalized anxiety disorder (GAD), as well as separation anxiety disorder and selective mutism[1] – represent the most common mental disorders, with an estimated combined 12-month prevalence of 10-14%[2-4]. They confer a substantial socioeconomic burden[5-7] and often take a debilitating course, with a high proportion of cases having only intermittent recovery (32.1%) or consistent chronicity (8.6%) at 9-year follow-up[8]. Accordingly, they rank sixth among all disorders regarding years lived with disability (YLDs)[9], and seventh in the group of 15-24 year olds and 15th among 25-49 year olds in terms of disability-adjusted life years (DALYs)[10].

One factor contributing to the chronicity of anxiety disorders is the clinical challenge of treatment resistance, particularly in panic disorder/agoraphobia, GAD, and social anxiety disorder[11-14]. While effective pharmacological and psychotherapeutic options are available for these disorders as first-line treatments endorsed by clinical guidelines[15] – i.e., selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and cognitive behavioral therapy (CBT) – only 50 to 67%

of patients show an adequate clinical response after the first treatment trial[16-21]. There is, therefore, a pressing need for clinical trials probing novel pharmacological and psychotherapeutic interventions specifically for patients with treatment-resistant anxiety disorders (TR-AD)[22], and for studies exploring predictive markers and mechanistic underpinnings of treatment resistance in anxiety disorders[23-25].

A prerequisite for conducting these clinical trials and mechanistic studies is an international consensus on the definition of TR-AD, which is currently lacking[17,26]. International guidelines focusing on anxiety disorders do not provide explicit criteria aiding in the identification or treatment of patients with TR-AD[15,27-50], with only two exceptions. First, the Canadian Clinical Practice Guidelines for the Management of Anxiety Disorders[51] suggest that patients who "do not respond to first- or second-line agents" (in panic disorder), who "do not respond to several medication trials and/or CBT" (in social anxiety disorder), or who "do not respond to multiple courses of therapy" (in GAD) should be considered treatment-refractory. Second, the most recent version of the Australian Therapeutic Guidelines[52] states that "non-response to initial pharmacotherapy for GAD, panic disorder and social anxiety disorder in adults and young people is assumed if symptoms persist despite using an effective dose of at least two SSRIs or SNRIs as sequential monotherapy, each for a minimum of 4 weeks (full benefit may take 6 weeks or longer); and discounting alternative reasons for treatment non-response".

A search of the Core Outcome Measures in Effectiveness Trials (COMET) database[53] for a core outcome set defining TR-AD yielded no results. Also, the International Consortium for Health Outcomes Measurement (ICHOM) Depression and Anxiety Working Group[54] did not provide an explicit definition of TR-AD. Searching clinicaltrials.gov for ongoing or terminated studies on TR-AD revealed either no or only vague definitions of this condition. Only one terminated study on social anxiety disorder (ID: NCT00182455) used non-response or partial response – i.e., a score >4 on the Clinical Global Impression Scale - Severity (CGI-S) and >40 on the Liebowitz Social Anxiety Scale (LSAS) – to SSRI treatment (14 weeks) to define treatment resistance more precisely.

A narrative review[11] suggested to define treatment-resistant panic disorder as the failure to achieve remission – i.e., a post-treatment Hamilton Anxiety Rating Scale (HAM-A) score ≤7-10, a Sheehan Disability Scale score ≤1 on each item, and a Panic Disorder Severity Scale score ≤3, after at least 6 months of "optimal treatment" (not further specified). A systematic review[14] proposed to define treatment-resistant panic disorder as a condition which has not responded to at least two adequate 8-week treatment trials with drugs recognized as effective for that disorder in adequate doses, or to a standard course of CBT[14].

The only systematic review available to date[55] could not discern a consistent definition in 62 studies investigating treatment resistance in anxiety disorders. In 62.9% of definitions, treatment resistance was already assumed after failure of a single therapeutic trial. Most studies (93%) required pharmacological, and only 29% psychotherapeutic treatment failure. A large proportion of studies (43.5%) did not specify the type of medication, while some studies (24.2%) deemed one trial of SSRI/SNRI treatment necessary. Most studies (54.8%) required a minimal trial duration ranging from 4 weeks to 6 months, with 24.2% of studies applying an 8-week time frame. While some studies (41.9%) provided a non-response criterion (e.g., post-treatment HAM-A score improvement <50%), the definition of "treatment failure" remained unclear in 58.1% of studies. "High post-treatment anxiety severity" was identified as the most common (46.8%) criterion required to define TR-AD across studies. Having summarized these findings, the authors proposed a definition of TR-AD requiring that the severity of anxiety remains above a specified threshold after failure of at least one first-line pharmacological (SSRI, SNRI) and at least one psychological (CBT) treatment trial, delivered according to protocol for at least 8 weeks. "Treatment failure" was suggested to be defined as a pre- to post-treatment difference in HAM-A score of <50%, or a post-treatment Clinical Global Impression Scale - Improvement (CGI-I) score >2.

Against this background, a recent perspective paper[56], after identifying treatment resistance in mental health conditions as a pressing issue, stated that "for certain conditions such as mania, anxiety disorders and PTSD, consensus definitions of resistance have yet to be agreed". In the present study, we used for the first time a Delphi method-based consensus approach in order to provide internationally agreed, consistent and clinically useful operational criteria for TR-AD in adults, particularly for the clinical phenotypes of panic disorder/agoraphobia, GAD, and social anxiety disorder. This operational definition of TR-AD is expected to inform future mechanistic studies as well as clinical trials of both pharmacotherapies and psychotherapies conducted for regulatory purposes, in an effort to develop more targeted and personalized treatment options reducing the individual and collective socioeconomic burden of anxiety disorders.

METHODS

This study was initiated by the Anxiety Disorders Research Network (ADRN), an international collaborative cross-disciplinary research group, with support from the European College of Neuropsychopharmacology (ECNP). The ADRN presently includes 28 members across 14 countries and has the principal goal of addressing currently unmet needs in anxiety and related disorders.

A subgroup of 15 ADRN members with clinical and/or basic scientific expertise in TR-AD formed the core expert team for the study. A further 18 experts (academics, clinicians, basic scientists) and three key stakeholders (two representatives of regulatory bodies, and a representative from a mutual aid advocacy organization) were selected to form the final panel (see supplementary information).

The Delphi method was considered the most appropriate tool for developing a consensus definition of TR-AD[57-60]. The method was applied according to the Guidance on Conducting and REporting DElphi studies (CREDES)[61], and following the approach recently used to develop a consensus guideline for the definition of treatment-resistant depression in clinical trials[62]. The study was registered with the Freiburger Register für Klinische Studien

(FRKS) (FRKS004463) and was approved by the Ethics Committee of the University of Freiburg (23-1021-S1).

Twenty-nine items were identified for inclusion in an initial questionnaire on TR-AD, based on a review of the literature and an in-person meeting of the ADRN core expert team in October 2022. The questionnaire, along with a narrative review of the current state of the evidence, was sent to the panel in November 2022. Anonymized responses to the questionnaire and a revised version of the narrative review were sent back to the panel and discussed in an online meeting in March 2023, using a nominal group technique to agree on the selection and wording of consensus statements. A resulting set of initially 15 draft consensus statements was subsequently sent out to the panel using the REDCap® online platform. In three *a priori* defined iterative rounds (in May, June and July 2023), all participants anonymously rated their agreement with each of the individual statements on a labelled, horizontal 9-point Likert scale (a "no answer" option was available) and could comment on or suggest changes to the phrasing or substance of the statements. After each iterative round, participants received feedback in the form of a cumulative statistical representation of the overall panel's response, and had access to anonymized comments by their fellow panelists (see Figure 1 and supplementary information).

Where participants gave a score of 1 to 3 to a statement on the Likert scale, low agreement was assumed. A score of 4 to 6 indicated moderate agreement with a statement. When a statement was scored 7 to 9, it was considered to be agreed upon substantially[63]. Consensus regarding a statement was considered reached when ≥75% of the panel voted in substantial agreement with it, i.e. gave a score of 7 to 9. This aligns with the development of other core outcome sets[64-67], and with the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[68]. Those who had chosen the "no answer" option were removed from the denominator when ascertaining whether consensus had been reached. Statements reaching less than or only around 75% consensus in iteration rounds 1 and 2 were dropped or amended on the basis of free-text responses provided by the panel and entered as such into voting rounds 2 and 3, respectively (see supplementary information). The 14 final consensus recommendations on TR-AD as emerging from round 3 are summarized in Table 1.

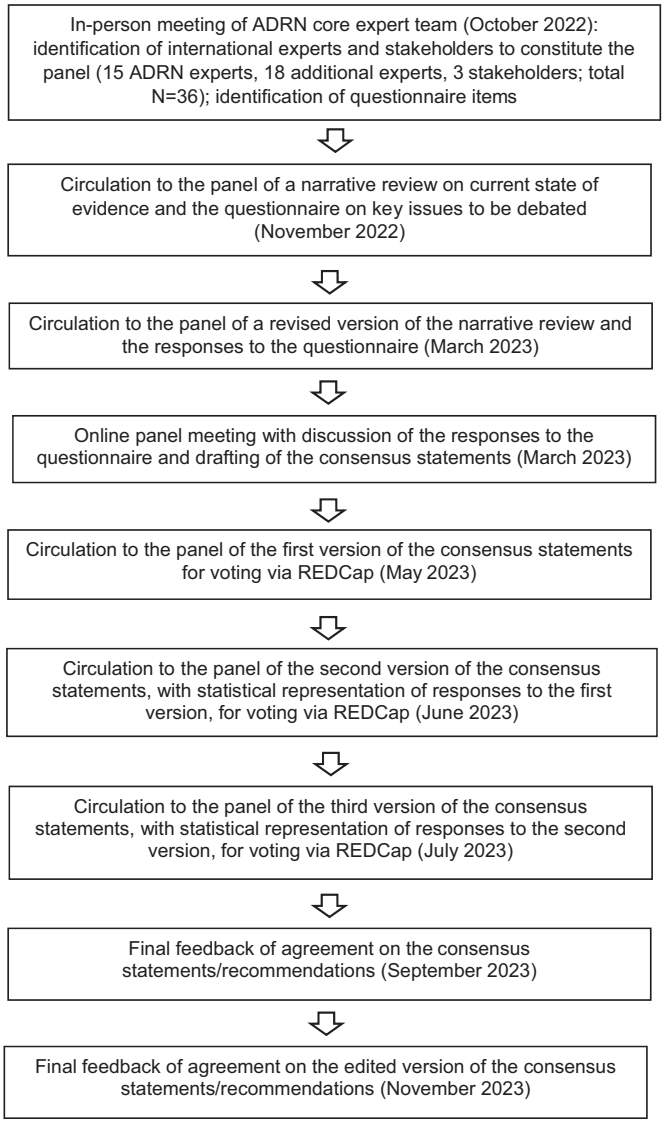

Figure 1 Flow diagram of the Delphi method-based process. ADRN – Anxiety Disorders Research Network

RESULTS

The panel considered an operational definition of TR-AD to be useful for regulatory clinical trials probing pharmacotherapy and psychotherapy (as well as neuromodulation or virtual reality techniques, and repurposed options such as ketamine, psilocybin, or 3,4-methylendioxy-N-methylamphetamine, MDMA) (see Table 1, statement 1). This definition will allow to carry out clinical trials with good external validity, ultimately aiming at improving evidence-based treatment algorithms and guidelines in case of treatment non-response or resistance. This was seen as particularly important since patients with TR-AD have so far mostly been excluded from clinical trials conducted for regulatory purposes.

An operational definition of TR-AD was additionally considered to be essential for research on (bio)markers and (bio)mechanisms of treatment non-response or resistance (see Table 1, statement 2).

Operationalization of treatment failure

The panel voted for the definition of response/non-response to ideally but not necessarily rest on both clinician- and self-report scales (see Table 1, statement 3). Some panelists suggested that clinician ratings are probably most apt for pharmacological trials, and self-reports for psychotherapeutic trials. Clinician ratings have been suggested to possibly increase the effect sizes[69,70], but might at the same time be more sensitive to change and can be applied in an adequately blinded way. Self-report ratings are better able to capture the patient's core emotional experience[71,72], quality of life

Table 1 Consensus results on the definition of treatment-resistant anxiety disorders (TR-AD)

No.	Statement	Mean score ± SD on 9-point Likert scale	% of agreement
General remarks			
1	A definition of TR-AD is useful for both pharmacological and psychotherapeutic clinical trials conducted for regulatory purposes.	8.74±0.58	100
2	A definition of TR-AD is useful for research, e.g. in the search for disease or treatment response mechanisms and biomarkers.	8.68±0.60	100
Operational definition			
3	The definition of treatment failure should ideally, but not necessarily, rest on both observer-rated and self-report scales.	8.23±0.99	90.3
4	Treatment failure in anxiety disorders can be operationally defined by the failure to achieve clinically significant reduction in symptom severity from pre- to post-treatment. This can be reflected by a <50% reduction in Hamilton Anxiety Scale score or a <50% reduction in Beck Anxiety Inventory score or a Clinical Global Impression Scale - Improvement >2.	8.35±0.75	96.8
4a	Optional specific criteria for treatment failure in social anxiety disorder: Liebowitz Social Anxiety Scale (LSAS)-SR (self-rating) score reduction <28% or LSAS-CA (clinician-administered) score reduction <29%.	8.21±1.11	89.7
4b	Optional specific criteria for treatment failure in GAD: Generalized Anxiety Disorder 7-item (GAD-7) scale score <4-point reduction, or Penn State Worry Questionnaire score <9% or <4-point reduction.	8.03±1.09	89.7
4c	Optional specific criteria for treatment failure in panic disorder/agoraphobia: Panic Disorder Severity Scale score reduction <40% or Panic Agoraphobia Scale score reduction <23%.	8.03±1.09	89.7
5	The definition of pharmacological treatment resistance in anxiety disorders should rest on at least two failed trials of pharmacological monotherapy with first-line agents approved for the treatment of anxiety disorders and recommended by guidelines (two different classes, e.g. one SSRI plus one SNRI, clomipramine or pregabalin, in the case of GAD) using at least the minimal approved dose, for the duration of at least 6-8 weeks each, ideally with documented therapy adherence.	8.50±0.73	100
6	The definition of psychotherapeutic treatment resistance in anxiety disorders should rest on at least one failed trial of adequately delivered (e.g., qualified therapist) first-line psychotherapy such as cognitive behavioral therapy (CBT) with adequate intensity (e.g., a sufficient number of exposure exercises, homework, adherence) and duration (depending on the type of anxiety disorder, e.g., 12-20 weeks in GAD, panic disorder/agoraphobia or social anxiety disorder).	8.07±1.55	96.7
Staging model			
7	A staging model might capture the spectrum of TR-AD with various levels of treatment resistance, comprising: i) failure of either two adequate courses of pharmacotherapy or ≥1 adequate trial of psychotherapy ii) failure of both two adequate courses of pharmacotherapy and ≥1 adequate trial of psychotherapy iii) failure of multiple adequate courses of (poly)pharmacotherapy and multiple adequate trials of psychotherapy (connoting multi-modal TR-AD, MTR-AD).	8.29±0.82	100
Additional aspects			
8	Comorbidities with depression, substance abuse or personality disorders should not influence the operational definition of TR-AD, but their presence should be recorded and considered *post-hoc*.	8.65±0.61	100
9	Subgroups of AD (e.g., by sex, age, menopause, peri-partum period) should not influence the operational definition of TR-AD, but should be recorded and considered *post-hoc*.	8.61±0.62	100
10	Specific biographical factors (e.g., life events, history of trauma) should not influence the operational definition of TR-AD, but their presence should be recorded and considered *post-hoc*.	8.58±0.67	100
11	Duration of illness and number of episodes should not influence the operational definition of TR-AD, but they should be recorded *post-hoc*, considering that TR-AD by definition might entail a longer duration of illness and that delineation of distinct episodes might be difficult.	8.65±0.61	100
12	Research into biomarkers and other predictors and mechanisms of TR-AD might be useful in the future.	8.71±0.59	100
13	It is essential to be sensitive and not judgmental towards patients suffering from TR-AD, to include their social environment in the diagnostic and therapeutic process where appropriate, and to respect patients' preferences after they are fully informed about the comparative efficacy of the various treatment modalities based on current official guidelines.	8.68±0.60	100
14	In the future, the merits of the term TR-AD in a regulatory context are to be discussed against potential drawbacks, with consideration of a potentially more comprehensive term such as "difficult-to-treat" anxiety disorders, which might be more useful in a clinical context.	8.32±0.79	100

GAD – generalized anxiety disorder

and symptoms affecting broader dimensions of real life, but may be more relevant for the definition of remission than treatment failure. For an international consensus, the recommended scales should be translated, validated and available in as many languages and countries as possible.

The panel agreed on treatment failure in anxiety disorders to be defined as the failure to achieve a clinically significant symptom reduction from pre- to post-treatment, reflected by a <50% reduction in the HAM-A score, or a <50% reduction in the Beck Anxiety Inventory score, or a CGI-I score >2 (see Table 1, statement 4). This was the final consensus, although some panelists suggested to rather use a 25% or 30% reduction cut-off. In general, a percentage reduction to indicate non-response seemed preferable to post-treatment scores alone, since there may be considerable heterogeneity in before-treatment severity scores. It was also noted that operationalization of treatment resistance based on symptom reduction may not sufficiently portray the full picture of how well a patient does in the long term, which might be better reflected by Sheehan Disability Scale scores.

Several additional, but optional, recommendations on how to define treatment failure in regulatory trials concerning specific anxiety disorders were agreed upon by the panel.

For social anxiety disorder, a score reduction of <28% on the LSAS-SR (self-rating) or <29% on the LSAS-CA (clinician-administered) was suggested to indicate treatment failure (see Table 1, statement 4a). Although a LSAS total cut-off score of 30 has been reported to represent the best balance of specificity and sensitivity[73], the panel once again agreed that absolute scores do not account for initial disease severity and thus should not be included in definitions of treatment failure.

As optional operational criteria for treatment failure in GAD, the panel agreed on a <4 point reduction on the Generalized Anxiety Disorder 7-item (GAD-7) scale score, or a <9% or <4-point reduction on the Penn State Worry Questionnaire score (see Table 1, statement 4b). GAD-7 cut-off scores ≥8 or ≥10 were also discussed, but discarded because absolute scores do not account for initial disease severity. Some panelists argued that the GAD-7 should not be used as the sole measure for treatment failure in GAD, as some studies failed to define a cut-off score with adequately balanced sensitivity and specificity for GAD[74-76], or reported that the GAD-7 had good sensitivity and specificity for any anxiety disorders, but low specificity for GAD[77].

For treatment failure in panic disorder and/or agoraphobia, the panel recommended optional operational criteria of a <40% score reduction on the Panic Disorder Severity Scale or a <23% score reduction on the Panic and Agoraphobia Scale (see Table 1, statement 4c). Criteria of a <50% score reduction on the Panic Disorder Severity Scale or a <50% decrease in the number of panic attacks were discussed, but were not included in the operational definition.

Resistance to pharmacological treatment (pharmacotherapy TR-AD)

For regulatory trials, it might be useful to differentiate between resistance to pharmacotherapy and psychotherapy. The panel agreed that resistance to pharmacological treatment in anxiety disorders (pharmacotherapy TR-AD) should be defined as at least two separate failed full trials of pharmacological monotherapy with first-line agents approved for those disorders by the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA) or other equivalent regulatory agencies, and recommended by guidelines. These trials should involve two different classes of medications (e.g., one SSRI plus one SNRI, clomipramine or pregabalin in the case of GAD), used for at least 6-8 weeks each at a dose corresponding to at least the minimal approved one, ideally with documented treatment adherence (see Table 1, statement 5).

It was discussed whether failure of a trial with benzodiazepines should be included in the definition of pharmacotherapy TR-AD. It was argued that the majority of guidelines do not recommend benzodiazepines as first-line options for treatment of anxiety disorders. Regarding the definition of how long one trial of pharmacological treatment should last to be able to evaluate its efficacy, time frames spanning 4 to 12 weeks were considered, but the final consensus was for a treatment duration of 6-8 weeks. Monitoring plasma levels to allow for an optimized dosing and the assessment of treatment "pseudo-resistance" due to non-adherence or a rapid metabolizer status was considered desirable, but not feasible in most routine clinical settings. Treatment pseudo-resistance in general, however, should be excluded by taking into account adherence to treatment as well as additional factors such as age and renal/hepatic function.

Resistance to psychotherapy (psychotherapy TR-AD)

The panel agreed that resistance to psychotherapy in anxiety disorders (psychotherapy TR-AD) should be defined as at least one failed trial of an evidence-based, first-line, standardized, ideally manualized psychotherapy, such as CBT. Treatment should be delivered by a qualified psychotherapist with an adequate intensity and duration, ideally including a sufficient number of exposure exercises as well as monitored between-session work ("homework") and adherence (see Table 1, statement 6).

Depending on the type of anxiety disorder, a range of one session (for specific phobias) to up to 20 weeks (in GAD, panic disorder/agoraphobia or social anxiety disorder) was proposed to constitute an adequate time frame. For the latter conditions, the consensus was for a minimal duration of 12-20 weeks, with a minimum number of 20 sessions. Individual one-to-one sessions seemed preferable, while group or online formats were discussed as potential alternatives.

Staging model and multi-modal treatment resistance (MTR-AD)

The panel additionally proposed a non-dichotomous, escalating staging model of TR-AD, in analogy to those suggested for obsessive-compulsive disorder[78] and major depressive disorder[79-81] (see Table 1, statement 7). This model – or alternatively a pseudo-

linear scale of degree of resistance – would allow clinical trials for regulatory purposes or other studies to describe a particular population on a dimensional spectrum of treatment resistance, ranging from isolated resistance to pharmacological or psychotherapeutic treatment to composite resistance to several trials of multiple modalities delivered in different episodes of the anxiety disorder. This flexibility is particularly relevant for anxiety disorders, as pharmacotherapy and psychotherapy have been considered similarly effective in these disorders, and as resistance to pharmacotherapy does not preclude response to psychotherapy and *vice versa*, or to a combination of the two modalities. Also, the (bio)mechanisms of treatment resistance to pharmacotherapy and psychotherapy might be partly distinct.

The model proposed by the panel in order to capture the spectrum of levels of treatment resistance in anxiety disorders comprises a first stage of failure of either two adequate courses of pharmacotherapy or at least one adequate trial of psychotherapy; a second stage of failure of both two adequate courses of pharmacotherapy and at least one adequate trial of psychotherapy; and a third stage of failure of multiple adequate courses of (poly)pharmacotherapy and multiple adequate trials of psychotherapy. This last stage connotes multi-modal TR-AD (MTR-AD) (see Table 1, statement 7), which requires an intensified subsequent treatment approach, including referral to secondary or tertiary specialist care. The (bio)mechanisms underlying MTR-AD might be different from those involved in isolated pharmacotherapy TR-AD or psychotherapy TR-AD.

Additional aspects

The panel agreed that comorbidity with other mental disorders – particularly depression, substance use disorders and personality disorders – should not influence the operational definition of TR-AD, but should be recorded and considered *post-hoc* (see Table 1, statement 8). Furthermore, the identification of sex and age subgroups was not considered necessary for the operational definition of TR-AD, but relevant for *post-hoc* analyses as well as for differential treatment. For instance, women in the peri- and postmenopausal or in the peri-partum period, children/adolescents, as well as elderly patients with declining renal or hepatic function, might warrant particular attention (see Table 1, statement 9).

Biographical factors such as socioeconomic status, social support, specific life events (e.g., childhood trauma, acute or chronic stress), as well as exposure to novel anxiogenic stimuli or situations during treatment, were considered to possibly influence treatment resistance[19,82,83]. However, for the sake of simplicity and to reflect a naturalistic setting, those factors were suggested by the panel not to be included in the operational definition of TR-AD, but to be recorded, possibly as "specifiers", monitored and taken into consideration in *post-hoc* analyses to reduce the study population variability and, in a clinical setting, to be targeted specifically (see Table 1, statement 10).

The panel agreed that duration of (untreated) illness and number of episodes or relapses, while influencing treatment resistance in several patients[84-86], should not be included in the definition of TR-AD, but recorded and considered *post-hoc* (see Table 1, statement 11). It has to be noted that TR-AD usually involves a longer duration of illness, entailing a potential tautology. Additionally, it might be difficult to delineate distinct episodes. While for TR-AD regulatory trials it might be useful to restrict the number of previous failed treatments, in order to increase the likelihood of improvement, the panel agreed not to propose a statement on the maximum number of failed previous treatments. However, it suggested that they should be routinely recorded and considered *post-hoc*.

TR-AD vs. difficult-to-treat AD

The panel agreed to use the term "treatment-resistant" anxiety disorders (TR-AD), since it is routinely adopted and widely understood in the present regulatory context, and is already established for other disorders in the international nomenclature. However, it acknowledged that "difficult-to-treat" AD could be considered as a potentially more comprehensive term, which might be more useful in a clinical context (see Table 1, statement 14).

The term TR-AD was considered to clearly refer to the disorder and not to the patient as being treatment-resistant, to the existing treatment options being inadequate, to relate to the patient's history and not the future, to be respectful of the patient-clinician relationship, and to allow a precise definition relevant for drug approval and commissioning of services. The alternative term "difficult-to-treat" AD – in analogy to "difficult-to-treat" depression[87] – has been suggested to represent a more comprehensive and multidimensional concept, to potentially be more apt to inform clinical practice rather than research or regulatory affairs, and to seem less stigmatizing, pessimistic, discouraging or defamatory from a patient's perspective[88].

The concept of "difficult-to-treat" AD might furthermore allow for considering intolerance or refusal or contraindication of treatment, and the impact of living conditions, comorbidities and other factors on treatment outcome, rather than just non-response, and does not relate simply to one point in time when TR-AD criteria are met. Some panelists, however, raised concerns that the term "difficult" could inadvertently be taken to refer to the patient, and even reduce hope for future treatments. Also, it could imply that successful treatments should be "easy" and straightforward, while treatment can still be highly effective despite a very complex, atypical or "difficult" clinical presentation or a "difficult" therapeutic process.

In sum, both terms might be needed, with TR-AD constituting a pragmatic nomothetic construct for clinical trials conducted for regulatory purposes, as well as for other research projects, while "difficult-to-treat" AD could represent a more holistic, idiographic concept as well as a "roadmap" for clinicians relevant to effectiveness trials as well as clinical care. However, the boundaries of "difficult-to-treat" AD are uncertain, and an evidence-based taxonomy as well as reliable assessment tools beyond traditional outcome metrics remain to be established for this condition[89]. Re-

search into this topic has been deemed to be of importance.

Preferences and attitudes of persons with anxiety disorders

In general, labelling a condition as either TR-AD, MTR-AD, "treatment-refractory" AD or "difficult-to-treat" AD might be regarded as stigmatizing. Consequently, it is essential to be sensitive and not judgmental towards persons experiencing treatment resistance, and to ensure respectful language awareness and use (e.g., "patient with TR-AD", not "TR patient" or "difficult-to-treat patient"). On the other hand, providing an operational definition of TR-AD might in fact relieve patients from the feeling of having failed themselves, and aid in destigmatizing the condition.

It is imperative that persons with anxiety disorders are fully informed about the comparative efficacy of the various treatment modalities based on current official guidelines, and that their preferences are respected. It is to be taken into consideration that certain classes of medication or psychotherapy might be unacceptable or untimely from a patient's point of view, or that certain treatment options might simply not be available or delivered optimally. Additionally, given that many patients with TR-AD have already gone through numerous pharmacological and/or psychotherapeutic treatment trials, the definition of TR-AD should not be limited to a relatively short duration of disease or to a maximum number of failed previous trials, as this would discriminate against those patients by excluding them from regulatory trials that may potentially offer more efficacious treatment options.

In future attempts to further refine the definition of TR-AD, the inclusion of questionnaires focusing on self-reported quality of life and level of functioning – for instance, the Sheehan Disability Scale or the Psychosocial fActors Relevant to BrAin DISorders in Europe (PARADISE 24) metric[90] – should be considered. Furthermore, "minimal important differences" for patient reported outcomes (i.e., the smallest changes in outcome measures that patients perceive as an important improvement or deterioration) should increasingly be defined and taken into account[91]. In general, it is essential to engage with patients, to include patients' social environment in the diagnostic and therapeutic process where appropriate, to be transparent, to promote inclusivity, to ensure continuity of care, and to convey hope and perspective (see Table 1, statement 13).

Research directions

Research into clinical, (epi)genetic, proteomic, metabolomic, microbiome, physiological and neuroimaging biomarkers as predictors of treatment resistance in anxiety disorders, allowing for a more personalized and precise care in this field, was welcomed by the panel (see Table 1, statement 12). However, the very limited currently available evidence was acknowledged[92-95].

Real-world data such as gait analysis or time/event-contingent actigraphy data using ecological momentary assessment might provide additional markers predicting TR-AD[96-99]. Machine learning approaches could aid in integrating biological, biographical and ecological momentary assessment markers[82].

DISCUSSION

The present Delphi method-based consensus on operational criteria for TR-AD (see Table 2) is hoped to serve as a systematic, consistent and practical guideline to define this condition and thereby aid in designing future clinical trials for regulatory purposes as well as other research projects. This effort could ultimately lead to the development of more effective evidence-based stepped-care treatment algorithms for patients with TR-AD.

The Delphi method-based process is considered "state-of-the art" to achieve international consensus on a given research or clinical issue. The international experts and stakeholders selected for this study represent a broad range of expertise in the field. Response rates in the three separate voting rounds did not reach 100% (first round: 80.6%; second round: 94.4%; third round: 86.1%), but

Table 2 Definition of treatment-resistant anxiety disorders (TR-AD): main consensus recommendations

Treatment failure

- <50% reduction in HAM-A score
  OR
- <50% reduction in BAI score
  OR
- CGI-I score >2

Pharmacological treatment resistance

- At least two separate failed full trials of pharmacological monotherapy
- First-line agents approved for the treatment of anxiety disorders and recommended by guidelines (two different classes, e.g. one SSRI plus one SNRI, clomipramine or pregabalin, in the case of GAD)
- At least at the minimal approved dose
- Duration of at least 6-8 weeks each
- Ideally with documented therapy adherence

Psychotherapeutic treatment resistance

- At least one failed trial of adequately delivered (e.g., qualified therapist) first-line psychotherapy (e.g., CBT)
- Adequate intensity (e.g., a sufficient number of exposure exercises, homework, adherence)
- Adequate duration (e.g., 12-20 weeks in GAD, PD/AG or SAD)

Staging model

i. Failure of *EITHER* two adequate courses of pharmacotherapy *OR* ≥1 adequate trial of psychotherapy
ii. Failure of *BOTH* two adequate courses of pharmacotherapy *AND* ≥1 adequate trial of psychotherapy
iii. Failure of multiple adequate courses of (poly)pharmacotherapy *AND* multiple adequate trials of psychotherapy (MTR-AD)

HAM-A – Hamilton Anxiety Scale, BAI – Beck Anxiety Inventory, CGI-I – Clinical Global Impression Scale - Improvement, SSRI – selective serotonin reuptake inhibitor, SNRI – serotonin and norepinephrine reuptake inhibitor, GAD – generalized anxiety disorder, CBT – cognitive behavioral therapy, PD/AG – panic disorder/agoraphobia, SAD – social anxiety disorder, MTR-AD – multi-modal treatment-resistant anxiety disorder

this corresponds to the upper part of the range of other published Delphi method-based studies, where response rates between 45% and 93% have been reported across three rounds of voting[100].

The coverage of both pharmacological interventions and psychotherapies in the proposed operational criteria for TR-AD is not a common feature in currently available definitions for other treatment-resistant mental disorders, although frequently regarded as appropriate or even necessary[101-103]. This represents in itself an important development.

We acknowledge that experts or stakeholders outside the present panel might have differing views on how TR-AD should be conceptualized, which may limit the generalizability of the proposed criteria. Therefore, in a next step, the conceptualization of TR-AD presented here should be empirically investigated and validated. In the future, a more fine-grained and potentially dimensional definition of TR-AD, comprising multiple modalities (e.g., self-report and clinician ratings, biological/physiological recordings), covering a variety of factors (e.g., life events, treatment intolerance, psychosocial functioning, comorbidities), and incorporating a lifespan perspective, might increase construct validity and better reflect the complex and multifaceted nature of anxiety, including its waxing and waning course[17,20,104,105]. The definition of such core outcome sets could follow the Core Outcome Set-STAndards for Development (COS-STAD)[106] and Core Outcome Set-STAndards for Reporting (COS-STAR)[107].

It has to be noted that the presently proposed consensus criteria for TR-AD are limited to the population of adult patients, while criteria for TR-AD in childhood and adolescence and in elderly patients remain to be established in future studies[108-111]. Along this line, the diagnostic entities "separation anxiety disorder" and "selective mutism", previously classified in the DSM-IV section "Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence" and now listed in the DSM-5 chapter on Anxiety Disorders[112-114], warrant investigation with regard to treatment resistance in adulthood.

It is desirable to identify factors predicting and mechanistically underlying treatment resistance in anxiety disorders. Some studies of limited quality and highly heterogeneous in design suggest a number of potential risk factors – such as high expressed emotions within the family, higher severity and longer duration of the disorder, earlier age of onset, or presence of comorbid conditions – which however have not been consistently replicated[13,19,81,82]. In a similar vein, the identification of reliable and valid biomarkers indicating an increased risk of treatment resistance would be helpful to inform algorithms for individually tailoring an intensified treatment for those patients[22,23,25,93,94,115].

To date, no internationally endorsed evidence-based guidelines exist for the treatment of patients with TR-AD. Clinical recommendations[13,18,19,26,116-119] comprise switching medication within one class or to a different class; augmentation strategies with other antidepressants, antipsychotics or anticonvulsants; combining pharmacotherapy and psychotherapy, as well as treating comorbid mental and/or somatic disorders complicating the treatment course. The present Delphi method-based consensus operational criteria for TR-AD may help to foster clinical trials probing innovative pharmacological, psychotherapeutic and non-invasive brain stimulation approaches in order to establish more effective treatment options for this condition. For instance, "third-wave" psychotherapeutic interventions such as acceptance and commitment therapy, mindfulness-based stress reduction, meta-cognitive therapy and compassion-focused therapy[120-124], as well as novel pharmacological compounds targeting monoamines (including psychedelics), GABA, glutamate, cannabinoid, cholinergic and neuropeptide systems[125,126] might prove useful in treating TR-AD.

In sum, the presently proposed Delphi method-based consensus operational criteria for TR-AD are expected to inform both pharmacological and psychotherapeutic clinical trials for regulatory purposes towards more targeted and personalized treatment options for persons with TR-AD, thus reducing the individual and collective socioeconomic burden of anxiety disorders. If they are empirically validated, a dissemination plan could include their endorsement by professional associations and health care authorities to facilitate their implementation in practice.

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Outcomes in people with eating disorders: a transdiagnostic and disorder-specific systematic review, meta-analysis and multivariable meta-regression analysis

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Eating disorders (EDs) are known to be associated with high mortality and often chronic and severe course, but a recent comprehensive systematic review of their outcomes is currently missing. In the present systematic review and meta-analysis, we examined cohort studies and clinical trials published between 1980 and 2021 that reported, for DSM/ICD-defined EDs, overall ED outcomes (i.e., recovery, improvement and relapse, all-cause and ED-related hospitalization, and chronicity); the same outcomes related to purging, binge eating and body weight status; as well as mortality. We included 415 studies (N=88,372, mean age: 25.7±6.9 years, females: 72.4%, mean follow-up: 38.3±76.5 months), conducted in persons with anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED), other specified feeding and eating disorders (OSFED), and/or mixed EDs, from all continents except Africa. In all EDs pooled together, overall recovery occurred in 46% of patients (95% CI: 44-49, n=283, mean follow-up: 44.9±62.8 months, no significant ED-group difference). The recovery rate was 42% at <2 years, 43% at 2 to <4 years, 54% at 4 to <6 years, 59% at 6 to <8 years, 64% at 8 to <10 years, and 67% at ≥10 years. Overall chronicity occurred in 25% of patients (95% CI: 23-29, n=170, mean follow-up: 59.3±71.2 months, no significant ED-group difference). The chronicity rate was 33% at <2 years, 40% at 2 to <4 years, 23% at 4 to <6 years, 25% at 6 to <8 years, 12% at 8 to <10 years, and 18% at ≥10 years. Mortality occurred in 0.4% of patients (95% CI: 0.2-0.7, n=214, mean follow-up: 72.2±117.7 months, no significant ED-group difference). Considering observational studies, the mortality rate was 5.2 deaths/1,000 person-years (95% CI: 4.4-6.1, n=167, mean follow-up: 88.7±120.5 months; significant difference among EDs: p<0.01, range: from 8.2 for mixed ED to 3.4 for BN). Hospitalization occurred in 26% of patients (95% CI: 18-36, n=18, mean follow-up: 43.2±41.6 months; significant difference among EDs: p<0.001, range: from 32% for AN to 4% for BN). Regarding diagnostic migration, 8% of patients with AN migrated to BN and 16% to OSFED; 2% of patients with BN migrated to AN, 5% to BED, and 19% to OSFED; 9% of patients with BED migrated to BN and 19% to OSFED; 7% of patients with OSFED migrated to AN and 10% to BN. Children/adolescents had more favorable outcomes across and within EDs than adults. Self-injurious behaviors were associated with lower recovery rates in pooled EDs. A higher socio-demographic index moderated lower recovery and higher chronicity in AN across countries. Specific treatments associated with higher recovery rates were family-based therapy, cognitive-behavioral therapy (CBT), psychodynamic therapy, and nutritional interventions for AN; self-help, CBT, dialectical behavioral therapy (DBT), psychodynamic therapy, nutritional and pharmacological treatments for BN; CBT, nutritional and pharmacological interventions, and DBT for BED; and CBT and psychodynamic therapy for OSFED. In AN, pharmacological treatment was associated with lower recovery, and waiting list with higher mortality. These results should inform future research, clinical practice and health service organization for persons with EDs.

Key words: Eating disorders, anorexia nervosa, bulimia nervosa, binge eating disorder, recovery, chronicity, mortality, hospitalization, diagnostic migration, cognitive-behavioral therapy, family-based therapy, nutritional interventions

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Eating disorders (EDs) are severe psychiatric conditions characterized by altered eating behavior, that can lead to severe weight loss and underweight, or to weight gain and obesity[1]. They have been recently reclassified as "feeding and eating disorders" in the DSM-5[2,3] and ICD-11[4-6]. According to these classifications, they encompass anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED), and other specified feeding and eating disorders (OSFED) as the most common and studied conditions.

The most important psychopathological feature of AN and BN is the overvaluation of body shape and weight[7-10]. Individuals with AN are underweight, refuse to gain weight and/or deny the severity of underweight status with/without engaging in binge eating and compensatory behaviors. Binge episodes are defined as introducing an amount of food that is larger than what an average person would have eaten, in a short period of time, with sensations of loss of control over eating[11]. Compensatory behaviors consist of purging behaviors (self-induced vomiting, or using laxatives or diuretics) or excessive exercise to prevent weight gain or

lose weight. People with BN are not underweight and engage in recurring episodes of binge eating and compensatory behaviors and/or fasting or compulsive exercise. Individuals with BED engage in recurring episodes of binge eating that are not followed by compensatory behaviors. The overvaluation of shape and weight is not a characteristic feature of BED, and this condition is often associated with, or leads to, obesity[12]. OSFED is a residual category including individuals who do not meet full threshold criteria for the main EDs, and encompassing atypical AN, purging disorder, subthreshold BN and BED, and night eating syndrome. A proportion of these patients move to a diagnosis of a main ED over time[13].

All EDs are marked by frequent psychiatric and physical comorbidity[14-16], and impaired physical, social and work functioning[17-19]. People of all ages, ethnicities and socio-economic conditions[20] can be affected by EDs, although adolescents and young adults are particularly at risk, and the mean age of onset is decreasing[21]. AN is more common in women and starts earlier than BN and BED[22]. BN and BED show less gender differences and a higher prevalence in ethnic minorities than AN[23].

The etiopathogenesis of EDs is thought to be multifactorial, with models postulating the presence of predisposing factors (genetic vulnerability[24,25], temperamental traits, and childhood traumatic experiences[26]), precipitating factors (the environmental context at the time of onset[1]), and maintaining factors (secondary aspects of the illness, such as brain adaptation induced by malnutrition, social isolation, and changes in the environment[27]). However, a clear understanding of this etiopathogenesis is currently lacking, although it would be essential to improve treatment effectiveness[28].

Access to treatment for EDs is inadequate, with only 20-25% of individuals receiving professional consultation for their symptoms[29]. Barriers to treatment access include stigma, lacking insight into the illness, shame, scarce availability of evidence-based interventions, and fragmented or underfunded health services[30,31], which contribute to low recovery rates and frequent chronicity[32]. The complexity of EDs requires a multidisciplinary treatment approach to address psychological, environmental, nutritional, behavioral and physical problems, as well as mental health comorbidities[33,34]. Psychological and nutritional treatments are recommended by guidelines for all EDs[35,36]. Evidence-based psychotherapies have been developed, but their effectiveness in adults with AN does not differ from treatment as usual (TAU)[37], and there is no superiority of a specific approach[38]. In contrast, family-based interventions have shown long-term superiority on other active treatments in adolescents and young adults with AN and in adolescents with BN[39]. Cognitive-behavioral therapy (CBT) is the most validated treatment in people with BN and BED[20], with some indications of long-term effectiveness[39]. Pharmacological augmentation has been effective in the short term, namely antidepressants in BN and antidepressants or lisdexamfetamine in BED[39].

Studies reporting on outcomes of EDs have been heterogeneous with respect to definitions of recovery, relapse, remission and hospitalization; sample size, study design, duration of follow-up, and overall quality[40-45]. Thus, a systematic review is needed which is comprehensive enough to explore outcome moderators and explain heterogeneity of findings. The most extensive reviews of outcomes in EDs have been published over one decade ago, and reported only on the course of AN and BN[46,47]. An update and extension of their findings, and an evaluation of outcomes also in BED and OSFED, are now timely.

Although several therapeutic interventions for EDs have been validated by research and are implemented in real-world clinical practice, they have a different impact on patients with the same diagnosis[48]. More tailored and individualized therapies are a research and clinical priority to overcome the "therapeutic stagnation" in EDs[49]. A variety of predictors and moderators of treatment outcomes have been reported in patients with EDs[50-52], but the overall picture remains unclear.

The primary aim of this review and meta-analysis was to explore clinically relevant outcomes of specific EDs – including recovery, improvement, relapse after recovery, hospitalization, chronicity and mortality – over different follow-up times. Additional objectives included exploring the presence of moderators and mediators of the main outcomes within and across EDs, evaluating the proportion of patients migrating between ED diagnoses, and estimating the real-world effectiveness of different interventions.

METHODS

Search strategy and inclusion/exclusion criteria

We conducted a PRISMA 2020[53]-compliant systematic review searching Embase, Medline and PsycINFO from 1980 to 2021, aiming to include prospective or database cohort studies as well as trials reporting on clinical outcomes of EDs. The search key included terms related to EDs and outcomes of interest (see supplementary information). Additionally, a manual search was conducted to identify further studies not detected by the systematic search, through Medline and Google Scholar.

Inclusion criteria were: a) original peer-reviewed articles; b) published in English; c) based on controlled or non-controlled trials, longitudinal database studies or prospective cohort studies, including patients with EDs (i.e., AN, BN, BED, OSFED) defined according to any version of the DSM or ICD; and d) reporting frequencies of at least one of the following outcomes: recovery, improvement, chronicity, all-cause hospitalization, relapse after recovery, and mortality.

Exclusion criteria were: a) meta-analyses, review articles and case reports/case series; b) retrospective studies (except database studies) and case-control studies; c) animal studies; d) studies published before 1980; e) studies that did not report any binary outcome of interest; f) studies that included patients with ED symptoms but no full ED diagnosis; and g) studies with <10 participants.

Outcomes and data extraction

The co-primary outcomes were recovery and chronicity of the overall ED symptomatology – which we defined as "overall" recov-

ery and chronicity – and mortality. Recovery was defined as absence of ED symptoms or "good outcome" assessed by a validated scale (e.g., the Morgan-Russell Outcome Assessment Schedule[54] for AN, BN and mixed EDs). Chronicity was defined as continued presence of an ED diagnosis or "poor outcome" assessed by a validated scale (see also supplementary information).

Additional outcomes were recovery and chronicity of specific ED symptoms (i.e., binge eating, purging, abnormal weight), and all-cause hospitalization. Moreover, we considered overall as well as specific binge eating, purging and weight improvement (i.e., symptom improvement or "intermediate outcome") and relapse (i.e., symptom relapse after recovery), as well as ED-related hospitalization (see also supplementary information).

In addition to outcomes, pairs of independent authors extracted the following data from eligible studies: bibliographic identifiers, country, year of data collection, primary component of the intervention, mean age of included sample at baseline, study design, treatment setting, proportion of females, mean body mass index (BMI) at baseline, duration of treatment, duration of illness, total follow-up duration, proportion of persons with individual psychiatric comorbidities (i.e., major depressive disorder, anxiety disorders, obsessive-compulsive disorder, substance use disorders, personality disorders, and history of self-injurious behaviors). Moreover, a socio-demographic index (accounting for income *per capita*, average educational attainment, and fertility rates) was assigned to each country[55], to explore regional differences.

The quality of observational studies was assessed with the Newcastle-Ottawa scale[56]. The risk of bias of trials was evaluated using the Cochrane's risk of bias (RoB) tool[57].

Statistical analyses

We conducted random-effects meta-analyses of the frequency of clinical outcomes. We used the longest time point if more than one was available. We reported the pooled percentage of individuals with the outcome of interest as well as the average follow-up duration, in months, within each ED and pooling all EDs together. We also calculated the frequency of outcomes by follow-up duration, considering the following time points: <2 months, 2 to <4 years, 4 to <6 years, 6 to <8 years, 8 to <10 years, and ≥10 years. For mortality, we also calculated deaths/1,000 person-years considering observational studies.

We conducted subgroup analyses testing whether the frequency of outcomes differed across EDs. We also conducted subgroup analyses by decade of data collection, primary ingredient of treatment, age group, study design, treatment setting, and continent where the study was conducted.

We used multivariable mixed-effects meta-regression adjusted for mean age, illness duration, and duration of follow-up, testing the following potential moderators or mediators: sample size, data collection year, percentage of females, mean BMI, duration of treatment, proportion of patients with the individual psychiatric comorbidities, and socio-demographic index of the country where the study was conducted. The meta-regression analysis with sample size also served to measure publication bias[58].

We conducted sensitivity analyses by number of outcome categories reported in eligible studies, to investigate if higher granularity and specificity of outcome description would affect the frequency of the outcome.

From meta-regression analyses we computed beta, that is the change in log of the proportion of individuals with the outcome of interest for each unit change in the moderator. R packages used in these analyses were *metaprop* and *metareg* commands from the *meta* package[59], in R 4.1.3.

RESULTS

Database search results and characteristics of included studies

From an initial 7,929 hits, we ultimately included 415 studies, reporting data on 88,372 persons with EDs. The PRISMA flow chart is reported in Figure 1. The lists of included studies and of studies excluded after full text assessment, with references and the reason for exclusion, are available in the supplementary information.

Overall, 55.4% of the studies had an observational design. Patients had a weighted mean age of 25.7±6.9 years, and 72.4% were females. The mean follow-up duration across all studies was 38.3±76.5 months. Studies were conducted most frequently in Europe (50.6%), followed by North America (38.8%), Oceania (5.5%), Asia (3.1%), South America (1.2%), and across multiple continents (0.7%).

Patients were most frequently diagnosed with AN (41.7%, n=173; N=37,160; mean follow-up: 64.1±102.8 months); and progressively less frequently with BN (35.4%, n=147; N=23,197; mean follow-up: 30.4±72.9 months); BED (17.1%, n=71; N=5,781; mean follow-up: 8.8±16.0 months); OSFED (5.3%, n=22; N=11,930; mean follow-up: 98.6±205.2 months); and mixed EDs (14.7%, n=61; N=10,304; mean follow-up: 31.1±46.9 months).

Only 12% of observational studies had high quality, and 24% of randomized controlled trials (RCTs) had low risk of bias.

Frequency of outcomes across and within eating disorders

The frequencies of primary and additional overall outcomes across EDs, and their rates at the different follow-up time points, are visualized in Figures 2 and 3.

Pooling all EDs together, overall recovery occurred in 46% of patients (95% CI: 44-49, n=283, mean follow-up: 44.9±62.8 months), without a significant difference among EDs (p=0.17). The recovery rate was 42% at <2 years, 43% at 2 to <4 years, 54% at 4 to <6 years, 59% at 6 to <8 years, 64% at 8 to <10 years, and 67% at ≥10 years. There was an increase of the recovery rate over follow-up in AN, BN and OSFED, whereas the rate decreased (from 57% at <2 years to 16% at 6 to <8 years) in BED (see supplementary information).

Overall chronicity occurred in 25% of patients (95% CI: 23-29, n=170, mean follow-up: 59.3±71.2 months), without a significant

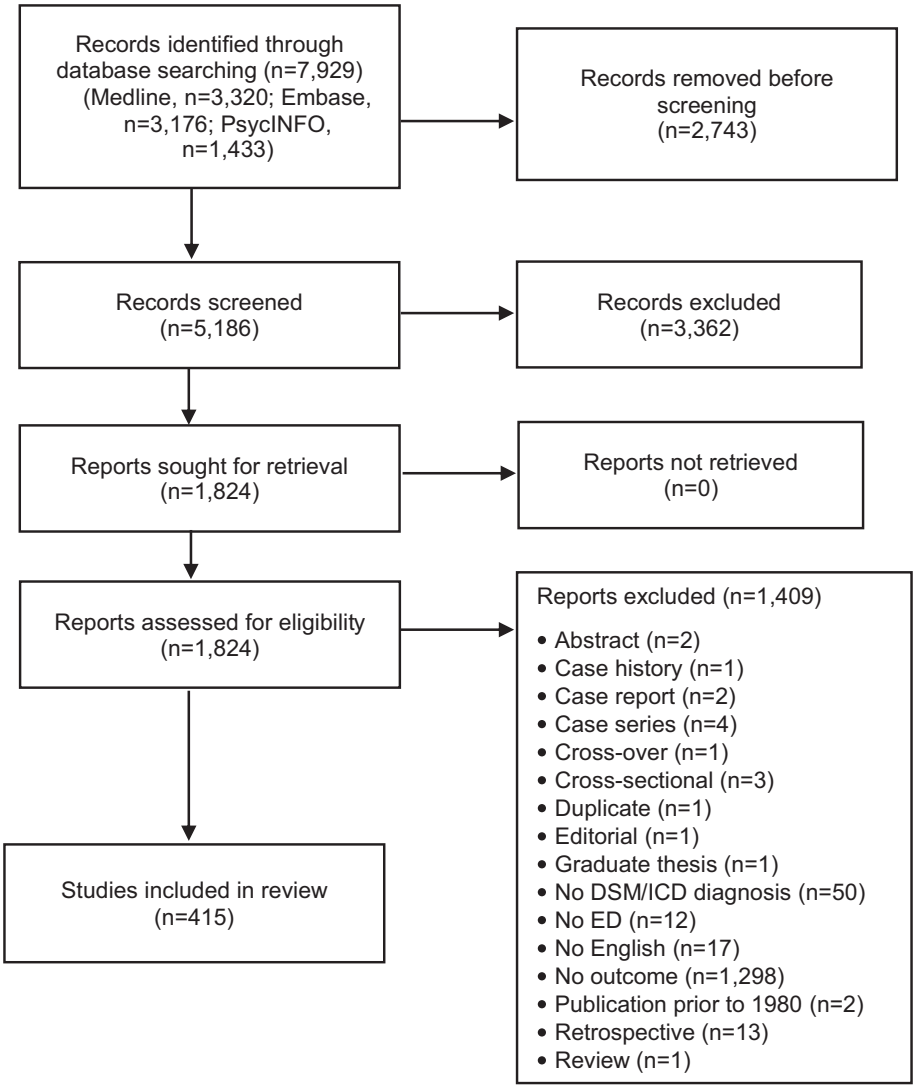

Figure 1 PRISMA flow chart. ED – eating disorder

difference among EDs (p=0.23). The chronicity rate was 33% at <2 years, 40% at 2 to <4 years, 23% at 4 to <6 years, 25% at 6 to <8 years, 12% at 8 to <10 years, and 18% at ≥10 years. There was a decrease of the chronicity rate over follow-up in AN, BN and OSFED, whereas the rate increased (from 17% at <2 years to 72% at 4 to <6 years) in BED (see supplementary information).

Mortality during follow-up occurred in 0.4% of patients (95% CI: 0.2-0.7, n=214, mean follow-up: 72.2±117.7 months), without a significant difference among EDs (p=0.058), due to large confidence intervals. Mortality increased with longer follow-up duration across and within EDs (see Figure 4). When focusing on observational studies, the mortality rate was 5.2 deaths/1,000 person-years (95% CI: 4.4-6.1, n=167, mean follow-up: 88.7±120.5 months; significant difference among EDs: p<0.01, range: from 8.2 for mixed ED to 3.4 for BN) (see also supplementary information).

Hospitalization occurred in 26% of patients (95% CI: 18-36, n=18, mean follow-up: 43.2±41.6 months), with a significant difference among EDs (p<0.001). It was highest in AN (32%, 95% CI: 23-43, n=14, mean follow-up: 47.4±44.7 months) and lowest in BN (4%, 95% CI: 1-10, n=2, mean follow-up: 26.9±17.3 months). ED-related hospitalization (reported in 11 studies, of which 10 focusing on AN) occurred in 34% of ED patients (95% CI: 24-47, N=896) and 35% of AN patients (95% CI: 24-49, N=777).

Among additional outcomes, improvement occurred in 28% of patients (95% CI: 25-32, n=101, mean follow-up: 54.9±69.8 months), with a significant difference among EDs (p=0.02). It was highest in BN (40%, 95% CI: 31-50, n=31, mean follow-up: 26.3±33.2 months) and lowest in AN (24%, 95% CI: 20-29, n=56, mean follow-up: 82.8±80.5 months).

Relapse after recovery occurred in 26% of patients (95% CI: 21-31, n=45, mean follow-up: 42.8±45.4 months), with a significant difference among specific EDs (p<0.001). It was highest in BN (31%, 95% CI: 25-39, n=19, mean follow-up: 37.7±40.4 months) and lowest in BED (10%, 95% CI: 6-17, n=1, follow-up: 45.1 months).

The results of sensitivity analyses accounting for heterogeneity

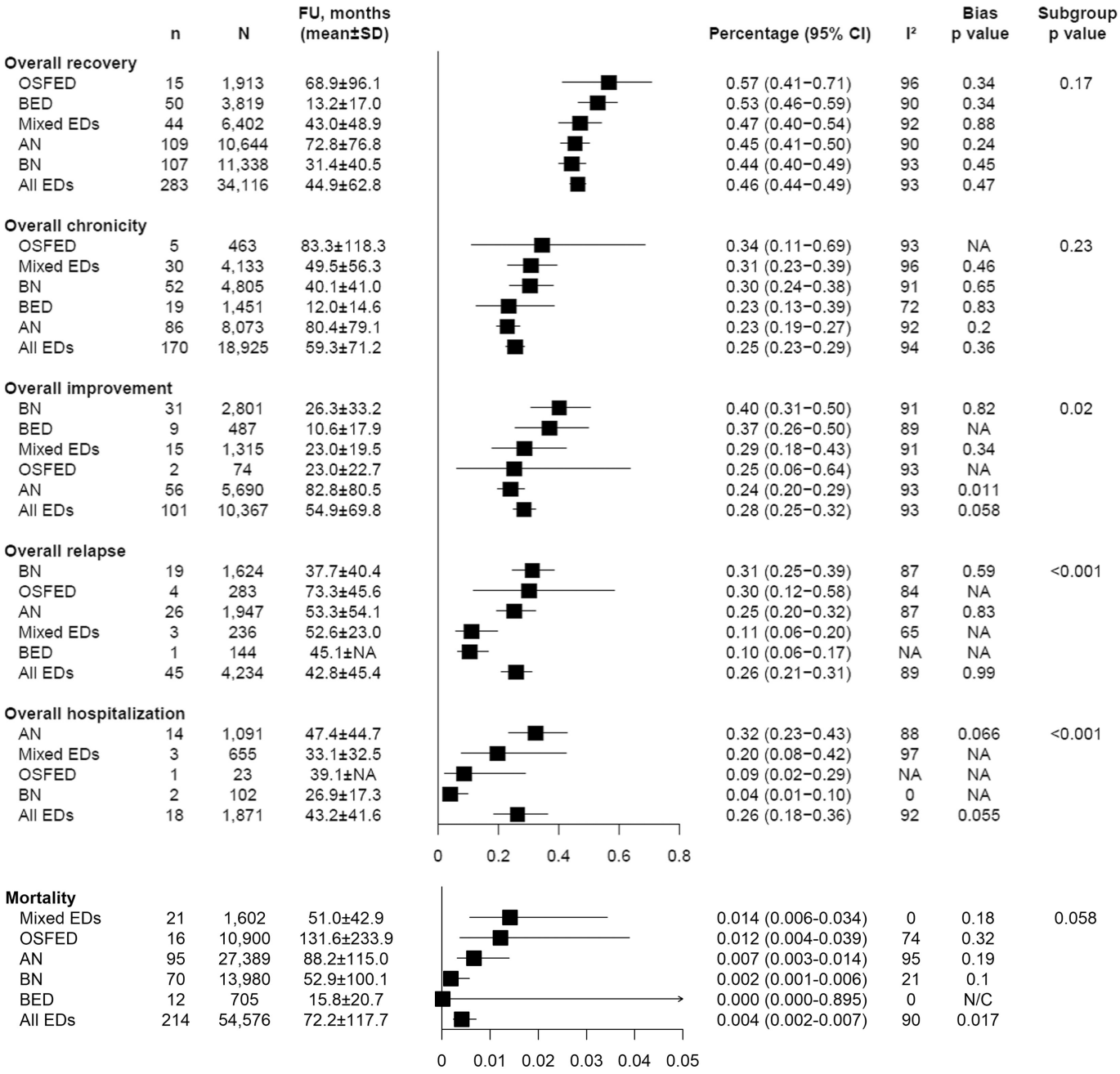

Figure 2 Overall recovery, improvement, relapse, hospitalization, chronicity and mortality across persons with eating disorders (EDs). FU – follow-up, AN – anorexia nervosa, BN – bulimia nervosa, BED – binge eating disorder, OSFED – other specified feeding and eating disorders, NA – not applicable, N/C – not calculable.

of definitions and granularity in defining different outcome categories were largely consistent with the main findings (see supplementary information).

Frequency of eating disorder-specific symptom outcomes across and within eating disorders

The frequencies of outcomes of specific ED symptoms are reported in Figure 5 and supplementary information.

Pooling all EDs, the rate of recovery was 43% for purging (95% CI: 37-49, n=30, no ED subgroup difference). It was 43% for binge eating (95% CI: 37-48, n=67), being highest in OSFED (83%; 95% CI: 53-96, n=1) and lowest in AN (31%; 95% CI: 23-41, n=3), with a significant subgroup difference (p=0.018). Recovery of weight occurred in 49% of patients (95% CI: 43-55, n=48), being highest in OSFED (69%, 95% CI: 63-74, n=1) and lowest in BED (17%, 95% CI: 12-24, n=1), with a significant ED subgroup difference (p<0.001).

Pooling all EDs, the rate of chronicity was 23% for purging (95%

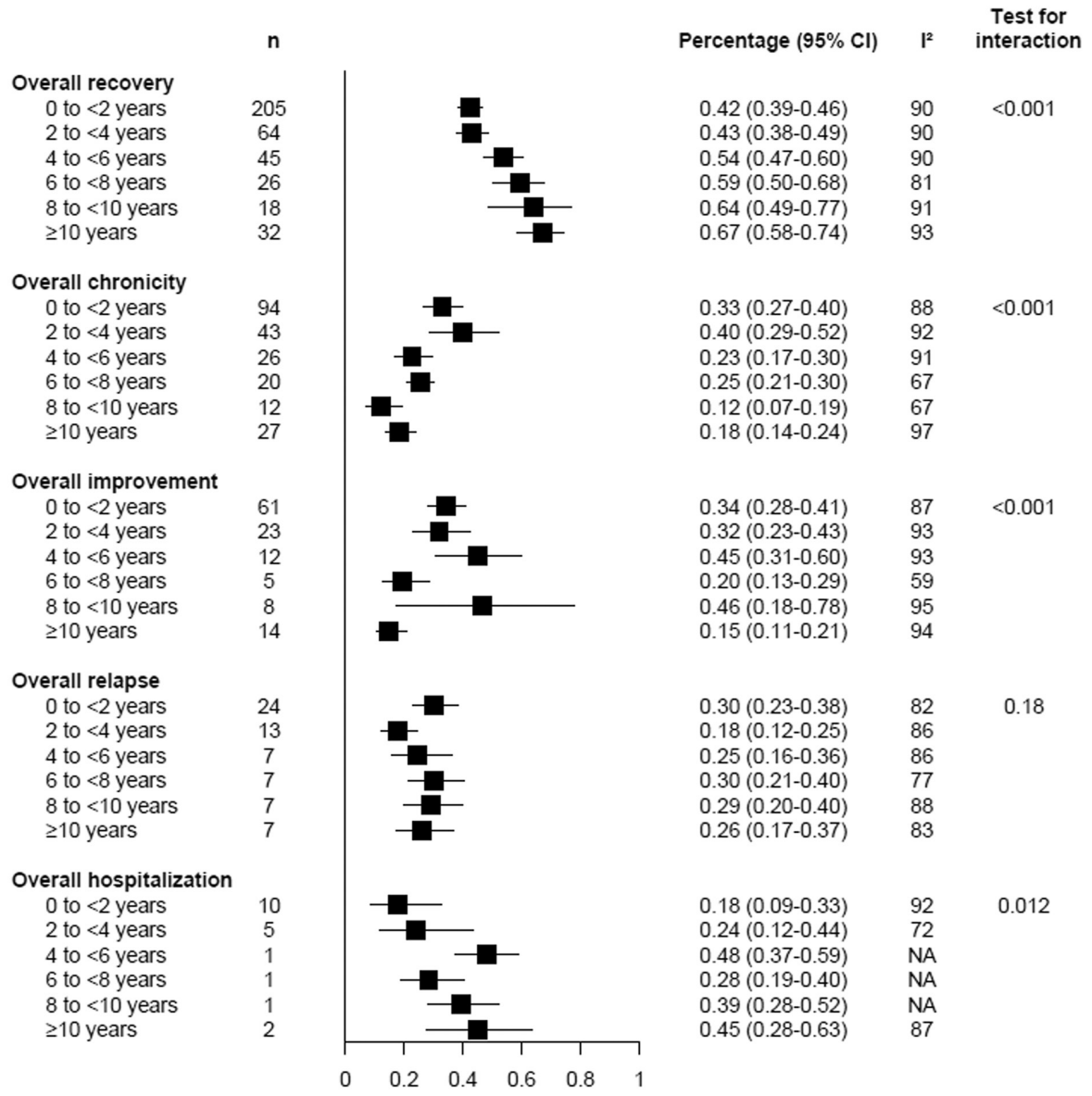

Figure 3 Overall recovery, improvement, relapse, hospitalization and chronicity in persons with all eating disorders pooled together over follow-up duration. NA – not applicable.

CI: 15-34, n=13, no ED subgroup difference); and 29% for binge eating (95% CI: 22-37, n=22, no ED subgroup difference). It was 23% for abnormal weight (95% CI: 16-31, n=28), being highest in AN (31%; 95% CI: 22-41, n=20) and lowest in BN (7%; 95% CI: 6-10, n=4), with a significant ED subgroup difference (p<0.001).

Diagnostic migration across eating disorders

Frequencies of diagnostic migration across EDs are reported in Table 1. From AN, 8% of patients migrated to BN and 16% to OSFED. From BN, 2% migrated to AN, 5% to BED, and 19% to OSFED. From BED, 9% migrated to BN and 19% to OSFED. From OSFED, 7% migrated to AN and 10% to BN.

Moderators and mediators of outcomes across and within eating disorders in subgroup analyses

A synopsis of statistically significant moderators and mediators of outcomes across and within EDs in subgroup analyses is provided in Table 2 (see supplementary information for a complete report).

Children/adolescents had significantly higher recovery rates than adults across and within all EDs; lower chronicity rates across all EDs and in AN; and lower mortality rates across EDs and within AN and BN.

Pooling all EDs, nutritional intervention was the primary treatment component associated with the largest recovery. CBT was the only specific intervention that had recovery rates of 26% or

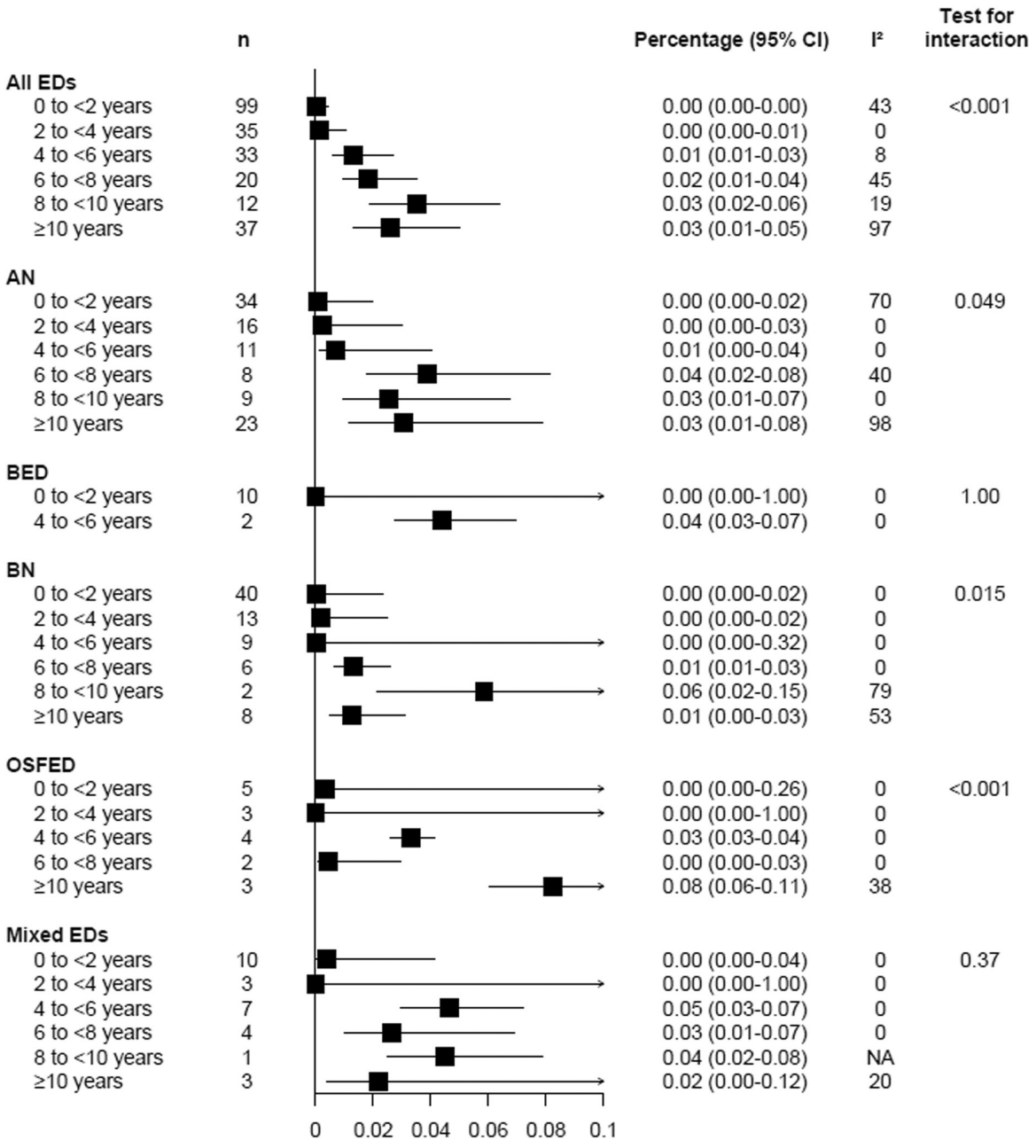

Figure 4 Mortality in persons with eating disorders (EDs) over follow-up duration. AN – anorexia nervosa, BN – bulimia nervosa, BED – binge eating disorder, OSFED – other specified feeding and eating disorders, NA – not applicable.

higher across all EDs. In AN, additional specific treatments that were associated with higher rates of recovery in ≥2 studies were family-based therapy, psychodynamic therapy, and multidisciplinary specific treatment. In BN, they were self-help, psychodynamic therapy, pharmacological treatment, multidisciplinary specific treatment, and DBT. In BED, they were pharmacological treatment, and DBT. In OSFED, they were multidisciplinary specific treatment and psychodynamic therapy. In AN, the use of pharmacotherapy was associated with low recovery rates. Waiting list was associated with the highest mortality rate in both pooled EDs and AN.

A significant difference in rates of recovery across continents only emerged for BN (highest in Asia, lowest in North America) and OSFED (highest in North America, lowest in Europe). Differences across continents regarding chronicity only emerged for pooled EDs (lowest chronicity in Asia, highest in South America) and AN (lowest chronicity in Asia, highest in Oceania). No differences among continents emerged for mortality either across or within EDs.

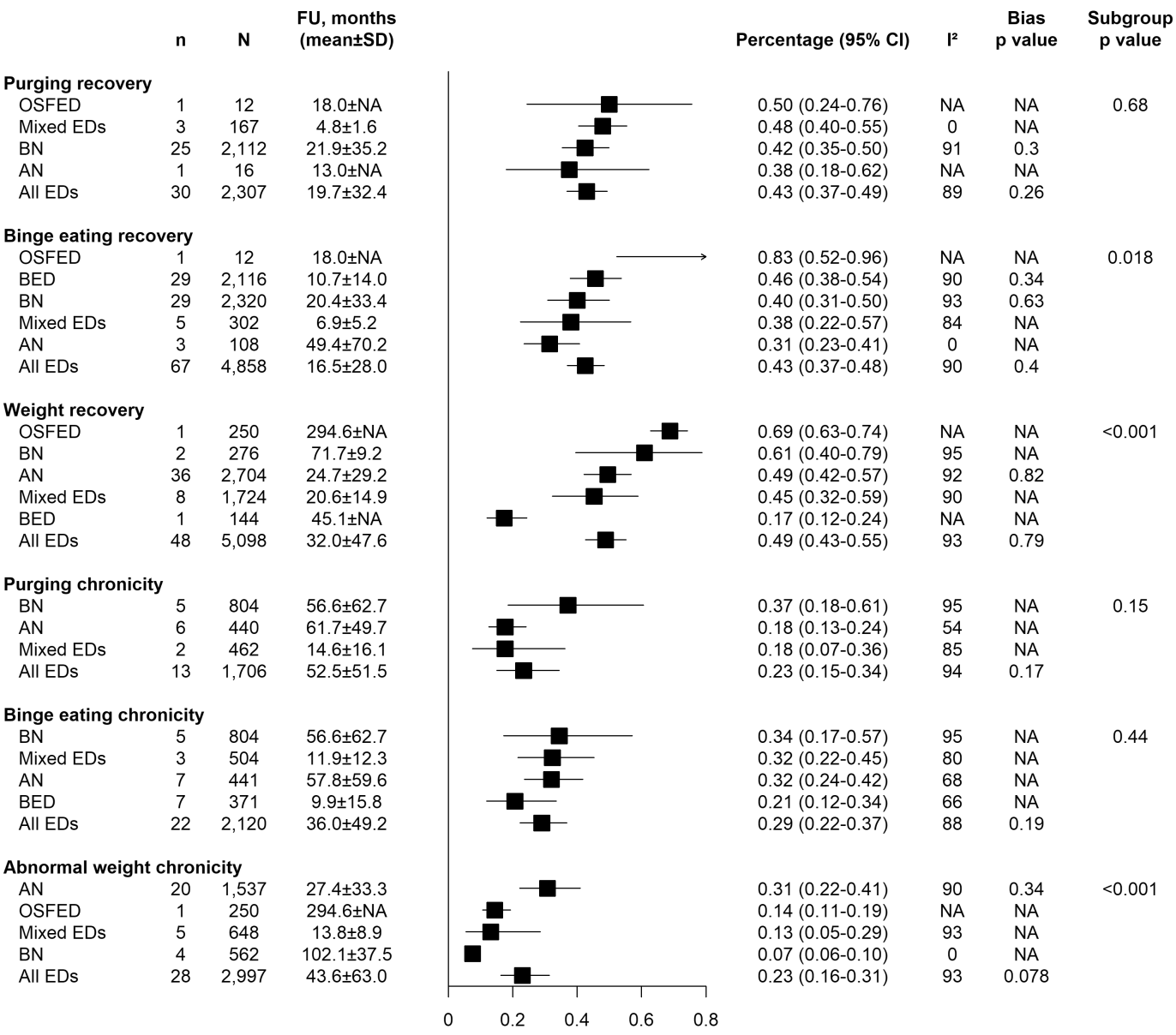

Figure 5 Purging, binge eating, and abnormal weight recovery and chronicity across persons with eating disorders (EDs). FU – follow-up, AN – anorexia nervosa, BN – bulimia nervosa, BED – binge eating disorder, OSFED – other specified feeding and eating disorders, NA – not applicable.

Moderators of outcomes across and within specific eating disorders in meta-regression analyses

Across all EDs, recovery increased with mean baseline BMI, and percentage of patients with obsessive-compulsive disorder, and decreased with proportion of patients with self-injurious behaviors. In AN, a higher recovery rate was associated with higher percentage of patients with obsessive-compulsive disorder, less recent data collection, and lower country socio-demographic index. In BN, higher recovery rate was associated with longer duration of treatment, higher proportion of patients with major depressive disorder, and higher number of treatment ingredients. Lower chronicity rate in AN was associated with smaller sample size and lower country socio-demographic index (see Table 3).

For mortality, across all EDs pooled together, rates decreased with more recent data collection and higher baseline BMI, which was confirmed in AN, where also longer treatment duration was associated with lower mortality. In BN, a higher proportion of females was associated with lower mortality rates, while in OSFED lower mortality was associated with higher socio-demographic index (see Table 3).

DISCUSSION

This systematic review meta-analyzed 415 studies from all continents, except Africa, that investigated clinically relevant outcomes of specific EDs – including recovery, improvement, relapse

Table 1 Conversion rates among eating disorders

	n	N	Prevalence (95% CI)	I^2
From anorexia nervosa				
To bulimia nervosa	35	5,758	0.08 (0.05-0.11)	96
To other specified feeding and eating disorders	23	3,211	0.16 (0.11-0.21)	90
From bulimia nervosa				
To anorexia nervosa	12	3,121	0.02 (0.01-0.04)	76
To binge eating disorder	9	957	0.05 (0.02-0.13)	89
To other specified feeding and eating disorders	13	1,561	0.19 (0.12-0.29)	88
From binge eating disorder				
To bulimia nervosa	4	225	0.09 (0.02-0.31)	89
To other specified feeding and eating disorders	2	57	0.19 (0.11-0.32)	59
From other specified feeding and eating disorders				
To anorexia nervosa	4	236	0.07 (0.02-0.21)	12
To bulimia nervosa	5	288	0.10 (0.05-0.18)	46

after recovery, hospitalization, chronicity and mortality – over different follow-up times. Additional objectives included exploring the presence of moderators and mediators of the main outcomes within and across EDs, evaluating the proportion of patients migrating between ED diagnoses, and estimating the real-world effectiveness of different interventions.

This is the first meta-analysis that provides a systematic atlas of the clinical outcomes of EDs – including AN, BN, BED and OSFED – over up to more than 10 years of follow-up. Its findings can inform the clinical management of persons with EDs, the relevant research agenda, as well as appropriate health services and resource allocation aiming to improve outcomes in people with EDs.

Results indicate that recovery rates are similar among different EDs when considering overall symptoms and purging, but different regarding binge eating (with OSFED having the highest and AN the lowest recovery rate) and abnormal weight (with OSFED having the highest and BED the lowest recovery rate). BED is frequently associated with overweight or obesity, which can cause physical complications, including arthritis, diabetes, cardiovascular and respiratory conditions, that limit the ability to exercise, might contribute to further weight gain and are barriers to weight loss[60-62]. Moreover, BED is associated with mental comorbidities, including depressive and bipolar disorder as well as borderline personality disorder[60], which are associated with lower physical activity levels, as well as poor physical and mental health status, which are each barriers to a healthy weight status[63-67]. It is crucial to intervene early in BED, to avoid that the network of psychological, behavioral and physical symptoms sustaining obesity clusters and aggregates to the point of becoming refractory to treatment[68-71].

AN had the most severe outcomes among EDs, including highest relapse and chronicity of weight loss, and highest rates of hospitalization. These outcomes are consistent with the numerous physical health complications that are associated with underweight and malnourishment[72-77], and with the importance of early weight gain for a positive disease course[78,79]. BN, instead, had the highest rates of overall improvement and relapse, suggesting a more episodic course compared to other EDs.

Recovery is not achieved by more than half of patients with EDs. Moreover, pooled across EDs, 26% experience relapses after recovery, and 26% require hospitalization during follow-up. The overall mortality risk in EDs is 0.4% (range: 0-1.4%), which is a relatively high rate for individuals at a mean age of 25.7±6.9 years. Moreover, the mean follow-up period of 38.3±76.5 months was likely too short to capture the full mortality risk, and differential attrition rate may have affected the capturing of mortality in sicker patients, who may have been less likely to remain in longer-term follow-up. Also, since studies with longer duration reported higher mortality risk, future representative studies following individuals with EDs for sufficient periods of time will likely report higher lifetime mortality rates.

Recovery rates increased and chronicity rates decreased over follow-up across all EDs, except for BED. The significant effect of time indicates that short-term RCTs might be prone to type I error, with shorter trials overestimating the efficacy of experimental interventions versus TAU, which might not hold true at longer follow-up. In BED, an opposite trend of outcomes emerged over follow-up, with recovery decreasing and chronicity increasing over time, confirming that early remission is crucial, before ED symptoms, overweight or obesity, and physical health implications cluster tightly.

The most common diagnostic migration from AN, BN and BED is to OSFED (16% to 19%), with lower rates in the opposite direction (7% to 10%), or among other EDs (2% to 9%). Diagnostic migration from AN, BN or BED to OSFED implies that some symptoms of a specific ED have improved, while other symptoms have persisted, so that not all diagnostic criteria are met. OSFED may evolve in three different directions: relapse of AN (7%) or BN (10%), a chronic course (34%), or transition to recovery (57%).

As OSFED is a less well-defined and more heterogeneous diagnosis, it may pose a challenge to clinicians when deciding on the best course of treatment[80]. Indeed, it may be implicitly considered as a residual category and a less severe disorder[4]. However, results from this meta-analysis indicate that recovery and chronicity rates are not different from those of AN or BN, and that the risk of relapse of OSFED actually increases with follow-up time, from 8% within 2 years to 52% after over 10 years.

Children and adolescents had the highest recovery rate in pooled EDs, and the lowest chronicity rate in AN. These results are in line with the staging model of EDs[27], which suggests that, while illness progresses, neurobiological and psychosocial maintaining factors develop and make persons suffering from EDs more resistant to treatment[81]. These data further indicate the importance of providing sufficient resources to enable early diagnosis and treatment, and of reducing barriers and delays to treatment access in young people[82,83]. For this purpose, services and policy makers

Table 2 Statistically significant moderators of recovery, chronicity and mortality across eating disorders (EDs) identified by subgroup analyses

Moderator	AN	BN	BED	OSFED	All EDs
Age group with 26-50% recovery	Adults	Adults		Adults	Adults
Age group with 51-75% recovery	Children/adolescents		Adults		Children/adolescents
Age group with 76-100% recovery		Children/ adolescents	Children/ adolescents	Children/ adolescents	
Primary treatment component with 0-25% recovery	Pharmacological				
Primary treatment component with 26-50% recovery	Nutritional, FBT, CBT, psychodynamic, multidisciplinary (specific)	Self-help, CBT, psychodynamic, nutritional, pharmacological	CBT, pharmacological, DBT	CBT, multidisciplinary (specific), psychodynamic	FBT, self-help, CBT, psychodynamic, DBT, pharmacological, multidisciplinary (specific)
Primary treatment component with 51-75% recovery		Multidisciplinary (specific), DBT			Nutritional
Primary treatment component with 76-100% recovery			Nutritional		
Continents with 26-50% recovery		Europe, North America		Europe	
Continents with 51-75% recovery		Asia, Oceania		North America, Asia, Oceania	
Age group with 51-75% chronicity				Adults	
Age group with 26-50% chronicity	Adults			Children/ adolescents	Adults
Age group with 0-25% chronicity	Children/adolescents		Adults		Children/adolescents
Continents with 26-50% chronicity	Oceania, North America, South America				South America, North America, Oceania
Continents with 0-25% chronicity	Asia, Europe				Asia, Europe
Age group with 1-5% mortality	Adults				
Age group with <1% mortality	Children/adolescents	Adults, children/ adolescents			Children/adolescents, adults
Primary treatment component with >5% mortality	Waiting list				Waiting list
Primary treatment component with 1-5% mortality	CBT, psychodynamic			CBT	CBT, psychodynamic, FBT
Primary treatment component with <1% mortality	FBT, nutritional, multidisciplinary (specific)			Psychodynamic	Psychoeducation, nutritional, multidisciplinary (specific)

AN – anorexia nervosa, BN – bulimia nervosa, BED – binge eating disorder, OSFED – other specified feeding and eating disorders, CBT – cognitive-behavioral therapy, DBT – dialectical behavioral therapy, FBT – family-based therapy. Treatment-as-usual and interventions tested in one study only are not included. Results of additional subgroup analyses are reported in the supplementary information.

should look at family and general practitioner education[31], and the strict division still existing in many settings between child and adult mental health services should be overcome[34,84,85].

Among interventions for EDs included in more than one study, treatments with a primary nutritional component were associated with the highest rates of overall recovery. Prescription of a healthy meal plan, psychoeducation on physiologic nutritional needs, and supervised meals in intensive or family-based settings are crucial to normalize the eating pattern, and interrupt some of the behavioral symptoms. Moreover, psychopathological symptoms can indirectly benefit from the improvement of eating behaviors.

However, a treatment exclusively focused on nutrition would not offer the necessary insight on the personalized cycle and network of symptoms of each person's ED, nor would it train coping skills to address environmental (interpersonal) triggers, target body checking, address mental comorbidities, and ultimately facilitate full recovery and prevent relapse.

Our findings support the role of family-based therapy and CBT in AN[39]. All main guidelines[35] indicate the effectiveness of family-based interventions in adolescents with AN. Additionally, according to a recent umbrella review[39], also young adults with AN may benefit from these interventions. Most guidelines also suggest the effectiveness of CBT, and two of them point to CBT as the first-line individual psychotherapy for people with AN[35].

Table 3 Statistically significant moderators of recovery, chronicity and mortality across eating disorders (EDs) identified by multivariable meta-regression analyses

Moderator	AN	BN	BED	OSFED	All EDs
		Recovery			
Data collection year	Beta=–0.001 (–0.002 to 0.000), n=64, p=0.0081				
Treatment duration		Beta=0.019 (0.004-0.034), n=52, p=0.011			
Mean body mass index					Beta=0.102 (0.042-0.162), n=91, p=0.00088
% obsessive-compulsive disorder	Beta=3.517 (1.452-5.581), n=11, p=0.00084				Beta=3.576 (1.579-5.574), n=12, p<0.00045
% major depressive disorder		Beta=3.928 (2.213-5.643), n=7, p<0.0001			
% self-injurious behaviors					Beta=–4.452 (–6.832 to –2.072), n=8, p=0.00025
Country socio-demographic index	Beta=–6.473 (–11.503 to –1.443), n=63, p=0.012				
Number of treatment ingredients		Beta=0.172 (0.011-0.332), n=52, p=0.036			
		Chronicity			
Sample size	Beta=0.002 (0.001-0.003), n=49, p=0.00019				
Country socio-demographic index	Beta=6.430 (0.539-12.321), n=49, p=0.032				
		Mortality			
Data collection year	Beta=–0.109 (–0.177 to –0.041), n=52, p=0.0016				Beta=–0.066 (–0.125 to –0.007), n=85, p=0.028
% females		Beta=–3.401 (–6.001 to –0.801), n=31, p=0.01			
Mean body mass index	Beta=–0.799 (–1.264 to –0.335), n=34, p=0.00074				Beta=–0.290 (–0.496 to –0.083), n=57, p=0.0059
Treatment duration	Beta=–0.054 (–0.104 to –0.005), n=52, p=0.031				
Country socio-demographic index				Beta=–15.279 (–29.432 to –1.125), n=7, p=0.034	

Beta values are reported with 95% CIs. The analyses were adjusted for mean age, illness duration and duration of follow-up. AN – anorexia nervosa, BN – bulimia nervosa, BED – binge eating disorder, OSFED – other specified feeding and eating disorders. All results are available in the supplementary information.

Importantly, waiting list was associated with the highest mortality in AN. This finding is of crucial clinical relevance, and should encourage ED services offering treatment for AN to avoid passive waiting list, and to offer psychoeducational elements and active monitoring to those awaiting admission, to capture worsening of behavioral and clinical symptoms early.

Our data suggest that self-help, CBT and DBT are effective in BN. Most guidelines outline CBT as the first-line psychotherapy for this condition[35], while the National Institute for Health and Care Excellence (NICE) guidelines[86] point to guided self-help as first-line treatment, probably in light of cost-effectiveness considerations. Compared with guidelines[35], our finding concerning DBT is novel. DBT is one of the "third wave" psychotherapies, which include CBT elements (i.e., skills training, exposure, self-monitoring) but focus more on the context and on interpersonal functioning, which are maintaining factors of EDs[87,88]. DBT can also address comorbid borderline personality symptoms, which do have an impact on outcomes of EDs, especially in BN and AN binge-purge type.

In individuals with BED, CBT and pharmacotherapy are supported by the current findings, which is in line with guidelines[35] that suggest the use of CBT, selective serotonin reuptake inhibitors, anticonvulsants (topiramate) and anti-obesity (orlistat) drugs. Lisdexamfetamine has been approved only in some countries, and long-term effectiveness of medications has not been proven[89,90]. The efficacy of stimulants or topiramate in BED might be partially

mediated by appetite suppression. Improvement in cognition as well as in impulse control and comorbid anxiety and depressive symptoms is also likely to mediate the efficacy of pharmacological options to treat BED[91].

Beyond age group and specific treatment components, other factors moderated outcomes of EDs in this meta-analysis. For example, comorbid mental disorders or symptoms were associated with better or worse outcomes across EDs, and had the largest effect sizes among outcome moderators. This finding reflects the central role of non-ED psychopathology in maintaining the symptoms of EDs, and the importance of targeting comorbid mental conditions when treating EDs[70,92]. OCD and major depressive disorder moderated higher rates of recovery in AN and BN, respectively, possibly because these conditions are pharmacologically addressable. Self-injurious behaviors were associated with lower recovery rates in pooled EDs. They can be considered a proxy of borderline personality disorder traits[93], which do not respond to most pharmacological treatments[94], but which do respond to DBT[95].

In BN, a higher number of treatment components and a longer duration of treatment were associated with higher rates of recovery. These results reflect the multidimensional nature of symptoms in BN, the frequent presence of comorbid mental disorders and symptoms, and the need to provide multidisciplinary care that is not too limited in time[39,70,96,97].

Pooling all EDs, mortality decreased in more recent studies, although this finding was driven by studies in AN. While education and training on AN vary across countries, and are frequently suboptimal[98,99], our data suggest that physical health of subjects with AN has improved over decades, possibly reflecting decreased stigma[100] and increasing knowledge and attention to physical comorbidities[101].

However, as reflected by the decrease in recovery rates of AN over the last decades, decreasing mortality is not enough. AN symptoms can evolve to a state of severe and enduring illness, in which patients describe their life as permeated by the disease, that assumes an identity role[102]. On the other hand, residual eating-related cognitions may persist throughout the life of a substantial group of patients, without being necessarily incompatible with a reasonable degree of psychological well-being[103]. The issue of personal recovery, implying an emphasis on the affected persons' perceptions and values, has not been explored sufficiently in people with EDs, representing an important potential focus for future research.

Higher BMI was associated with decreased mortality in AN, supporting the current classification of severity in the DSM-5.

A higher proportion of males predicted higher mortality in BN. The prevalence of EDs in males is increasing at a faster rate than in females[104]. Although some data point to similarities with females, some qualitative differences have been detected, such as a more frequent history of overweight and drive for leanness and muscularity, which can promote the use of specific drugs (i.e., anabolic steroids)[105]. The sensitivity of most commonly used tools to quantify ED symptoms may be suboptimal in males[106], and EDs may be under-detected in these individuals[106-108]. Our findings call for additional research examining sex and gender as moderators of different clinical characteristics and outcomes in EDs[105,109].

A higher socio-demographic index moderated lower recovery and higher chronicity in AN. Countries with a higher index might culturally be more impregnated with thinness pressure, while other sociocultural systems might be less thinness- or body image-centred[110,111].

This meta-analysis pools quantitative results from over twice as many studies as the previous available reviews[44,46,47], which were conducted over 20 to almost 15 years ago, and did not meta-analyze the data. Our work confirms prior findings and adds novel results. For instance, in AN, this work confirms the rates of chronicity being above 20%, and at the same time the need to communicate hope even to persons with severe clinical presentations, as rates of recovery increased and rates of chronicity decreased over the patients' follow-up time. However, the outcome of EDs in general has not improved over decades, apart from lower mortality in AN.

This meta-analysis adds evidence from observational and interventional studies about the impact of several interventions on clinical outcomes in EDs, accounting for longer follow-up and quantitatively testing moderators and mediators of outcomes in subgroup and multivariable analyses, thus informing clinical care and organization of services. Results from these additional approaches indicate, for example, the need to offer nutritional interventions and avoid unmonitored waiting list status.

This work has several strengths. First, it covers over 40 years of observational and interventional studies, providing a comprehensive overview of the current knowledge on EDs. Second, the inclusion of a large number of studies allowed the exploration and identification of several moderators and mediators, providing insights that can inform research, clinical practice and policy-making. Third, this work is unique in that it pooled data from studies conducted across all continents, except for Africa, providing a global perspective on EDs. Fourth, including observational studies allowed the measurement of long-term outcomes, enabling a more generalizable assessment of the effectiveness of different interventions and the frequency of relevant outcomes in people with EDs.

The meta-analysis also has some limitations. First, not limiting ourselves to RCTs, we could not compare specific treatments or rank them. These meta-analyses already exist[37,38], but generally have a short time frame and cannot capture all of the clinically relevant outcomes this work focused on. Moreover, compared to RCTs, the inclusion of observational studies allowed us to capture and comment on a population that is more representative of real-world patients, which supports the generalizability of the findings. Second, including both RCTs and observational studies might have increased heterogeneity of the samples to some degree. Third, the diagnostic criteria for EDs in DSM and ICD have changed over time, and this may have influenced the results of this study.

Fourth, we did not conduct a meta-analysis of diagnostic migration from EDs to other mental disorders, because this was beyond the scope of this work, and future systematic reviews should quantify rates of this migration. Fifth, psychosocial determinants of health (i.e., early life trauma or emotion regulation), that have

more recently emerged as outcome predictors[112], were not widely available in the meta-analyzed studies, and could thus not be taken into account. Sixth, findings do not include outcomes of EDs in Africa, where research in this field should be promoted. Seventh, we did not investigate the impact of ED subtypes – i.e., restricting versus binge-purge AN, or atypical AN – as data were too limited concerning the outcomes this meta-analysis focused on. Eighth, the definition of outcomes was heterogeneous in the included studies. In order to account for this heterogeneity of definitions and granularity in defining different outcome categories, we have conducted several sensitivity analyses by the number of outcome categories, whose results were largely consistent with the main findings. Finally, despite the large number of eligible studies, some outcomes were based on only few studies, and the relative findings should be considered preliminary.

In conclusion, this systematic review and meta-analysis contributes to the understanding of EDs and provides insights into their treatment and real-world outcomes, both overall and regarding specific EDs. The results highlight the severe course of EDs, although there has been a decrease in mortality rates over time. It is imperative that patients with EDs are identified early and moved from waitlists to active care as quickly as possible, with a particular focus on those with a low BMI and comorbid self-injurious behaviors. Comorbid depression and OCD are treatable and should be monitored and addressed.

It is also important to identify and treat EDs in children and adolescents as early as possible, to improve outcomes and prevent delays in managing EDs into adulthood. Management plans should include a nutritional intervention across all EDs. For AN, a multi-component intervention should include family-based therapy for children/adolescents and young adults, as well as CBT. Self-help, CBT and DBT are effective interventions for BN, while CBT and pharmacotherapy are recommended for BED.

There is a need for long-term observational studies to fully capture outcomes of individuals with EDs. International consensus should be reached in defining recovery, improvement, chronicity and relapse in this population. The issue of personal recovery in people with EDs should be explicitly addressed by research. Future studies should also aim to improve the detection of moderators and mediators that can help stratify patient subgroups, in order to allow a more personalized treatment approach to persons with EDs.

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Current evidence on the efficacy of mental health smartphone apps for symptoms of depression and anxiety. A meta-analysis of 176 randomized controlled trials

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The mental health care available for depression and anxiety has recently undergone a major technological revolution, with growing interest towards the potential of smartphone apps as a scalable tool to treat these conditions. Since the last comprehensive meta-analysis in 2019 established positive yet variable effects of apps on depressive and anxiety symptoms, more than 100 new randomized controlled trials (RCTs) have been carried out. We conducted an updated meta-analysis with the objectives of providing more precise estimates of effects, quantifying generalizability from this evidence base, and understanding whether major app and trial characteristics moderate effect sizes. We included 176 RCTs that aimed to treat depressive or anxiety symptoms. Apps had overall significant although small effects on symptoms of depression (N=33,567, g=0.28, p<0.001; number needed to treat, NNT=11.5) and generalized anxiety (N=22,394, g=0.26, p<0.001, NNT=12.4) as compared to control groups. These effects were robust at different follow-ups and after removing small sample and higher risk of bias trials. There was less variability in outcome scores at post-test in app compared to control conditions (ratio of variance, RoV=–0.14, 95% CI: –0.24 to –0.05 for depressive symptoms; RoV=–0.21, 95% CI: –0.31 to –0.12 for generalized anxiety symptoms). Effect sizes for depression were significantly larger when apps incorporated cognitive behavioral therapy (CBT) features or included chatbot technology. Effect sizes for anxiety were significantly larger when trials had generalized anxiety as a primary target and administered a CBT app or an app with mood monitoring features. We found evidence of moderate effects of apps on social anxiety (g=0.52) and obsessive-compulsive (g=0.51) symptoms, a small effect on post-traumatic stress symptoms (g=0.12), a large effect on acrophobia symptoms (g=0.90), and a non-significant negative effect on panic symptoms (g=–0.12), although these results should be considered with caution, because most trials had high risk of bias and were based on small sample sizes. We conclude that apps have overall small but significant effects on symptoms of depression and generalized anxiety, and that specific features of apps – such as CBT or mood monitoring features and chatbot technology – are associated with larger effect sizes.

Key words: Smartphone apps, depression, generalized anxiety, social anxiety, post-traumatic stress, panic, cognitive behavioral therapy, mood monitoring, chatbot technology

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Depressive and anxiety disorders are common mental health conditions associated with significant disease burden, profound economic costs, premature mortality, and severe quality of life impairments for affected individuals and their relatives[1,2]. Widely accessible treatments are required to reduce these impacts. Both psychotherapies and pharmacotherapies can effectively treat symptoms of depression and anxiety[3-7]. However, there are many barriers that prevent people from accessing these traditional forms of treatment, including limited availability of trained psychiatrists and psychologists, high cost of treatment, stigma associated with help-seeking, and low mental health literacy[8,9].

Over the past two decades, the mental health care available for depression and anxiety has undergone a major technological revolution. Empirically validated components of psychological interventions that were once delivered solely in-person have now been translated for delivery via low-cost, private and scalable digital tools[10,11].

Smartphone applications ("apps") are one form of digital treatment delivery which is receiving substantial attention. Smartphones are among the most rapidly adopted technological innovations in recent history. Over 6.5 billion people own a smartphone, that is typically checked multiple times per day and always kept within arm's reach[12]. Treatment content delivered via an app can thus be accessed anytime and anywhere, enabling users to practice those critical therapeutic skills that are necessary for preventing the onset or escalation of symptoms in moments of need[8]. Digital monitoring systems and complex machine learning algorithms also enable treatment content to be regularly updated and personalized to the needs of the user based on data collected passively (e.g., global positioning system coordinates to infer social determinants of health) and actively (e.g., symptom tracking)[13,14].

The potential of apps to treat depressive and anxiety symptoms is attracting an increasing interest among patients, clinicians, technology companies, and health care regulators. However, there are risks associated with depression and anxiety apps, such as privacy violations; possible easy access to ineffective, inaccurate or potentially harmful content[15,16]; low rates of engagement[17,18], and exclusion of the potential therapeutic ingredient represented by the personal relationship between a clinician and a patient. All this, coupled with the fact that mental health apps for depression and anxiety are some of the most widely publicly offered and downloaded categories of health apps[19,20], generates the duty to provide the public with up-to-date information on the evidence base supporting their use[21].

In a 2019 meta-analysis, Linardon et al[13] found apps to outperform control conditions in reducing symptoms of depression (g=0.28) and generalized anxiety (g=0.30) based on 41 and 28 trials, respectively. This meta-analysis also found early evidence

for the efficacy of apps on social anxiety – but not post-traumatic stress or panic – symptoms (≤6 trials). Heterogeneity in efficacy was noted, although few robust effect modifiers were identified, perhaps reflecting the relatively low numbers of trials available[22] and the focus on univariate moderator effects rather than more complex multivariate moderator models.

Research testing mental health apps on depressive and anxiety symptoms is growing exponentially, offering greater opportunity to explore whether recent innovations in digital health have promoted improved efficacy, and to examine the individual and combined effects of moderators on treatment efficacy. Since 2019, there have been more than 100 randomized controlled trials (RCTs) published, some of which include large sample sizes, use credible comparison conditions, and have a lower risk of bias. Each of these elements had been raised as critical features absent in this field according to the conclusions drawn by the authors of earlier meta-analyses[13,21,23]. Furthermore, the large number of available trials now enables more precise, complex and adequately powered analysis of those app and trial characteristics that may be associated with effect sizes.

In light of the limitations of past reviews, and with interest in research on mental health apps further expanding, we conducted an updated meta-analysis testing the effects of mental health apps on symptoms of depression and anxiety. In addition to typical pooling of mean differences between intervention and control conditions, we also explored group differences in variability of outcomes, as a means to gauge the potential generalizability of the effects of these apps. As argued recently[24,25], if an intervention has variable effect on participants, this may be observed through greater variability around the post-test mean for the intervention group relative to the control group. Finally, in light of evident heterogeneity of effect sizes from prior reviews[13,21], we attempted to identify moderators (specifically, major characteristics of the app, study population, and trial design) that may account for larger or smaller effect sizes than the pooled average.

Furthermore, this meta-analysis aimed to move beyond examination of individual moderators, to also – for the first time – evaluate potential combinations and interactions among the pre-selected moderator variables[26]. This will help shed new light on the contexts in which specific intervention components may be most effective, and further characterize subgroups of individuals who respond particularly well to mental health apps.

METHODS

Identification and selection of trials

This review was conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[27], and adhered to a pre-registered protocol (CRD42023437664). We searched (last updated June 2023) the Medline, PsycINFO, Web of Science, and ProQuest Database for Dissertations online databases combining key terms related to smartphones, RCTs, and anxiety or depression (see supplementary information for the full search strategy). We also hand-searched through relevant reviews[13,14,21] and reference lists of included studies to identify any potentially eligible trials not captured in the primary search.

We included RCTs that tested the effects of a stand-alone, smartphone-based, mental health app against a control condition (e.g., waitlist, placebo, information resources) or an active comparison (e.g., face-to-face treatment) for symptoms of depression or anxiety. Trials that conducted one psychoeducational or information session prior to the delivery of the app program were eligible for inclusion. Blended web and app-based programs were excluded, as were apps not focused – solely or in part – on targeting mental health (e.g., weight loss or diet apps). Text-message only interventions were excluded. Adjunctive treatments were also excluded, such as when apps were incorporated within a broader face-to-face psychotherapy program. However, trial arms comprised of a mental health app plus usual care were included, as long as the usual care component did not consist of a structured psychological treatment program (e.g., trials of patients with a medical condition continuing their usual care were permitted). Published and unpublished trials were eligible for inclusion. If a study did not include data for effect size calculation, the authors were contacted, and the study was excluded if they failed to provide the data.

Quality assessment and data extraction

We used criteria from the Cochrane Collaboration Risk of Bias tool[28] to assess for risk of bias. These criteria include random sequence generation, allocation concealment, blinding of participants or personnel, blinding of outcome assessment, and completeness of outcome data. Each domain was rated as high risk, low risk, or unclear. Selection bias was rated as low risk if there was a random component in the allocation sequence generation. Allocation concealment was rated as low risk when a clear method that prevented foreseeing group allocation before or during enrolment was explicitly stated. Blinding of participants was rated as low risk when the trial incorporated a comparison condition that prevented participants from knowing whether they were assigned to the experimental or control condition (e.g., a placebo app or an intervention intended to be therapeutic). Blinding of outcome assessors was rated as low risk if proper measures were taken to conceal participants' group membership, or if the outcome measures were self-reported, which does not involve direct contact with the researcher. Completeness of outcome data was rated as low risk if the trial authors included all randomized participants in their analyses (i.e., they adhered to the intention-to-treat principle).

We also extracted several characteristics pertaining to the study (year, author, sample size), participants (target group, selection criteria), app intervention (orientation, primary target, key features, prescription of human guidance), comparison (type of control condition), and outcome assessment (tool used, length assessed, primary vs. secondary). Two researchers performed data extraction, and any disagreement was resolved through consensus.

Meta-analysis

Analyses were conducted using Comprehensive Meta-Analysis Version 3.0[29] for effect size estimates of between-group mean differences and univariate subgroup analyses, and R for comparing variability between intervention and control groups and for probing interactions among moderators. For each comparison of means between the app intervention and the control condition, the effect size was calculated by dividing the difference between the two group means at post-test by the pooled standard deviation. We reported Hedges' g over Cohen's d to correct for small sample bias[30]. If means and standard deviations were not reported, effect sizes were calculated using change scores or other reported statistics (t or p values for group comparisons). To calculate a pooled effect size, each study's effect size was weighted by its inverse variance. If multiple measures of a given outcome variable were used, the mean of the effect sizes for each measure within the study was calculated, before the effect sizes were pooled[29]. A positive g indicates that the app condition achieved higher symptom reduction than the comparison condition. Effect sizes of 0.8 were interpreted as large, while effect sizes of 0.5 as moderate, and effect sizes of 0.2 as small[31]. In the protocol we had stated that we would conduct meta-analyses on rates of remission, recovery and reliable change. However, because these outcomes were rarely (<10% of eligible trials) and inconsistently reported, we were not able to conduct these analyses.

Meta-analysis of differences in variability at post-test for app and control groups was undertaken, as it provides indication of whether intervention effects are reasonably uniform. If variability estimates for the app group are comparable to, or smaller than, those found for the control group, it is suggested that the intervention may have good generalizability potential. In contrast, greater variability for the app group suggests that effects may be limited to a subset of participants[24]. We conducted this comparison of variability estimates by deriving a log-transformed estimate of the ratio of app group variance to control group variance in post-test outcomes[24]. Alternate ways of quantifying differences in variability[24] were tested for robustness of our initial results. The significance and direction of differences in variance between groups remained the same regardless of operationalization used.

We also conducted several other sensitivity analyses to assess whether the above main outcomes were robust. We re-calculated the pooled effects when restricting the analyses to: a) lower risk of bias trials (defined as meeting 4 or 5 of the quality criteria); b) larger sample trials (defined as 75 or more randomized participants per condition); c) trials delivering an app that was explicitly designed to address depression or anxiety symptoms, or when depression or anxiety was declared as the primary outcome; d) the smallest and largest effect in each study, if multiple conditions were used (to maintain statistical independence); and e) different post-test lengths (1-4 weeks, 5-12 weeks, or 13 or more weeks). We also pooled effects while excluding outliers using the non-overlapping confidence interval (CI) approach, in which a study is defined as an outlier when the 95% CI of the effect size does not overlap with the 95% CI of the pooled effect size[32]. Small-study bias was also examined through the trim-and-fill method[33].

Between-group effect size estimates were supplemented with estimates of the number needed to treat (NNT), to convey the practical impact of the weighted mean for intervention effects. NNT indicates the number of additional participants in the intervention group who would need to be treated in order to observe one participant who shows positive symptom change relative to the control group[34].

We also calculated the weighted average dropout rate from app conditions of included trials. This was defined as the proportion of participants assigned to the app condition who did not complete the post-test assessment, divided by the total number of participants randomized to that condition. Event rates calculated through Comprehensive Meta-Analysis were converted to percentages for ease of readability.

Since we expected considerable heterogeneity among the studies, random effects models were employed for all analyses[29]. Heterogeneity was examined by calculating the I^2 statistic, which quantifies heterogeneity revealed by the Q statistic and reports how much overall variance (0-100%) is attributed to between-study variance[35]. We conducted a series of univariate subgroup analyses, examining the effects of the intervention according to major characteristics of participants, app features, and trials (see also supplementary information). Subgroup analyses were conducted under a mixed effects model[29].

Finally, recognizing that determinants of effect size may interact in complex ways that are not adequately captured through univariate subgroup analysis techniques, we evaluated interactive effects of moderators on effect estimates through meta-CART[26]. This takes a list of potential moderators and seeks to partition scores on a key outcome variable (in this case, effect sizes from each trial) according to combinations of these moderators that maximize between-group differences in the outcome whilst minimizing within-group variance. This process of partitioning continues until the set of effect sizes cannot be significantly improved through further splitting into subgroups. We used 10-fold cross-validation and random-effects modelling, given expectations of multiple sources of variability per effect size in the analysis. Past research[36] suggests that meta-CART is well powered to detect interaction among potential moderators for cases where there are at least 80 estimates in the sample – a condition met in the present review.

RESULTS

Study characteristics

Figure 1 presents a flow chart of the literature search. A total of 176 RCTs from 174 papers met full inclusion criteria (see supplementary information for the characteristics of individual studies). More than two-thirds of eligible trials (67%) were conducted between 2020 and 2023. Many trials (43%) recruited an

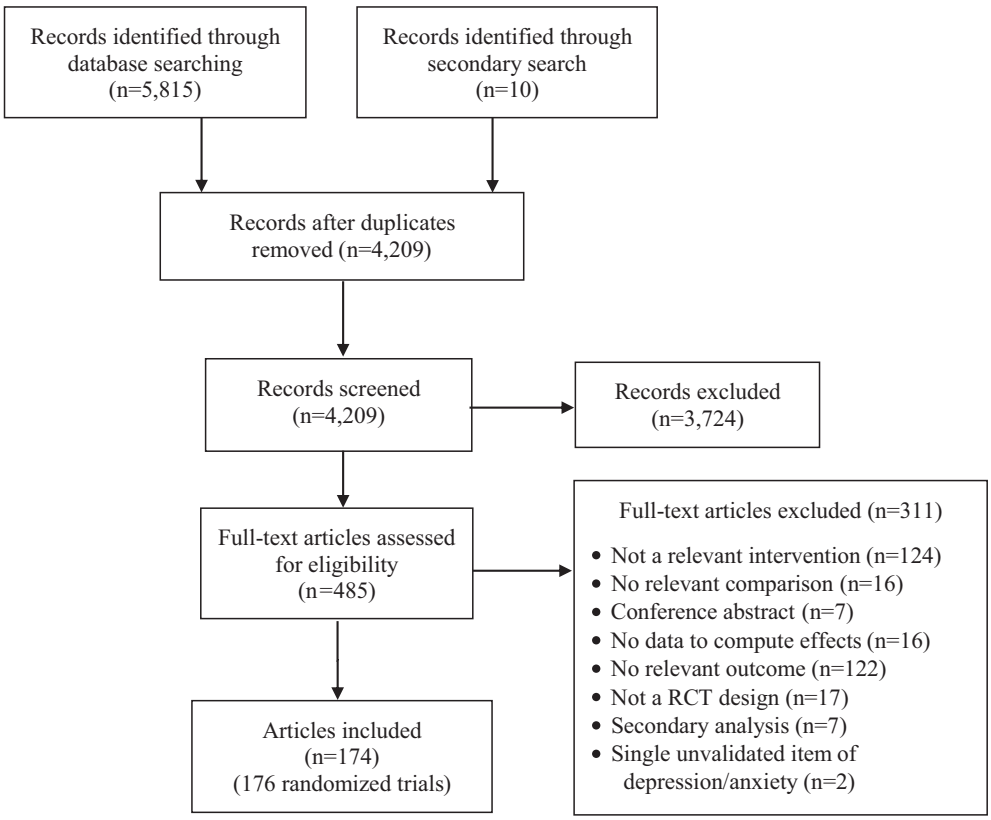

Figure 1 PRISMA flow chart. RCT – randomized controlled trial

unselected convenience sample, while a smaller number recruited people with depression or generalized anxiety, either meeting diagnostic criteria (6%) or scoring above a cut-off on a validated measure (26%). Fewer trials recruited participants with post-traumatic stress, social anxiety, obsessive-compulsive or panic symptoms (10%).

Nearly half of the apps delivered (48%) were based on cognitive behavioral therapy (CBT) principles; fewer apps were based on mindfulness (21%) or cognitive training (10%). A third of the apps (34%) had mood monitoring features, while only 5% incorporated chatbot technology. Human guidance was offered in 14% of the apps delivered.

Most trials delivered an inactive control (60%), comprised of a waitlist, assessment only, or information resources. Fewer trials (23%) delivered a placebo control (e.g., non-therapeutic app, ecological momentary assessments) that attempted to control for participant time, attention or expectations. Care as usual was delivered in 11% of trials. Only ten trials used an active psychological comparison, such as face-to-face treatment sessions or a web-based program. Most trials employed a short-term follow-up of 1-4 (56%) or 5-12 (40%) weeks.

Risk of bias also varied. All trials used a self-report measure of depression or anxiety; 70% met criteria for adequate sequence generation; 25% met criteria for adequate allocation concealment; 26% met criteria for sufficiently blinding participants to study conditions, and 62% reported use of intention-to-treat analyses. Few trials (6%) met all five criteria, 21% met four criteria, 32% met three criteria, 31% met two criteria, and 8% only met one criterion.

Effects on depressive symptoms

Apps versus control conditions

The pooled effect size for the 181 comparisons between apps (N=16,569) and control conditions (N=17,007) on symptoms of depression was g=0.28 (95% CI: 0.23-0.33, p<0.001; I^2=72%, 95% CI: 67-75), corresponding to an NNT of 11.5 (see Table 1). The pooled estimate for ratio of variance (RoV) analyses was –0.14 (95% CI: –0.24 to –0.05), indicating less variance in post-test outcome scores for the app intervention group relative to control group. However, heterogeneity was high for differences in variance (I^2=78%), suggesting variable effects of app interventions.

Sensitivity analyses supported the main findings (see Table 1). The pooled effect size was similar when restricting the analyses to lower risk of bias and larger sample trials; when adjusting for small-study bias according to the trim-and-fill procedure; when limiting to trials where depression was the primary intervention target or outcome; and at different follow-up lengths. When excluding outliers, the pooled effect size was also similar, and heterogeneity substantially decreased. Across sensitivity analyses, heterogeneity was high for differences in variance, further suggesting variable effects of app interventions (see supplementary information).

Table 1 Meta-analyses on the effects of apps on symptoms of depression and generalized anxiety

Analysis	Depressive symptoms					Generalized anxiety symptoms				
	n	g (95% CI)	p	I^2	NNT	n	g (95% CI)	p	I^2	NNT
Apps vs. control conditions	181	0.28 (0.23-0.33)	<0.001	72%	11.5	150	0.26 (0.21-0.31)	<0.001	64%	12.4
Lower risk of bias trials only	48	0.32 (0.23-0.40)	<0.001	80%	9.9	35	0.25 (0.18-0.33)	<0.001	49%	12.9
Small sample trials removed	60	0.22 (0.15-0.28)	<0.001	79%	14.9	47	0.22 (0.16-0.28)	<0.001	67%	14.9
Primary intervention target or outcome	60	0.38 (0.28-0.48)	<0.001	84%	8.1	45	0.20 (0.13-0.28)	<0.001	53%	16.5
Outliers removed	147	0.25 (0.21-0.28)	<0.001	24%	12.9	131	0.23 (0.20-0.27)	<0.001	16%	14.2
One effect per study (smallest)	145	0.27 (0.22-0.32)	<0.001	73%	11.9	121	0.25 (0.20-0.31)	<0.001	69%	12.9
One effect per study (largest)	146	0.31 (0.25-0.35)	<0.001	75%	10.2	121	0.29 (0.24-0.35)	<0.001	68%	11.0
Trim-and-fill procedure	177	0.29 (0.24-0.33)	-	75%	11.0	148	0.26 (0.21-0.31)	-	64%	12.4
Follow-up duration										
1-4 weeks	102	0.23 (0.17-0.29)	<0.001	65%	14.2	95	0.21 (0.16-0.26)	<0.001	53%	15.6
5-12 weeks	76	0.35 (0.27-0.43)	<0.001	70%	8.9	54	0.34 (0.24-0.44)	<0.001	74%	9.2
≥13 weeks	3	0.29 (–0.17 to 0.76)	0.214	87%	11.0	1	0.29 (–0.13 to 0.73)	0.180	0%	11.0
Apps vs. active comparisons	8	–0.08 (–0.25 to 0.08)	0.340	0%	-	6	0.11 (–0.24 to 0.47)	0.537	64%	31.0
Face-to-face comparator only	5	–0.12 (–0.35 to 0.09)	0.257	0%	-	5	0.16 (–0.25 to 0.59)	0.441	65%	20.9
Web-based comparator only	3	–0.01 (–0.31 to 0.29)	0.962	16%	-	1	–0.11 (–0.52 to 0.29)	0.575	0%	-

n – number of comparisons, NNT – number needed to treat

Table 2 presents the results from the univariate subgroup analyses. Effect sizes for depression were significantly larger when trials used an inactive control group (relative to placebo or care as usual), studied a pre-selected sample (relative to an unselected sample), administered a CBT app (relative to a non-CBT app), and delivered an app that contained chatbot technology (relative to no chatbot technology).

We re-computed the univariate subgroup analyses only among trials where depression was the primary intervention target or outcome (see Table 3). In these exploratory analyses, the same subgroup effects emerged, with one exception: trials that delivered a mindfulness app produced significantly lower effect sizes than those that did not deliver a mindfulness app.

Meta-CART analyses identified five key trial features (pre-selected sample, sample size, control group, psychiatric diagnosis, and delivery of a cognitive training app) that characterized subgroups with higher or lower effect estimates for mean differences than for the sample overall. The sample of effect size estimates for depression was first split by whether the sample was pre-selected. Effect estimates from samples that were not pre-selected (g=0.22, 95% CI: 0.18-0.27, n=136) could not be split into further subgroups. Effect sizes for trials involving pre-selected samples were further split into subgroups reflecting: a) larger sample trials (≥75 per condition) plus placebo control groups (g=0.06, 95% CI: –0.14 to 0.25, n=6); b) larger sample trials plus inactive control groups (g=0.54, 95% CI: 0.35-0.74, n=6); c) smaller sample trials plus samples with a psychiatric diagnosis (g=0.14, 95% CI: –0.19 to 0.47, n=4); d) smaller sample trials plus samples without a psychiatric diagnosis plus apps that were not cognitive training-focused (g=0.59, 95% CI: –0.46 to 0.72, n=26), and e) smaller sample trials plus samples without a psychiatric diagnosis plus cognitive training app (g=1.16, 95% CI: 0.73- 1.60, n=3) (see also supplementary information).

Apps versus active interventions

The pooled effect size for the eight comparisons between apps and active interventions was g=–0.08 (95% CI: –0.25 to 0.08, p=0.340). The effect size was g=–0.12 (95% CI: –0.35 to 0.09, p=0.257) when restricting the analyses to comparisons with face-to-face treatments and g=–0.01 (95% CI: –0.31 to 0.29, p=0.962) when restricting the analyses to comparisons with web-based interventions, although the number of studies in these analyses was low (see Table 1).

Effects on generalized anxiety symptoms

Apps versus control conditions

The pooled effect size for the 150 comparisons between apps (N=10,972) and control conditions (N=11,422) on symptoms of generalized anxiety was g=0.26 (95% CI: 0.21-0.31, p<0.001; I^2=64%, 95% CI: 57-69), corresponding to an NNT of 12.4 (see Table 1). The pooled RoV estimate was –0.21 (95% CI: –0.31 to –0.12), indicating less variance in post-test outcome scores for the app group relative to control group. However, heterogeneity was high for differences in variance (I^2=75%), suggesting variable efficacy of app interventions. Effects were similar across extensive sensitivity analyses reported in Table 1.

Table 2 Subgroup analyses on all available trials

Analysis	Depressive symptoms					Generalized anxiety symptoms				
	n	g (95% CI)	I^2	NNT	p	n	g (95% CI)	I^2	NNT	p
Control group					0.003					0.216
Inactive	112	0.33 (0.27-0.39)	68%	9.5		96	0.28 (0.23-0.33)	48%	11.4	
Placebo	49	0.19 (0.11-0.27)	70%	17.4		38	0.19 (0.11-0.28)	55%	17.4	
Care as usual	20	0.18 (0.07-0.27)	49%	18.4		16	0.32 (0.09-0.54)	88%	9.2	
Sample					<0.001					0.080
Pre-selected	45	0.52 (0.38-0.65)	88%	5.2		32	0.35 (0.23-0.46)	62%	8.9	
Unselected	136	0.21 (0.17-0.26)	56%	15.6		118	0.24 (0.18-0.29)	64%	13.5	
Psychiatric diagnosis					0.669					0.068
Yes	14	0.23 (0.05-0.40)	60%	14.2		10	0.41 (0.24-0.58)	35%	7.5	
No	167	0.28 (0.23-0.33)	73%	11.4		140	0.25 (0.20-0.30)	65%	12.9	
CBT app					0.003					0.147
Yes	86	0.35 (0.28-0.42)	79%	8.9		59	0.30 (0.24-0.36)	46%	10.6	
No	95	0.21 (0.15-0.27)	59%	15.6		91	0.23 (0.16-0.30)	69%	14.2	
Mindfulness app					0.549					0.258
Yes	43	0.26 (0.19-0.33)	45%	12.4		45	0.23 (0.15-0.30)	46%	14.2	
No	138	0.29 (0.23-0.34)	75%	11.0		105	0.28 (0.22-0.35)	68%	11.4	
Cognitive training app					0.238					0.370
Yes	21	0.18 (0.02-0.35)	66%	18.4		18	0.20 (0.07-0.33)	39%	16.5	
No	160	0.29 (0.24-0.34)	73%	11.0		132	0.26 (0.21-0.31)	65%	12.4	
Mood monitoring features					0.257					0.369
Yes	65	0.24 (0.19-0.30)	44%	13.5		51	0.23 (0.17-0.29)	33%	14.2	
No/Not reported	116	0.29 (0.23-0.36)	78%	11.0		99	0.27 (0.20-0.34)	71%	11.9	
Chatbot feature					0.009					0.258
Yes	12	0.53 (0.33-0.74)	61%	5.6		10	0.18 (0.06-0.31)	0%	18.4	
No/Not reported	169	0.26 (0.21-0.31)	72%	12.4		140	0.26 (0.21-0.32)	66%	12.4	
Human guidance offered					0.936					0.477
Yes	27	0.29 (0.13-0.46)	65%	11.0		18	0.37 (0.03-0.71)	88%	8.4	
No/Not reported	154	0.28 (0.23-0.32)	73%	11.4		132	0.24 (0.20-0.29)	52%	13.5	

n – number of comparisons, NNT – number needed to treat, CBT – cognitive behavioral therapy

In the univariate subgroup analyses of all available trials reporting generalized anxiety as an outcome, no significant moderation effects were found (see Table 2). However, when restricting these analyses to trials where generalized anxiety was the primary target, several univariate moderation effects emerged: trials that used an inactive control (relative to placebo or care as usual), pre-selected participants for generalized anxiety symptoms (relative to an unselected sample), administered a CBT app (relative to a non-CBT app), and delivered an app with mood monitoring features produced significantly larger effect sizes on generalized anxiety symptoms. In contrast, trials that delivered a mindfulness or cognitive training app produced significantly smaller effect sizes on generalized anxiety symptoms (see Table 3).

Meta-CART analyses identified three key moderators (pre-selection, whether generalized anxiety was the primary target/outcome, and apps with mood monitoring features) that characterized subgroups with higher or lower effect estimates of mean differences than for the sample overall. The sample of effect size estimates was first split by whether the sample was pre-selected. For samples that were pre-selected, effect estimates were further split into whether the app included mood monitoring features (g=0.54, 95% CI: 0.36-0.27, n=12) or not (g=0.26, 95% CIs: 0.13,-0.39, n=20). For samples that were not pre-selected, effect estimates were split based on whether anxiety was the primary target/outcome

Table 3 *Post-hoc* subgroup analyses on trials where depression or generalized anxiety was the primary intervention target or outcome

	Depressive symptoms					Generalized anxiety symptoms				
Analysis	**n**	**g (95% CI)**	**I^2**	**NNT**	**p**	**n**	**g (95% CI)**	**I^2**	**NNT**	**p**
Control group					0.005					0.050
Inactive	29	0.56 (0.37-0.74)	82%	5.2		25	0.30 (0.18-0.41)	47%	10.6	
Placebo	21	0.30 (0.16-0.44)	82$	10.6		15	0.12 (0.02-0.21)	32%	28.3	
Care as usual	10	0.16 (0.01-0.31)	67%	20.9		5	0.11 (–0.10 to 0.33)	72%	31.0	
Sample					<0.001					<0.001
Pre-selected	40	0.55 (0.40-0.70)	88%	5.4		24	0.34 (0.22-0.47)	61%	9.2	
Unselected	20	0.12 (0.04-0.21)	35%	28.3		21	0.09 (0.03-0.15)	0%	38.2	
Psychiatric diagnosis					0.364					0.071
Yes	4	0.18 (–0.26 to 0.63)	67%	18.4		7	0.40 (0.16-0.64)	46%	7.7	
No	56	0.40 (0.29-0.50)	85%	7.7		38	0.17 (0.09-0.24)	46%	19.6	
CBT app					0.041					0.029
Yes	40	0.46 (0.32-0.58)	87%	6.6		22	0.28 (0.18-0.38)	41%	11.4	
No	20	0.24 (0.09-0.40)	78%	13.5		23	0.12 (0.01-0.23)	52%	28.3	
Mindfulness app					0.024					0.036
Yes	9	0.21 (0.07-0.35)	31%	15.6		9	0.07 (–0.06 to 0.21)	24%	49.5	
No	51	0.42 (0.31-0.53)	85%	7.3		36	0.24 (0.15-0.33)	56%	13.5	
Cognitive training app					0.218					0.016
Yes	4	0.85 (0.07-1.63)	83%	3.3		7	0.03 (–0.10 to 0.17)	52%	117.5	
No	56	0.35 (0.26-0.45)	83%	8.9		38	0.23 (0.15-0.31)	19%	14.2	
Mood monitoring features					0.327					0.033
Yes	26	0.33 (0.21-0.45)	65%	9.5		25	0.28 (0.18-0.37)	44%	11.4	
No/Not reported	34	0.42 (0.27-0.57)	88%	7.3		20	0.12 (0.01-0.22)	52%	28.3	
Chatbot feature					0.005					0.493
Yes	5	0.80 (0.50-1.10)	47%	3.5		5	0.21 (0.13-0.29)	0%	15.6	
No/Not reported	55	0.34 (0.25-0.44)	84%	9.2		40	0.14 (–0.04 to 0.33)	56%	24.1	
Human guidance offered					0.503					0.358
Yes	8	0.52 (0.11-0.92)	80%	5.7		3	0.45 (–0.10 to 1.01)	84%	6.7	
No/Not reported	52	0.37 (0.27-0.47)	85%	8.4		42	0.19 (0.11-0.26)	47%	17.4	

n – number of comparisons, NNT – number needed to treat, CBT – cognitive behavioral therapy

(g=0.08, 95% CI: –0.05 to 0.19, n=21) or not (g=0.28, 95% CI: 0.22-0.34, n=97) (see also supplementary information).

Apps versus active interventions

The pooled effect size for the six comparisons between apps and active interventions was g=0.11 (95% CI: –0.24 to 0.47, p=0.537). The effect size was g=0.16 (95% CI: –0.25 to 0.59, p=0.441) when restricting the analyses to comparisons with face-to-face treatments, and g=–0.11 (95% CI: –0.52 to 0.29, p=0.575) when restricting the analyses to the one comparison with a web-based intervention (see Table 1).

Effects on specific anxiety symptoms

The effects of apps as compared to control conditions on specific anxiety symptoms are presented in Table 4. Subgroup analyses and analyses comparing apps to active interventions were not performed on these outcomes due to the limited number of available trials.

The pooled effect size for the 17 comparisons between apps (N=1,371) and control conditions (N=1,385) on post-traumatic

Table 4 Meta-analyses on the effects of apps on specific anxiety symptoms

Outcome	Analysis	n	g (95% CI)	p	I^2	NNT
Post-traumatic stress symptoms						
	Apps vs. control conditions	17	0.12 (0.03-0.21)	0.007	24%	28.3
	Lower risk of bias trials only	3	0.34 (0.11-0.57)	0.004	22%	9.2
	Small sample trials removed	5	0.11 (–0.04 to 0.25)	0.150	59%	31.0
	One effect per study (smallest)	15	0.13 (0.03-0.23)	0.008	29%	26.0
	One effect per study (largest)	15	0.14 (0.04-0.24)	0.005	30%	24.1
	Trim-and-fill procedure	14	0.13 (0.02-0.24)	-	-	26.0
	Post-traumatic stress primary target/outcome	12	0.12 (0.01-0.24)	0.039	44%	28.3
	Pre-selected for post-traumatic stress symptoms	10	0.14 (0.04-0.25)	0.006	29%	24.1
	CBT apps only	12	0.15 (0.02-0.29)	0.019	35%	22.4
Social anxiety symptoms						
	Apps vs. control conditions	10	0.52 (0.22-0.82)	0.001	75%	5.7
	Lower risk of bias trials only	1	0.10 (–0.16 to 0.37)	0.446	0%	34.3
	Small sample trials removed	1	0.10 (–0.16 to 0.37)	0.446	0%	34.3
	One effect per study (smallest)	9	0.53 (0.19-0.86)	0.002	77%	5.6
	One effect per study (largest)	9	0.61 (0.28-0.93)	<0.001	71%	4.8
	Trim-and-fill procedure	6	0.24 (–0.06 to 0.55)	-	-	13.5
	Social anxiety primary target/outcome	6	0.74 (0.24-1.24)	0.003	83%	3.9
	Pre-selected for social anxiety symptoms	5	0.75 (0.16-1.32)	0.011	86%	3.8
	CBT apps only	4	0.73 (0.01-1.45)	0.044	82%	3.9
Obsessive-compulsive symptoms						
	Apps vs. control conditions	5	0.51 (0.18-0.84)	0.002	42%	5.8
Panic symptoms						
	Apps vs. control conditions	2	–0.12 (–0.50 to 0.25)	0.515	0%	-
Acrophobia symptoms						
	Apps vs. control conditions	2	0.90 (0.38-1.42)	0.001	0%	3.0

n – number of comparisons, NNT – number needed to treat, CBT – cognitive behavioral therapy

stress symptoms was g=0.12 (95% CI: 0.03-0.21, p=0.007), corresponding to an NNT of 28.3. Heterogeneity was low (I^2=24%). Significant small effects were observed in all sensitivity analyses, except when smaller sample trials were removed.

The pooled effect size for the ten comparisons between apps (N=576) and control conditions (N=447) on social anxiety symptoms was g=0.52 (95% CI: 0.22-0.82, p=0.001), corresponding to an NNT of 5.7. Heterogeneity was high (I^2=75%). Effects remained stable and similar in magnitude when restricting the analyses to trials that pre-selected participants for social anxiety symptoms, delivered a CBT app, and where social anxiety was the primary target or outcome. Non-significant effects were observed when restricting the analyses to trials with a lower risk of bias rating and a larger sample. However, only one trial was rated as low risk and having a larger sample[37].

Significant pooled effect sizes were observed for the five comparisons between apps and control conditions on obsessive-compulsive symptoms (g=0.51, 95% CI: 0.18-0.84, p=0.002; NNT=5.8) and for the two comparisons on acrophobia symptoms (g=0.90, 95% CI: 0.38-1.42, p=0.001; NNT=3.0). A non-significant negative effect size was observed for the two comparisons between apps and control conditions on panic symptoms (g=–0.12, 95% CI: –0.50 to 0.25, p=0.515) (see Table 4).

Dropout rates

From 182 conditions with available data, the weighted dropout rate was estimated to be 23.6% (95% CI: 21.3-26.1, I^2=93%). When removing small sample studies, the dropout rate was 29.9% (95% CI: 26.0-34.0, I^2=96%) from 67 conditions. When restricting the analyses to lower risk of bias studies, the dropout rate was 26.6% (95% CI: 22.7-31.0, I^2=94%) from 50 conditions. For samples of participants with depression, the dropout rate was 28.7% (95% CI: 23.6-34.3, I^2=93%) from 42 conditions. For samples of participants with anxiety, the dropout rate was 25.4% (95% CI: 20.6-31.0,

I^2=92%) from 39 conditions. For CBT apps, the dropout rate was 23.3% (95% CI: 19.8-27.2, I^2=94%) from 89 conditions.

DISCUSSION

Interest in mental health apps as a scalable tool to treat symptoms of depression and anxiety continues to grow. Since the last comprehensive meta-analysis published in 2019[13], more than 100 RCTs have been conducted. To ensure that clinicians, policymakers and the public have access to the latest information on the evidence base of these apps, we conducted an updated meta-analysis of 176 research trials. A particular focus was on identifying features that may account for the evident and considerable heterogeneity in efficacy from study to study. This is the first meta-analysis of mental health apps to undertake a thorough analysis of how combinations of putative factors may interact, in order to provide new insights into the circumstances and subgroups of individuals for which certain app features may confer greatest effects.

Overall, results showed that mental health apps have overall small but significant effects on symptoms of depression (N= 33,576, g=0.28) and generalized anxiety (N=22,394, g=0.26), corresponding to an NNT of 11.5 and 12.4, respectively. Heterogeneity was high in main analyses, but substantially lower when removing outliers. Effects were robust across extensive sensitivity analyses, and were similar in magnitude at different follow-up lengths and after removing small sample and higher risk of bias trials. Larger effects were found for depression when it was the primary target of the app (g=0.38), while this was not the case for generalized anxiety (g=0.20). Attrition was apparent, with one in four participants prematurely dropping out of their allocated app program. Small non-significant effects for depression and generalized anxiety were observed when evaluating apps against web and face-to-face interventions, though the number of studies was low and confidence intervals wide.

There was less variability in outcome scores at post-test in app compared to control conditions (RoV=–0.14 for depressive symptoms and RoV=–0.21 for generalized anxiety symptoms). However, heterogeneity was high for differences in variance (I^2=78% for depressive symptoms and I^2=75% for generalized anxiety symptoms), suggesting variable efficacy of app interventions.

The expanding literature now enables us to assess the effects of mental health apps on specific symptoms of anxiety, and highlights the potential of more specialized approaches. Our previous meta-analytic estimates of apps on symptoms of social anxiety, panic and post-traumatic stress were only based on three to six comparisons, finding limited evidence of efficacy[13]. Now the literature has evolved, with the number of trials targeting certain symptoms more than tripling (e.g., post-traumatic stress), while newer trials have emerged that enable calculation of preliminary pooled effects for other symptoms (e.g., obsessive-compulsive symptoms, acrophobia). We found evidence of moderate effects of apps on social anxiety (n=10, g=0.52) and obsessive-compulsive (n=5, g=0.51) symptoms, a small effect on post-traumatic stress symptoms (n=17, g=0.12), a large effect on acrophobia symptoms (n=2, g=0.90), and a non-significant negative effect on panic symptoms (n=2, g=–0.12). However, these results should be considered with caution, because most trials contributing to these analyses had considerable risk of bias and were based on small sample sizes.

Our results also highlight how advances in trial methodology will aid in better assessing the efficacy of extant apps and the design of new ones. At the univariate level, the type of control condition emerged as a moderator, with inactive controls generating larger effects on depression and generalized anxiety (identified as primary target) than placebo controls or care as usual. This is a well-replicated finding observed across all modes of psychological treatment[38-41], and provides confirmation that some of the benefits of apps are explained by the "digital placebo" effect[42]. Now that this placebo effect has been well established, an imperative arises to ensure that its real-world implications are realized by both the clinicians who assess the efficacy or "prescribe" certain apps and the regulators who certify their claims. Furthermore, effects were larger among pre-selected samples of participants with threshold-level symptoms of depression and generalized anxiety (identified as primary target). This finding aligns with prior meta-analytic evidence that higher baseline severity is associated with better outcomes of digital interventions[43,44], suggesting that people with moderate to severe depression or anxiety at baseline benefit more from care augmented by these apps[45].

Features of the app were also associated with effect sizes at the univariate level. Apps that were based on CBT produced larger effects than other apps, such as those based on mindfulness. This finding is not surprising, given that the evidence base for all forms of CBT in depression and anxiety is substantially larger than for other approaches[46]. Perhaps a better insight towards the "active ingredients" of CBT for these conditions (compared to other approaches) has facilitated the development of apps that prioritize these effective components over other less effective or potentially harmful ones.

Furthermore, we found some evidence that effects were larger when apps specifically designed for depression incorporated chatbot technology, and when apps specifically designed for anxiety incorporated mood monitoring features. It is possible that these innovative technological features offer a greater degree of personalization, are more engaging, foster emotional self-awareness, and keep users more accountable for making progress[47,48], potentially resulting in greater benefit. However, these results were derived from *post-hoc* analyses and should be considered with caution, because the number of studies in these subgroups was relatively small. Randomized experiments that test the added effects of chatbot and mood monitoring technology as both mechanisms of action and drivers of engagement are needed.

At a multivariate level, combinations of proposed moderator variables helped to better identify subgroups where apps were more or less efficacious. For depression, studies with higher efficacy estimates tended to be characterized by pre-selected samples of smaller size and without a formal psychiatric diagnosis. Cognitive training apps had higher efficacy for depression when paired with

these trial features (g=1.16), but we emphasize the need for caution in interpreting this effect, given the paucity of studies in this grouping (n=3). For generalized anxiety, apps with mood monitoring were particularly efficacious for studies with pre-selected samples, while the positive benefits of this monitoring did not emerge for more universal samples.

There are some limitations to this meta-analysis that should be considered. First, analyses were restricted to the post-intervention period, because of inconsistent reporting and length of follow-up assessments, and variability in how dropouts were dealt with. Thus, whether the benefits of apps observed in the short term extend over longer periods remains an open question. Second, analyses could only be conducted on symptom change and not on other, clinically meaningful outcomes such as remission, recovery, or deterioration [49]. Despite a sufficient number of trials sampling individuals with depression or anxiety, very few reported these outcomes at all or, if they did, they defined them inconsistently. Third, heterogeneity was high in many of the main analyses. Even though we tried to explain this through subgroup analyses, we were not able to explain all of it, and many of the subgroups still had high heterogeneity. However, it is perhaps inevitable that some heterogeneity will always persist when aggregating data from trials of essentially different apps – regardless of how well the individual components and trial characteristics are categorized.

In conclusion, we present the most comprehensive meta-analysis of the effects of mental health apps on symptoms of depression and anxiety, including 176 trials. We conclude that apps have overall small but significant effects on symptoms of depression and generalized anxiety. Larger effects are observed in trials in which depression is the primary intervention target or outcome, suggesting that apps could be a suitable first step in treatment for those receptive to this approach or those who cannot access traditional forms of care. Certain features of apps, such as mood monitoring and chatbot technology, were associated with larger effect sizes, although this needs to be confirmed in future experimental research. Evidence supporting the efficacy of apps for specific anxiety symptoms is uncertain, largely due to trials with considerable risk of bias and small sample sizes. As responsiveness to mental health apps varies, future research would benefit from collecting and pooling large datasets (with passive and self-reported data) to generate predictive models capable of accurately detecting those for whom an app is sufficient from those who require different forms of treatment.

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Sleep and circadian rhythm disturbances: plausible pathways to major mental disorders?

The Mental Health Priority Area of the Wellcome Trust recently posited that sleep and circadian rhythm disturbances (SCRDs) are a plausible nexus for linking aspects of the biology, phenomenology, course and treatment of major mood, anxiety and psychotic disorders[1]. This emphasis fits well with the currently spreading trend to develop more effective and scalable forms of indicated prevention, early intervention, and secondary prevention (of both primary illness progression and physical illness).

This focus on SCRDs also aligns with broader studies as to why some specific periods of life (e.g., adolescence, postnatal, menopause, late life), accompanied by large shifts in the 24-hour patterns of the sleep-wake cycle, are also associated with elevated risk of major mood disorders[2]. Along the same line, several research groups have now prioritized understanding of chronobiology to advance the management of all phases of major mood disorders (e.g., the Chronobiology Task Force of the International Society for Bipolar Disorders)[3].

Developments in this area have been greatly assisted by increased understanding of the basic biology of the homeostatic circadian system – recognized by the Nobel Prize in Medicine or Physiology in 2017. Of note has been the delineation of the molecular architecture of the core circadian clock, along with the revelation that the circadian system's stability is fundamentally regulated by common environmental factors, such as the timing, intensity and spectrum of light exposure[4]. It appears that there are specific brain circuits in mammals by which light regulates mood, learning and activity, which are not wholly dependent on mediation by the master circadian timekeeper (the suprachiasmatic nucleus), including a recently identified region in the perihabenular nucleus.

The discovery of new light-sensitive brain circuits is of extreme interest to clinical psychiatry and psychiatric epidemiology. An intriguing finding from over 80,000 adults in the UK Biobank was that more exposure to artificial light at night was associated not only with increased rates of major depression, but also with an increased incidence of several other mental disorders, including bipolar disorder, generalized anxiety disorder and post-traumatic stress disorder, as well as with higher rates of self-harm behavior and psychosis-like experiences[4]. As predicted on the basis of the evidence that day-time light exposure is the primary synchronizer of the circadian clock in mammals, as well as the success of bright light therapy in the treatment of mood disorders, more light exposure during the day was also associated with lower rates of mental disorders[4]. Triangulation of evidence from animal models, experimental studies in humans, and epidemiology has provided strong evidence for a major role of daily light exposure to good mental health.

A focus on a possible causative role of SCRDs in the etiology and pathophysiology of at least some major mood disorders may surprise those who think of these disturbances as epiphenomena that accompany most mental disorders. However, recent discoveries regarding the regulation of many physiologic and behavioral parameters by the circadian system[2,3], alongside major developments in longitudinal psychiatric epidemiology[5], have challenged that assumption. Indeed, it is now strongly established by studies across clinical, laboratory and field-based settings that mood disorders such as bipolar disorder are related to SCRD-relevant features, including stable trait-like profiles of delayed sleep phase, long sleep time, and preference for eveningness[2,3]; delayed melatonin and core body temperature rhythms; and abnormal time relationships between circadian phase markers and the 24-hour sleep-wake cycle[6].

Accumulating evidence suggests that circadian dysregulation is likely to be cross-diagnostic rather than disorder-specific[3], and to be especially related to key mood (e.g., affective instability), behavioral (e.g., impulsivity), cognitive (e.g., disinhibition), and immune-metabolic (e.g., insulin resistance, raised C-reactive protein blood levels) phenotypes[2].

Empirical advances regarding the predictive significance of prior SCRDs for the first major episode have been most evident in the mood disorders domain. SCRD-related factors such as preference for eveningness and dysregulation of social rhythms are observed in at-risk groups (e.g., offspring of a parent with bipolar disorder) as well as in youth with early bipolar disorder, and meta-analytic evidence from prospective studies suggests that a pre-existing SCRD is associated with a 40% higher risk of onset of bipolar disorder[7]. A study of over 2,000 adolescents and young adults seeking help from early-intervention clinics found that prior circadian disturbance predicted the transition from an earlier to a later clinical stage of major mood, anxiety or psychotic disorders[8].

Studies focusing on intensive longitudinal measurement of within- and between-day dynamics of mood, sleep and motor activity in adults with mood disorders – which appear to be more dysregulated and cross-reactive than those of control populations – have highlighted the need to investigate biological interfaces linking these systems, of which the homeostatic circadian system is one plausible candidate[3].

The circadian system appears to be a potentially important target for more personalized treatment of at least a major subgroup of those with mood disorders. The discovery that treatments such as selective serotonin reuptake inhibitors (SSRIs) may increase sensitivity to light, and thereby destabilize the circadian system in at-risk individuals, is a major concern[9]. This finding requires urgent replication and extension to an examination of the possible positive or negative impacts of exposures to other common interventions, such as behavioral activation, sleep restriction, mood stabilizers, antipsychotic agents, and other antidepressants. Some new agents (e.g., orexin antagonists, melatonin-based antidepressants) and older pharmacotherapies (e.g., lithium) do appear to enhance

the stabilization of these systems in several animal models as well as in small studies of patients with mood disorders[3]. Further testing of the circadian effects of such medications, and the potential for treatment-relevant subtyping, is highly warranted[2,9].

There are major hurdles to the wider application of these new insights. Accurate, real-time, and repeated detection of the true timing of the internal circadian clock, and its alignment with the external light-dark cycle, remains a major goal. Current measures are largely limited to either intensive, expensive, in-lab methods, or indirect inferences from wearable recordings of the 24-hour patterns of motor activity and sleep. Hence, a clear research focus is the development of novel methods based on 24-hour patterns of gene expression, metabolic activity, and peripheral blood or urinary markers. More sophisticated modelling techniques, based on tracking symptom clusters and objective markers earlier in the course of illness, and then longitudinally, are also required to unpick the direction of causation between these phenomena.

Increased and coordinated global investment in this research area is timely, and may well lead to genuine new therapeutic insights.

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Sex differences need to be considered when treating women with psychotropic drugs

In a period in which they keep on struggling for equal chances in several fields, women still need to strive for a medical treatment which takes sex differences into account. Medical practice has long been implicitly led by the notion that only reproductive organs differ between the sexes. Yet, significant sex differences have been clearly documented in blood, immune system, liver, kidneys, stomach, gut, heart and brain[1]. Such differences can impact pharmacokinetic and pharmacodynamic mechanisms[2].

For example, women have a less acidic stomach[3], which increases the absorption of weak acids but decreases that of weak bases. Gastric and colonic emptying is slower, lending pharmaceuticals more time to be absorbed. The levels of protein-transporter p-glycoprotein are two-fold lower in women of fertile age than in men: as this transporter pumps substances out of the cell, a lower activity increases absorption in the body and the brain, while decreasing renal excretion[3]. Blood volume and blood protein fraction are lower in women, decreasing dilution and binding capacity compared to men. Women, on average, have more fat tissue, which can lead to stacking of lipophilic pharmaceuticals. In gut and liver, many cytochrome P450 (CYP) enzymes are influenced by estrogens, which can lead to higher (for CYP3A4, and to a lesser degree for CYP2D6) or lower (for CYP1A2 and CYP2C19) metabolic activity in women of reproductive age. Renal blood flow, glomerular filtration, tubular secretion and resorption are all lower in women. These sex differences are not only numerous; they are also sizable – a 10-50% sex difference per mechanism – and can significantly affect the efficacy and tolerability of pharmacotherapy.

In 1977, the US Food and Drug Administration (FDA) recommended that women of childbearing age should be excluded from phase 1 and early phase 2 clinical trials. This directive, intended to protect women, did quite the opposite: it halted the understanding of pharmacotherapy in the female body and widened the knowledge gap in women's health. In 1993, the US National Institutes of Health policy made the inclusion of women and minorities in trials mandatory, but drugs already registered at that time were never retested in large female study populations. At present, only a handful of drugs (such as alosetron, desmopressin and zolpidem) have different dosing recommendations for women, while there are over 100 commonly prescribed drugs with unequal pharmacokinetics between men and women[2]. This suggests that women are at high risk for both over- and under-dosing of many drugs across medical specialties.

For psychotropic drugs, sex differences in pharmacodynamics further contribute to inequalities in efficacy and tolerability. Dopamine release regulation and synaptic elimination are influenced by sex hormones and differ significantly between men and women[4]. Although less well studied, such sex differences in neurotransmitter trafficking are also described in the serotonergic, GABAergic and glutamatergic circuitry[5].

Many of the above mechanisms – such as increased or reduced activity of CYP enzymes or p-glycoprotein, gastric acid production, gastric and colonic emptying, and dopaminergic and serotonergic trafficking – are estrogen-dependent[3,5]. This means that changes in pharmacokinetics and pharmacodynamics occur over the phases of the menstrual cycle, affecting the efficacy and tolerability of psychotropic drugs. Robust changes in efficacy and safety occur when hormonal changes are large, such as during pregnan-

cy and menopause. With menopause, pharmacokinetic and pharmacodynamic mechanisms may both reduce the bioavailability of drugs, inducing a dramatic reduction in their efficacy. We recently demonstrated a massive increase in rehospitalization after menopause in women with schizophrenia spectrum disorders using commonly prescribed antipsychotics[6].

Olanzapine is absorbed more readily from the gastrointestinal tract in women, whereas renal clearance is lower. As this antipsychotic is predominantly metabolized by CYP1A2, which is inhibited by estrogens, blood levels may be about two-fold higher in pre-menopausal women than in men with equal dosing[7]. In addition, the pre-menopausal female brain is more sensitive to olanzapine treatment, with women achieving similar receptor occupancy rates at a 50% lower dose than men[3]. After menopause, gastric acidity and emptying equals that of men, and CYP1A2 is no longer inhibited by estrogens, so that the blood levels of the drug decrease. At the same time, declining estrogen levels reduce the sensitivity of the brain to olanzapine[3], which leads to much lower receptor occupancy and efficacy in post-menopausal women.

Quetiapine is mainly metabolized by CYP3A4, whose activity is induced by estrogens, while excretion in women is lower than in men. In pre-menopausal women, these mechanisms work in opposite directions, leading to approximately similar blood levels in men and women with the same dose of the drug[7]. After menopause, quetiapine metabolism slows down and blood levels rise, which may cause a rapid increase in side effects[7].

Imipramine is absorbed better in women than in men. Its main metabolizing enzyme, CYP2C19, is inhibited by estrogens and, with equal dosing, blood levels in women may be much higher. In practice, toxic serum levels are often corrected, as therapeutic drug monitoring is the standard of care for imipramine. After menopause, CYP2C19 inhibition stops and, with the same dose, bioavailability of imipramine decreases significantly, increasing the risk for relapse of depression.

Fluoxetine is transported by p-glycoproteins and metabolized by several CYP enzymes, including CYP2C19. In pre-menopausal women, serum levels are much higher than in men receiving the same dose. As therapeutic drug monitoring is not the standard for this medication, many young female patients are expected to be overdosed.

Zolpidem yields an about 30% higher exposure in women, especially after menopause[8]. The risk of morning drowsiness prompted the FDA to request sex-specific dose recommendations. The manufacturers now recommend prescribing half the male dose for women, without taking menopausal status into account[8].

Simply treating women with half the male dose of a psychotropic drug, as the manufacturers of zolpidem recommend, is not sufficient, as sex differences can be hormone-dependent and drug-specific. In order to provide women with a dose that fits their body and hormonal status, each psychotropic drug would need to be examined for its sex- and hormone-specific pharmacokinetic and pharmacodynamic mechanisms. Detailed knowledge of sex-specific dosing for all psychotropic drugs should be expanded rapidly, to stop over- and under-treatment of female patients, which now occurs for many of these drugs[2].

Female patients are a heterogeneous group. As many mechanisms are estrogen-dependent, hormonal status – especially during pregnancy and menopause – needs to be considered. We currently cannot oversee all sex- and hormone-dependent pharmacokinetic and pharmacodynamic mechanisms for each psychotropic drug, as this is a quite complicated matter. Therefore, therapeutic drug monitoring – when available – is recommended for female patients, especially during pregnancy and menopausal transition.

There are factors – such as age, body mass index, percentage of fat tissue, and genetic polymorphism of CYP enzymes – whose importance in determining the correct dosage of psychotropic drugs is widely acknowledged. However, sex and hormonal status also have a large impact on the efficacy and tolerability of many psychotropic drugs. It is now time to take them into account.

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The need to focus on perfectionism in suicide assessment, treatment and prevention

Perfectionists are people who not only want to be perfect; they also need to seem perfect. Several decades of global research on perfectionism have identified a host of worrisome realities. First, meta-analytic evidence indicates that perfectionism is on the rise among young people[1]. Second, perfectionism is associated with mental health problems, but also with physical health issues and early mortality[2]. Third, perfectionism is associated with heightened risk for suicide[3], as illustrated by the results of a comprehen-

sive meta-analysis[3].

The perfectionistic person who is experiencing psychological pain is at a heightened suicide risk due to a confluence of correlated attributes and tendencies[4]. These include a proclivity to hide psychache behind a perfect front while also experiencing elevated hopelessness[5]; a tendency to all-or-none views and cognitive rumination; an unwillingness or inability to seek help; and a degree of planfulness that can turn suicidal urges and plans into completed suicides. Here the voracious information seeking of perfectionists may extend to accessing information on the Internet that enables them to perfect their suicide plans. The risk is especially high for the perfectionist who has attempted suicide and remains suicidal while grappling with the humiliation of having engaged in a failed attempt.

The role of perfectionism in suicide is to some extent in the public consciousness. We are all aware of the deaths of highly perfectionistic luminaries such as V. Woolf, S. Plath and E. Hemingway. Public awareness was heightened further when S. Blatt published his seminal paper on the destructiveness of perfectionism, detailing the lives and demises of three well-known highly self-critical perfectionists[6]. We can add the recent attention given to the suicides of famous people such as director T. Scott in 2012 and fashion designer L'Wren Scott in 2014, as well as highly publicized public inquests investigating the suicides of perfectionists such as N. Worrall and C. Dragun. Unfortunately, clinical case examples of deceased perfectionists continue to mount, including the deaths of people such as K. Spade, M. Evans and L. Breen (the emergency room physician who died as stressors mounted during the COVID-19 pandemic). Sadly, there is also no shortage of deaths due to suicide among perfectionistic adolescents[7].

Constant additions to the above list are disconcerting, but just as troubling is the lack of evidence that research knowledge and public awareness of the role of perfectionism in suicide are being reflected in practice. Our informal survey of key organizations which provide lists of acknowledged suicide risk factors (e.g., the US Centers for Disease Control and Prevention) found little mention of the role of personality factors in general, and perfectionism in particular. More progress is needed immediately, because it is not hyperbole to state that many lives are in the balance. Education, training and heightened awareness are urgently needed.

Accordingly, we are issuing a call for a stronger proactive and comprehensive focus on perfectionism and its various elements in terms of their likely roles in suicide and suicidal tendencies. Perfectionism and its various facets merit extensive consideration and action when it comes to assessment, treatment and prevention of suicidal behavior.

It should be seen as a warning sign when someone known to be in psychological pain is also a perfectionist. Similarly, when a perfectionist with stressful experiences that should elicit psychological pain seems to be functioning exceptionally well on the surface, this too is a warning sign. In many of these instances, probing for suicide ideation and intent can be appropriate, along with an assessment of perfectionism using measures that have been linked empirically with elevated suicide ideation and risk. In adults, these include the Hewitt-Flett Multidimensional Perfectionism Scale, the Frost Multidimensional Perfectionism Scale (FMPS), and the Perfectionistic Self-Presentation Scale (PSPS), which have extensive evidence of reliability and validity. In younger people, dimensions of perfectionism can be assessed with the Child-Adolescent Perfectionism Scale and the junior version of the PSPS[7]. Also, the perfectionistic person with a recent suicide attempt should be closely monitored and frequently evaluated. Close evaluation is especially needed of the perfectionistic person brought to an emergency department due to being suicidal, but whose symptoms almost magically seem to disappear at the hospital.

All of the above applies to perfectionists from all backgrounds, but especially to people prone to burnout in exceptionally demanding jobs (e.g., doctors, lawyers). In general, people in roles that can provide experience in concealing symptoms behind a front should be closely scrutinized, in line with our conclusion that perfectionists are over-represented among people who commit a suicide that seems to take place without warning. The association between perfectionism and suicide needs to be examined from a perspective that involves careful consideration of life stressors and transitions. For instance, the work-obsessed perfectionist who is disquieted by and feels forced into retirement may also have heightened risk.

Our frustration about the lack of implementing knowledge and putting it into action is balanced by a modicum of hope. What accounts for this hope? First, by and large, perfectionism researchers are dedicated to making the world a better place, and this includes a commitment to sharing vital information with the public, including this topic. Second, there is mounting empirical evidence of the effectiveness of nuanced treatments addressing the complexities inherent in the perfectionism construct. A recent meta-analysis of 15 randomized control trials concluded that cognitive-behavioral therapy focusing on perfectionism is efficacious in reducing depression, anxiety and eating disorder symptoms[8]. However, a dynamic interpersonal approach to treatment may be preferred, especially for perfectionists who feel under pressure to meet extreme expectations imposed on them by others (i.e., socially prescribed perfectionism) and those with an excessive need to seem perfect that has been hidden behind a perfect front (i.e., perfectionistic self-presentation)[9].

A strong case can be made for prevention, given that many perfectionists experiencing psychological pain tend to suffer in silence and never come into contact with potential treatment providers[7]. Specific themes that need to be highlighted in preventive efforts include promoting self-compassion to combat self-criticism; seeing oneself as learning and growing rather than fixed and defective; limiting excessive self-reliance; training in problem-solving and cognitive restructuring; and role-playing responses to mistakes and failures.

Prevention efforts should be broad and designed to heighten awareness among not only mental health professionals, but also parents and educators. Efforts should also include a targeted focus on people in roles, or training for roles, in which the pressure to be perfect and never make mistakes can seem unbearable (e.g.,

elite athletes, medical personnel, lawyers, architects). Prevention is also needed to counter the impact of settings that promote unrealistic and unrelenting pressure to be perfect (e.g., schools and communities where high achievement is prescribed and seems normative).

Treatment and prevention offer hope and promise for perfectionists in general, including people experiencing suicidal tendencies that may or may not be openly expressed.

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Can a practical process-oriented strategy prevent suicidal ideation and behavior?

For several decades, research-based efforts have sought broadly applicable suicide prevention methods. A recent umbrella review of meta-analyses or systematic reviews of primary prevention found some limited evidence for multicomponent programs tailored for specific populations, and the possible value of restricting access to lethal means such as guns or pesticides, but concluded that there is "insufficient evidence to recommend a widespread implementation of suicide primary prevention in the general population"[1].

Such slow progress is paradoxical, given that reduction in suicidal ideation and behavior can be obtained from specific evidence-based psychotherapy methods for psychiatric disorders commonly associated with suicide. New research strategies for possible prevention approaches appear to be needed. A practical process-oriented strategy might provide a possible pathway forward, deploying methods that meet a wide range of other specific needs while altering processes of change that are known to link to suicidal ideation and behavior. The literature on acceptance and commitment therapy (or "acceptance and commitment training" outside of psychotherapy; "ACT" in either case) provides an example.

With nearly 1,050 randomized controlled trials spread across virtually every area of mental and behavioral health, performance, and social wellness[2], ACT is one of the most widely studied evidence-based psychological interventions. It is a transdiagnostic approach from within the behavioral and cognitive therapy tradition that uses acceptance, mindfulness, commitment, and behavior change methods to increase psychological flexibility[3].

Psychological flexibility is an integrated collection of six key processes of change that involve emotional openness, cognitive flexibility, flexible attention to the now, a perspective-taking sense of self, chosen values, and committed values-based action. The first four of these are taken to represent mindfulness processes within the ACT model, and it is argued that all six support each other interactively. Psychological inflexibility, conversely, involves experiential avoidance and emotional clinging; cognitive fusion and entanglement; worrying, rumination or other attentional problems; defensive attachment to a conceptualized self; absence of values clarity; and behavioral impulsivity, procrastination, or avoidant persistence[3]. Psychological flexibility/inflexibility and its components, in combination with closely allied processes such as self-compassion or behavioral activation, account for over half of all significant mediational findings on processes of change yielding improvements in mental health outcomes in randomized controlled trials of psychosocial interventions of all kinds[4].

In areas such as depression, there are randomized trials documenting both the direct effects of ACT on suicidal ideation and behavior, and the link between changes in psychological flexibility/inflexibility and these outcomes[5]. Those findings, however, do not assess whether suicidal ideation and behavior can be prevented using ACT.

Data on ACT processes of change are suggestive. Cross-sectional and longitudinal studies have found that psychological flexibility/inflexibility directly predicts suicidal ideation and behavior, controlling for relevant predictors such as distress and baseline levels of suicidality[6]. All six processes seem relevant to this issue. For example, greater cognitive flexibility and defusion skills might help reduce self-amplifying entanglement with suicidal thoughts; greater acceptance and emotional openness skills might help individuals feel and learn from losses and betrayals without suicide as an attractive avoidance strategy, using instead past pains to motivate healthy values-based behavior. As is predicted by the model, these effects appear empirically to be combinatorial. For example, psychological distress, cognitive fusion, and absence of values-based behavior have the strongest association with suicidal ideation among those individuals who are high in psychological inflexibility more generally[6].

This same basic pattern had been shown in response to significant life stressors such as physical disease, relationship break-ups, and enacted stigma. For instance, during the height of the COVID-19 outbreak, pandemic-related stressors such as resource strain and the death of loved ones led to an increased desire for death among individuals who perceived themselves to be a burden to others due to their struggles, but only for those with high levels of psychological inflexibility[7].

The extensive mediational data on psychological flexibility prove that it can be taught by ACT and some other intervention methods[4], but the weak data on universal prevention suggest that relevant preventive skills will be better learned and retained when doing so is personally and practically relevant. Because ACT is such a broadly applicable approach, however, a targeted process-oriented prevention strategy can be pursued by developing psychological flexibility in the context of spiritual care, routine medical care, self-help, or social wellness programs. Much as vectors are used in gene therapy to insert needed genes into cells, these programs can be thought of as psychiatric vectors for healthy change processes that might later deflect suicidality, if it emerges in the individual. Importantly, given the extreme level of mental health provider shortages, ACT can be successfully deployed for a wide variety of behavioral health and social wellness problems by non-mental health professionals.

A good example of this approach is the decision by the US military chaplains to establish a training program in three specific forms of psychosocial intervention thought to be especially easy to integrate with spiritual care: motivational interviewing, problem-solving therapy, and ACT. Training chaplains in such evidence-based methods makes practical sense, since military personnel often avoid psychiatric care because of its possible career-impacting consequences, but can freely access spiritual care without such difficulties. Chaplains who completed training in these methods both used them and found them helpful as part of spiritual care when military personnel were struggling with suicidality. ACT methods were particularly popular, being used 14 to 56% more frequently as compared to the other methods with recipients of care who were either at risk for suicide, or were acutely suicidal[8].

In another example, there is a large body of work on adding ACT methods to routine medical care, often by general medical personnel, for such problems as post-surgical care, advanced cancer, diabetes, chronic pain, traumatic brain injury, spinal code injuries, multiple sclerosis, stroke, and Parkinson's disease. Generally, these methods produce positive changes in psychological flexibility/inflexibility while impacting health outcomes and psychological distress. Importantly, as psychological flexibility/inflexibility processes change, so too does suicidal ideation, such as in a recent study with ACT for treatment adherence and psychological distress in patients with multi-drug resistant tuberculosis[9].

Still other "vectors" seem available. ACT self-help has ballooned, with hundreds of titles and millions of copies in print addressing a myriad of problems in all major languages – but always targeting the same small set of psychological flexibility/inflexibility processes. Indeed, the World Health Organization now deploys ACT self-help for free worldwide in more than 20 different languages, because well-crafted studies showed that it both treated and prevented mental and behavioral health problems for victims of war, stating that their program is "for anyone who experiences stress, wherever they live and whatever their circumstances" (https://www.who.int/publications/i/item/9789240003927). Sport, business and diversity programs provide other possible vectors with a growing body of data.

There is no available turnkey solution to suicide prevention, but the degree of social and clinical need demands that new strategies be explored. A practical process-oriented approach seems worth testing. Using ACT and other interventions targeting a wider range of practical processes that also modify psychological flexibility/inflexibility should be tested as a possible psychiatric vector for building resilience against entanglement with suicidal ideation and behavior.

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Cumulative remission rate after sequential treatments in depression: reappraisal of the STAR*D trial data

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) was a seminal clinical trial of 4,041 outpatients with major depressive disorder (MDD), examining the effectiveness of sequential treatment steps[1]. One of the key findings of the study was that the theoretical cumulative remission rate up to four treatment steps was 67% among those who initiated antidepressant treatment[1].

Although this finding has had a significant impact on clinical research and policy-making[2], this estimated rate is subject to two significant limitations. First, the estimate assumes that there were no dropouts during the study (and those who exited the study would have had the same remission rates as those who stayed in the protocol)[1]. In fact, only 995 subjects (24.6%) had complete data; 2,487 (61.5%) had dropout missing data patterns; and 559 (13.8%) had non-dropout intermittent missingness even within 12 weeks in Step 1 treatment[3]. Second, our recent re-analysis of the individual patient-level data from the trial revealed that 1,108 subjects (27.4%) had taken at least one antidepressant medication during the index episode prior to study entry. Given that those who required more treatment steps were less likely to achieve subsequent remission[1], the cumulative remission rates likely differ between the drug-naïve and previously treated subjects.

We therefore estimated the cumulative remission rate of the STAR*D trial by utilizing the inverse probability of censoring weighted (IPCW) Kaplan-Meier method. Furthermore, we investigated the cumulative remission rates among individuals with and without prior antidepressant treatment history during the ongoing episode.

We extracted sociodemographic factors at baseline, and the scores on the 16-item Quick Inventory of Depressive Symptomatology, self-report (QIDS-SR_{16}) and the Global Rating of Side Effect Burden (GRSEB) at weeks 0, 2, 4, 6, 9, 12 and 14 in Step 1-4 treatments from the STAR*D dataset. Remission was defined as a score ≤5 on the QIDS-SR_{16} at any time during the treatments. The IPCW method can incorporate possible influential factors for dropouts in the estimation of survival curves[4,5]. We utilized the stabilized weights estimated through a Cox regression[4,6] that included both time-dependent covariates (the QIDS-SR_{16} and the GRSEB scores at successive measurements) and time-independent covariates (age, sex, education history, the Hamilton Depression Rating Scale total score at baseline, family history, and history of taking any antidepressant medications). Missing data were addressed using the multiple imputations by chained equations with 100 imputed datasets[7].

We calculated the cumulative remission rates at 90, 180 and 360 days along with corresponding 95% confidence intervals (CIs). We applied the same methods separately to those who had received at least one antidepressant medication during the index episode prior to study entry and those who had not, and compared the cumulative remission rates between the two groups using the weighted log-rank test.

The cumulative remission rates among all samples were estimated to be 53.8% (95% CI: 51.6-55.9) at 90 days, 74.5% (95% CI: 72.1-76.9) at 180 days, and 87.5% (95% CI: 82.4-92.6) at 360 days. The median time to remission was 84 days (see also supplementary information). The estimated rates of cumulative remission among those who had received no antidepressant prior to study entry were 55.4% (95% CI: 53.0-57.9) at 90 days, 76.3% (95% CI: 73.7-78.9) at 180 days, and 89.1% (95% CI: 85.0-93.2) at 360 days. These rates were higher (hazard ratio: 1.28; 95% CI: 1.16-1.41, $p<0.001$) than among those who had had antidepressant exposure: 49.3% (95% CI: 45.5-53.2) by 90 days, 70.1% (95% CI: 65.6-74.6) by 180 days, and 82.1% (95% CI: 71.8-92.3) by 360 days. The median time to remission in these two groups was 80 days and 91 days, respectively (see also supplementary information).

So, our re-analysis of the STAR*D data shows a cumulative remission rate approximately 20% points higher than that reported in the original paper[1]. That paper did not account for those who dropped out from or discontinued the study, while we applied a survival analysis taking into account time-independent and time-dependent patient characteristics such as longitudinal symptoms and side effects.

Previous research has typically assumed that dropouts had the same outcome as non-dropouts (completer analysis) or would not have achieved remission in the intent-to-treat analysis (worst case scenario analysis). However, in a 9-week single-blind clinical trial of sertraline and mirtazapine in MDD, 147 participants who had dropped out from the intervention but were subsequently assessed had lower depressive scores and better treatment outcomes compared to 1,499 participants who completed the intervention and the assessment in the study[8]. Among those who dropped out, 32 participants who were difficult to contact had even lower depressive scores than 82 participants who were easily contactable[8]. These findings suggest that a greater tendency to drop out may be associated with better treatment outcomes.

The present findings align with prior reports of high rates of cumulative remission in individuals with depression who initiated antidepressant treatment for the first time. Specifically, a prospective follow-up study consisting of 90 drug-naïve patients diagnosed with MDD reported that 85% of the subjects achieved asymptomatic or minimally symptomatic status by 12 months[9].

There are several limitations to this study. First, the STAR*D trial included only outpatients with non-psychotic MDD who received citalopram in primary or secondary care settings in the US, limiting the generalizability of the findings to other populations in different treatment settings. Second, remission was defined only on the basis of the QIDS-SR_{16} scores, without considering functional outcomes. Third, remission in the acute phase treatment does not necessarily mean stable remission, as 40-71% of individuals who achieved remission were reported to experience relapse within

one year[1].

In conclusion, our re-analysis using the IPCW Kaplan-Meier method shows a much higher cumulative remission rate (i.e., 87.5% within a year after the initiation of treatment) than the 67% reported in the original STAR*D paper. This promising finding provides an opportunity to revisit the therapeutic potential of currently available treatment options for MDD, and underscores the relevance of employing sequential treatments until remission is achieved.

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How should psychotherapy proceed when adjoined with psychedelics?

Over the past few years, research and public interest in psychedelic agents – such as psilocybin and 3,4-methylenedioxymethamphetamine (MDMA) – for mental health purposes has skyrocketed. The therapeutic approach to the use of these agents involves three components: preparation, drug administration, and integration. This bundled treatment has been termed psychedelic-assisted therapy (PAT). The basic assumptions and methods of PAT, however, have remained unchanged since the 1950s, despite notable advances in the treatment of mental disorders.

The preparation phase involves building rapport between the patient and therapist(s), providing education about the psychedelic experience, and establishing a therapeutic intention (i.e., a set of goals) for the drug session. These practices are thought to facilitate a positive response to the drug and reduce the likelihood of adverse events (e.g., a "bad trip"). In the empirical literature, preparation has been described with consistent practices but wide-ranging durations, from two to eight hours over one to three sessions[1].

The drug administration session has been the most consistent practice in empirical studies. The participant is monitored by two clinicians with little interruption for 6-8 hours. During this interval, patients lay on a couch with eyeshades, listen through headphones to a pre-determined playlist of classical music, and are encouraged to be as introspective as possible. These sessions typically entail minimal involvement from the therapists, except to provide emotional support, safety monitoring and, when appropriate, therapeutic touch.

The most inconsistent offering within PAT has been the integration phase, which has ranged from an individual telephone call to nine psychotherapy sessions[1]. Integration sessions have traditionally involved various forms of non-directive, unstructured psychosocial support. The theoretical basis behind this approach is that the psychedelic drug assists patients in identifying what they need to heal. The integration sessions have been culled from various traditions, including classic psychoanalysis, Rogerian person-centered therapy, Maslow's theory of self-actualization, and inner healing intelligence[2].

Many questions remain about how the psychotherapy components of PAT produce meaningful benefits above and beyond the drug itself. Some experts claim that the current integration practices contribute little (if any) value beyond the drug's immediate psychiatric benefits, whereas others claim that it is the therapy enhanced by the drug that leads to psychiatric change[1,3]. While the psychedelic drugs have received the bulk of the attention, the psychosocial treatment components of PAT have not been studied to measure their relative benefits for symptomatic and functional improvements.

To advance the field further, it is important that the psychotherapy adjunct be updated and optimized from its 1950s origins through rigorous scientific testing. We recommend testing the efficacy of adjunctive psychosocial treatments with a strong evidence base for the psychiatric indication of interest. Cognitive-behavioral therapies (CBTs) have robust empirical bases across the core emotional disorders being approached with psychedelics (i.e., mood, anxiety and stress-related disorders). CBTs are most notable for their enduring effects in terms of symptom improvement and relapse prevention[4]. Importantly, these treatments are manualized, reducing the variability in treatment delivery and making the testing of treatment fidelity possible. Additionally, CBT can be disseminated safely and effectively by community clinicians, as shown by the Improving Access to Psychological Therapies (IAPT) programme in the UK[5].

Examining the comparative contributions of the drug and the accompanying psychotherapy is also critical to our understanding of the mechanisms of psychedelic treatment. The core emotional disorders have shared etiologies and psychological processes, in-

cluding poor emotion regulation that leads to emotional and behavioral avoidance of negative stimuli. Psychedelics have a range of acute effects on consciousness, including sensory and physical experiences; sense of self, time and space; and emotions and cognitions[6]. The changes in an individual's emotions and cognition help to foster greater social connectedness and self-esteem and may clarify priorities and values. Additionally, psychedelics appear to reduce patients' emotional sensitivity and cognitive rigidity in reaction to emotionally-laden stimuli, allowing them to approach emotional and cognitive content that they would otherwise avoid. For example, a patient can feel more able to undergo imaginal exposure to a previously avoided trauma. This can also be facilitated by the effects of the drug on the individual's perception of time and space through what can feel like actual movement through a trip or journey. Thus, psychedelics can help patients regulate their emotional sensitivity, appraise and approach stressful situations more flexibly, and connect to their social environment.

Structured empirically-based psychotherapies seek to modify these same psychological mechanisms of emotional regulation, cognitive flexibility, and prosocial engagement. Changes in cognition and behavior can also be tested as mediators of the impact of CBTs on symptomatic or functional outcomes. When combined with psychedelics, we expect psychosocial treatments to work synergistically with the drug to catalyze immediate and longer-term changes in thinking, feeling and behavior[7].

PAT has had varying lengths of treatment response, ranging in major depression from as little as a few weeks to as long as one year [8,9]. Helping patients make sense of the cognitive, affective and physiological changes produced by the drug through CBTs may instill longer-lasting benefits. Further, working with patients to concretely apply these insights into real-world cognitive and behavioral changes seems critical to producing deep-seated, durable improvement. For example, the effects of psychedelics on feelings of social connectedness may serve as catalysts for changes in thoughts and behaviors that foster social engagement. While the drug may motivate change initially, working with the patient to create behavioral activation plans, holding him/her accountable in making these changes, and solving problems that arise in the implementation of these plans may prolong the duration of the drugs' benefits.

To examine the effects of structured psychotherapy on psychedelics (and vice versa), it will be important to vary doses of the therapy in the preparation and integration phases. What is the minimal number of preparation sessions that are necessary to safely administer a psychedelic? Does a longer preparation phase magnify the psychedelic experience, facilitate therapeutic alliance, or increase opportunities to practice newly acquired skills (such as cognitive restructuring)? Would preparation be different for psychedelic-naïve participants compared to those who have prior experience with the drug? Do integration sessions gradually improve psychiatric outcomes and functioning, or are the majority of clinical benefits apparent shortly after drug administration? How many integration sessions are optimal? Seeking to identify the treatment ingredients necessary for effective and safe delivery of psychedelics can help to update therapeutic practices. Furthermore, determining whether more than one participant can be served at one time (be it in a group setting or in adjoining rooms), and how the addition of other co-patients affects the delivery of adjunctive psychotherapy, are questions ripe for investigation.

In our ongoing trial of a psilocybin-assisted CBT for patients with major depression[7], we are already impressed by the synergy between the psychotherapy and drug treatments. Our preliminary observations are that CBT skills can be leveraged during the drug experience and can increase the individual's accountability for behavioral change following the drug administration. Additionally, the psychedelic appears to increase prosocial emotions and cognitions to help enact behavioral change following the drug session.

The next generation of studies on psychedelics should consider the impact of the psychotherapeutic context of drug administration, which may prove to be as important for clinical change as the drug itself.

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Violence in schizophrenia: triangulating the evidence on perpetration risk

The question of the nature and magnitude of the association between schizophrenia and risk of violence perpetration has been the subject of considerable research and wider public interest. It is a complex relationship, and important to clarify for people with mental illness and their families, with implications for health policy, mental health law, criminal justice, and public mental health. It therefore requires careful, evidence-based consideration.

Over the last decade, complementary epidemiological study

and trial designs have provided triangulation of evidence on the association between schizophrenia and violence. These studies have shown robustly two main findings: that there is an elevated risk of violence in schizophrenia spectrum disorders, and that the absolute level is not large (and only a minority of people with severe mental illness will perpetrate serious violence over their lifetime). Another replicated research finding is that the violence perpetration risk is further increased if other factors, such as substance misuse comorbidity and previous violence perpetration and victimization, are also present. In addition, it has been clearly shown that widely available evidence-based treatments can reduce the risk.

The risk of perpetrating violence is not imminent or significant in most people with schizophrenia, but it is not so small that it can be ignored. Given its relevance to public perceptions of dangerousness and stigma, we agree that the evidence needs careful communication[1]. However, a simplistic approach which states that recognizing any association between violence and schizophrenia will inevitably be damaging for efforts to reduce stigma is problematic. It fails to take account of the evidence as a whole, presupposes that communication of the link cannot be undertaken without worsening stigma, and overlooks the lived experience of people for whom the impact of schizophrenia is compounded by the related perpetration of a violent offence.

Here, we present an alternative way forward, that: a) recognizes the findings of triangulated and replicated research evidence, that has considered key confounds, but properly contextualizes relative risks with information on absolute rates, and b) highlights that the implication of these findings is to improve clinical assessment, treatment and management of violence risk, which will be the most effective way to reduce associated stigma.

The epidemiological evidence for relative risk of violence perpetration in schizophrenia spectrum disorders compared with control groups was recently examined in a meta-analysis including over 50,000 affected people[2]. The increased risk compared with control groups was consistent in all studies despite different study designs, with varying violent outcome definitions (including criminal and non-criminal ones), study quality, geographical region, and whether included patient populations were identified by inpatient admission or from more community-based samples.

Where it was studied, risk remained increased in those without substance misuse comorbidity compared to control groups (around 4-fold risk), but was higher where substance misuse was also present (around 10-fold risk). Importantly, studies included those with longitudinal designs, whereby temporal ordering of diagnosis and violent outcome addressed previous concerns around reverse causality[3]. Further, there have been two studies using unaffected same-sex siblings as control groups which allowed confounding by unmeasured familial factors to be estimated[3]. This novel approach supports causal inference, as siblings share genes and early childhood factors.

Another area of concern when interpreting the link is whether it is explained by social factors such as different responses to people with and without serious mental illness by police and the justice system. However, for the rare outcome of homicide, where this argument is unlikely to apply as clearance rates (proportion of crimes known to police which are solved) are very high in the five high-income countries where it has been investigated, the relative risk in schizophrenia spectrum disorders was even higher – a 18-fold risk, with a lower 95% confidence interval for the pooled odds ratio of 14[2].

Trial data is a key part of the triangulation of evidence. The strongest evidence of the causal nature of the association is from a recent Cochrane meta-analysis of antipsychotic trials[4]. In people with schizophrenia spectrum disorders, those who were treated with antipsychotics had a large reduction of violence risk compared to the placebo arms (risk ratio: 0.37, 95% CI: 0.24-0.59), using an outcome which was not measured using arrest or crime data[4]. One reasonable explanation of this synthesis of trials is that psychotic symptoms, which decrease in intensity and frequency after treatment, are causally associated with violence perpetration.

Furthermore, real-world population-based pharmaco-epidemiological studies have compared violent crime outcomes in the same persons during periods in which they are dispensed antipsychotic medication compared to periods when they are not (a design that has also demonstrated the reduction of suicide mortality associated with antipsychotic treatment in schizophrenia[5]). Consistent with the trial evidence, these studies have shown the large impact of treatment in reducing violence risk[6]. Symptoms such as persecutory delusions might provide plausible therapeutic targets that sit along a causal pathway, which has been shown in richly phenotyped clinical populations[7].

Research has also highlighted the important issue of absolute risk. In studies included in the recent meta-analysis[2], fewer than 1 in 4 men and 1 in 20 women with schizophrenia spectrum disorders perpetrated violent crime during follow-up, which ranged to 35 years. This is key for a proportionate understanding and communication, and most relevant for clinical services. One such setting where the potential of prevention has been noted is in first-episode psychosis services. Studies have estimated that around 1 in 10 individuals presenting to such services perpetrate violence in the year after service contact, including a recent UK study that used a combination of clinical and police data to measure violence perpetration[8]. Despite this, related work has shown that clinicians working in these settings are hesitant to ask about violence risk, because of fear of reinforcing stigma[9]. This may in part account for the low sensitivity of clinical assessment – only 40% of those who perpetrated violence in the following year were assessed as at elevated risk – in first-episode services[8].

Legislation in many countries recognizes the potential for a link between someone's mental illness and a violent crime they have perpetrated, which can lead to appropriate treatment, rather than punishment or restriction alone. Consequently, we would argue that it is possible to recognize the association between a psychotic illness and increased risk of violence, and that this leads to better preventive treatment. Improving prevention requires clinicians and researchers to recognize this link, however unpalatable, and endeavour toward reducing it, whilst advocating for and working with patients and their families to ensure that it is seen in context and not exaggerated. These goals – recognizing the link and reduc-

ing the risk – are not mutually exclusive, and framing them as exclusive will not improve patient care.

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Management of generalized anxiety disorder and panic disorder in general health care settings: new WHO recommendations

Mental, neurological and substance use (MNS) disorders are highly prevalent and account for a significant burden of disease[1]. However, in many countries, there is a gap between the need for MNS services and the available health system capacity and resources. The World Health Organization (WHO)'s mhGAP Action Programme was launched to address this gap by developing recommendations for the identification and management of priority MNS conditions in non-specialist care settings. Several derivative tools, such as the mhGAP Intervention Guide (mhGAP-IG), have been developed to support the programme's implementation[2].

The mhGAP approach consists of interventions for the management of priority MNS conditions. These interventions are identified on the basis of evidence about their effectiveness and the feasibility of their scaling up in low- and middle-income countries. Among MNS conditions covered in the first and second iterations of the mhGAP-IG were depression, psychoses, self-harm/suicide, epilepsy, dementia, disorders due to substance use in adults, and mental and behavioural disorders in children and adolescents.

The need has emerged for additional guidance on conditions not covered in the programme. Among these are anxiety disorders, which as a group are the most common mental disorders worldwide, with over 300 million people, about 4% of the global population, living with an anxiety disorder as of 2019[3]. Anxiety disorders also represent the second leading cause of disability-adjusted life years (DALYs) among mental and substance use disorders[4], and carry a significant social and economic burden[5]. Moreover, anxiety disorders have an early onset, representing the most prevalent mental disorder among older adolescents overall (4.6%), and particularly among adolescent girls (5.5%)[3].

Although there are many effective treatments available, as many as 75% of people with anxiety disorders do not receive any care globally[6]. To address this gap, the WHO has developed a new module, as part of the mhGAP guideline update released in November 2023, to provide recommendations for the management of anxiety disorders and promote broader implementation of evidence-based interventions in low- and middle-income countries. This module focuses on generalized anxiety disorder (GAD) and panic disorder (PD), selected due to their prevalence, their estimated burden, the likelihood of their presentation in general health care settings, and the availability of evidence on feasibility and effectiveness of interventions in non-specialist care settings.

The new mhGAP anxiety recommendations have been developed according to the WHO's guideline development process[7]. A Guideline Development Group (GDG) was convened and was responsible for making recommendations based on systematic review and appraisal of available evidence. Seven PICO questions were identified based on expert consensus to guide evidence retrieval, review, synthesis and assessment using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system[8]. Results were then reviewed by the GDG to produce recommendations[9]. The mhGAP anxiety guidelines address the role of psychological interventions, pharmacotherapies, stress management, physical exercise, and collaborative care for adults with GAD or PD.

The guidelines recommend brief structured psychological interventions based on principles of cognitive behavioural therapy (CBT) for adults with GAD and/or PD. Most available evidence on the psychological treatment of GAD actually regards CBT, with third-wave CBT also frequently studied. Evidence indicates that guided self-help is likely to be more effective than unguided self-help, and that specialist delivered interventions are likely to be more effective than those provided by non-specialists, while there appear to be minimal to no differences between digital and face-to-face interventions, and between individual and group modalities.

The guidelines also recommend the use of selective serotonin reuptake inhibitors (SSRIs) for GAD and PD, while tricyclic antidepressants (TCAs) are recommended only for PD in cases where SSRIs are unavailable. No specific differentiation in terms of effectiveness or adverse effects emerged among the reviewed SSRIs, including citalopram, escitalopram, fluoxetine, paroxetine and sertraline. There was insufficient evidence for the use of TCAs in adults with GAD.

Stress management techniques, including relaxation and/or mindfulness training, are also recommended for adults with GAD and/or PD, as is engagement in structured physical exercise. The

guidelines recommend against the use of benzodiazepines in the treatment of adults with GAD and/or PD. These drugs should only be used for severe, acute anxiety symptoms and only as a very short-term measure (3-7 days). Finally, the guidelines recommend the consideration of collaborative care for adults with depression and/or anxiety and physical health conditions.

The GDG highlighted a number of key considerations in making these recommendations. First, the GDG emphasized that the WHO's process for guideline development does not intend to make recommendations that cover the totality of interventions proven effective in a given area[7]. Instead, the process focuses on areas or interventions where evidence is most substantial or where there have historically been controversies or the need for a policy change. Thus, the GDG noted that these initial guidelines may not encompass the totality of interventions that have been proven effective for GAD or PD.

Additionally, the GDG noted a limitation in the fact that the majority of evidence available comes from research conducted in high-income countries, and highlighted the need for increased distribution of research funding to institutions in low- and middle-income countries. It also noted considerable evidence for models of care, such as task-sharing and training and supervision of non-specialists, that are particularly appropriate for those countries. However, the GDG also specifically noted the challenges in human resources and health worker time and capacity to deliver certain interventions, particularly structured psychological interventions or collaborative care models.

Third, the GDG noted the need for further research to explore the longer-term impact of interventions on symptoms, functioning and other key outcomes, while also recognizing the substantial evidence for symptom reduction in medium to short term. Fourth, the GDG made particular note of the need to consider cultural variability and individual preferences in applying recommendations in practice. For instance, the GDG highlighted the value of physical exercise for anxiety disorders generally, while also noting the need to consider daily habits of communities receiving care, such as when physical exertion is already a part of their daily life (e.g., farmers, manual labor workers).

Fifth, the GDG emphasized the need to ensure adequate training and follow-up supervision for non-specialists in any setting. Sixth, the GDG discussed the frequent over-prescription of benzodiazepines for anxiety symptoms, particularly in non-specialist care settings, and emphasized the risks associated with these prescriptions. Lastly, the GDG described the importance of adaptation for delivery of these interventions, including the use of innovative and digital technologies.

To date, there were no evidence-based guidelines for managing common anxiety disorders in non-specialized care settings focusing on low- and middle-income countries. These recommendations were produced to fill this gap and will serve as a foundation for forming a new module in the mhGAP Intervention Guide, a tool frequently used to operationalize the mhGAP guidelines. Extensive work will be needed to scale up capacities in countries to act on these mhGAP recommendations and ensure effective management of anxiety disorders globally.

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Genetics for mental health clinicians: a call for a globally accessible and equitable psychiatric genetics education

The field of psychiatric genetics has evolved rapidly over the past decades, leading to major advancements in our understanding of the genetic architecture of mental disorders. Dozens of genes have been definitively linked to neurodevelopmental disorders (NDDs), and hundreds of genetic loci have been significantly associated with psychiatric diseases and/or traits (e.g., schizophrenia, neuroticism), potentially shining light on underlying biological disease processes and possible routes for targeted treatment[1]. Despite this progress, psychiatric genetics education for mental health clinicians remains fragmented and inconsistent across the globe[2], which has major implications for the quality of care that patients receive and the ability of mental health professionals to effectively incorporate genetics into clinical practice.

First and foremost, basic counseling about the genetic com-

ponent of the etiology of many mental disorders – as part of the broader psychoeducation mission – can help reduce stigma, guilt and misunderstanding about what mental illness is[3]. It can help families and patients focus on identifying resilience factors to counteract genetic risk, such as improved sleep, diet and exercise[3]. Effective counseling can be provided in almost any setting without additional resources or technologies.

A genetic diagnosis can be made in 25-40% of patients with NDDs[4]. For this patient population, genetic diagnoses have well-established clinical benefits, such as ending the diagnostic odyssey that many families face, informing family planning, enhancing prognostic counseling, offering the opportunity for earlier intervention to support neurodevelopment, and providing access to relevant clinical trials and support networks of other families with similar genetic conditions[4]. Furthermore, with the advancement of precision genetic therapies, there is now the possibility of disease-modifying treatment for NDDs.

Mental health clinicians should also understand the basic principles of pharmacogenetics (e.g., how an individual's genetic make-up affects his/her response to medications). Pharmacogenetic testing may allow for the selection of psychiatric medications that have fewer side effects[5]. For instance, pharmacogenetic testing for HLA class I variants can prevent serious cutaneous adverse reactions (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis) in individuals starting on carbamazepine or oxcarbazepine[5]. Moreover, a recent controlled, cluster-randomized crossover study demonstrated that a 12-gene pharmacogenetic panel (including the liver enzyme cytochrome P450 genes, *CYP2D6* and *CYP2C19*, which are responsible for the metabolism of most psychotropic medications) reduced the incidence of adverse drug reactions across diverse European health-care system organizations and settings[6].

Given the relatively low cost of pharmacogenetic testing and the high burden of adverse psychotropic drug effects, global implementation is plausible. Widespread psychiatric pharmacogenetic education can prepare mental health workforces to implement pharmacogenetic testing more rapidly and efficiently as access grows. However, education initiatives will need to emphasize the large variation in allele frequency of pharmacogenes between populations of difference ancestries, to ensure that clinical approaches are tailored accordingly[6].

Moreover, although not yet rigorously validated for clinical use in mental disorders, polygenic risk scores (PGS) have great potential as a future tool in psychiatric care[7]. A PGS is a measure that represents the combined effects of many common genetic variants associated with a complex trait or disease[7]. In psychiatry, PGS are being explored on their own and in combination with other risk factors as predictors of disease onset, such as schizophrenia in a population at high risk for psychosis[7]. Despite the need for ongoing research, an individual may already request his/her own psychiatric PGS from direct-to-consumer companies for a relatively small fee, highlighting the tension between clinical utility and industry profit. In fact, 10% of US-based child and adolescent psychiatrists report that they have had a patient or family member bring PGS results to them for interpretation[8].

There is an imperative for mental health clinicians to be able to counsel patients on the interpretation of psychiatric PGS. Without sufficient education and understanding, there is a significant risk for misinterpretation and misguidance, as occurred over the last decade with direct-to-consumer psychiatric pharmacogenetic testing in North America. Due in part to a lack of pharmacogenetics education in mental health training, many clinicians struggled to recognize the limitations (and potential harms) of the test results that patients brought to them, until the Food and Drug Administration started issuing cease-and-desist letters to commercial labs in 2019 for misleading marketing practices.

If similar widespread misuse of psychiatric PGS were to occur, there could be significant consequences. For example, PGS testing in pre-implanted embryos (i.e., "polygenic embryo screening") for psychiatric and cognitive traits is already offered by some private companies without a full understanding of the individual or societal implications. Indeed, the process of genetically selecting for "desirable" psychiatric traits, whether through PGS or otherwise, has a dark history associated with the eugenics movement, which has motivated human atrocity, including the Holocaust. In response, many professional societies, including our Society, have issued statements urging restraint and thoughtful consideration[9]. It is critical that mental health clinicians are sufficiently educated in genetics to take a nuanced approach to clinical testing, understanding when it is highly evidence-based and clinically informative (e.g., diagnosis in NDDs) and when it risks causing harm if misused (e.g., polygenic embryo screening).

How can we ensure inclusive psychiatric genetics education for all mental health clinicians, beyond just psychiatrists in well-resourced settings? We can start by utilizing existing high-quality, free online resources, such as the National Neuroscience Curriculum Initiative (https://nncionline.org), which offers interactive learning modules on diagnostic genetic testing for NDDs and pharmacogenetics. Other accessible resources include an easy-to-understand animated video on autism genetics (www.precisionmedicineinautism.org) and the National Human Genome Research Institute's comprehensive resources (www.genome.gov). Additionally, learning and implementing the "jar model" of psychiatric genetic counseling (https://genomicare.ca) can help clinicians effectively integrate genetic counseling into their practice[3].

Ultimately, medical education should empower trainees as independent learners, driven to acquire new knowledge that benefits their patients. In accordance with psychiatric genetic counseling principles, we must aim to impart foundational knowledge on the heritability of mental illness to all clinicians, reducing stigma and misconceptions while empowering patients to lead fulfilling lives. This is a call to action for our community to collaborate and strive for an accessible, equitable psychiatric genetics education for all.

Education Committee, International Society of Psychiatric Genetics (ISPG)

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The dynamic paradigm of illness in psychopathology

Medical thought oscillates between two representations of illness. According to the first, illness enters or leaves the organism as through a door, by either adding something that should not be there, or removing something that should be there. Infection is the paradigm of illness as a pathogenic addition; haemorrhage is the paradigm of illness as a pathogenic removal of something which is needed. This representation of illness, called "ontological"[1], is to some extent reassuring: what the organism has lost can be restored, and what has entered can be removed.

A different representation of illness is called "dynamic"[1]. According to this view, illness is not an accident that arrives from outside and upsets the state of equilibrium of an otherwise healthy organism. Humans are intrinsically vulnerable beings who fall ill when they respond incongruously to what they perceive as a threat for the unstable and vulnerable equilibrium characterizing their condition. This threat must not necessarily be an objective noxious entity; it is enough that it is subjectively experienced as such.

Are there good arguments to support the dynamic paradigm? Contemporary research in clinical phenomenology appeals to the notion of "position-taking" to provide a framework for the investigation of the person's attempts at healing as a fundamental component of the dialectics of symptom formation[2]. Psychotic symptoms, for instance, are understood as the expression of the person's efforts at making sense of "strange" self- and world-experiences. These basic uncanny experiences and the patient's resources to cope with them face one another. The manifestation and course of the illness can be understood as emerging from the person's efforts at fighting against or adapting to the existential challenges associated with the onset of the above uncanny self- and world-experiences[3].

This approach has the potential to address oft-neglected troubling experiences without threatening the person's epistemic agency. The recognition of psychopathological conditions from the viewpoint of a dynamic representation of illness is the gateway to a radical extension of our human perspective on mental disorders and in general on *humana condicio*. It helps thinking of the vulnerability to mental disorders as an *intrinsic* property of being human. Persons affected by mental symptoms may be closer than ourselves to the core of the human condition[4]. From this viewpoint, any research on psychopathological symptoms becomes an exploration of their meanings and an attempt to answer the question "What does it mean to be human?". Our research in psychopathology can become a means to investigate the core of human existence. This dynamic representation of mental symptoms can be integrated into a new medical, anthropological, technological and socio-political understanding of psychopathology.

Should we assume that uncanny self- and world-experiences are common to all, or at least most, human beings? The point is not whether an extrinsic stressful event facilitates the emergence of these experiences – this should be considered a fact. The question is whether these experiences emerge from a vulnerability intrinsic to the human condition. From this perspective, what comes from outside is at most the *occasion* for the unleashing of pathology, but not its *cause*.

Is there any evidence that occasional experiences of unreality of self, body and world are common to most human beings? We could tentatively refer to two kinds of "evidence": one derived from psychopathological research, and another that could be called "cultural". Regarding the former, epidemiological surveys document that transient depersonalization/derealization experiences occur rather frequently in the general population[5], and are common among adolescents without a psychiatric diagnosis[6]. These findings may be taken to suggest that feeling unreal, cut-off from the world; detached from oneself, one's thoughts and one's memories; seeing oneself from without, feeling like an "automaton", notwithstanding their color of "strangeness", are "quasi-physiological" experiences.

Coming to the "cultural" evidence, it is a common argument in the philosophical, anthropological and spiritual literature that what characterizes the human condition is its being "a work of indefinite nature"[7]. "Nothing has received more universal confirmation than the proof that the universe is a creation of chaos, life an epiphenomenon, and man an accident"[8]. To protect ourselves from the anxiety that comes with the awareness of being so intrinsically vulnerable, we seek refuge in our social identity and common-sense beliefs. But these defensive "housings" are precarious; they do not provide a secure shelter.

The acute awareness of our vulnerability typically arises during *limit-situations* which may take place in everyday life[9]. These are situations in which the "housing" of everydayness and common-sense assumptions is jeopardized. Our basic trust breaks down. During these limit-situations, we experience human basic "anxieties", e.g., unavoidability of guilt, inescapability of freedom, fragility of our body, loneliness of our existence, vertigo of unreality, meaninglessness. These feelings may unsettle some individuals, breaking them out of their common-sense beliefs, identifications and social bonds. States of depersonalization and derealization may emerge, together with an overall condition of bewilderment, from which psychopathological symptoms or growth opportunities may arise.

From an ethical perspective, only if we consider such experiences, and the existential questions accompanying them, as an integral part of the human condition, we can manage them with due respect and not merely undertake to eliminate them as one would eliminate something inhuman.

Care, in this dynamic view, involves supporting the person in his/her *search for meanings*. The clinician, as an expert in human limit-situations, is like a guide who helps the patient to find a new equilibrium with his/her existential conundrums. The therapeutic intervention is not aimed to eradicate these conundrums, which are radically human in nature, but to help the patient acknowledge the existential meaning of his/her uncanny feelings, achieving awareness of his/her own "housings" and specific "limit-situations", and taking responsibility for his/her choices.

This vision can also help update our perception of recovery: no longer the elimination of symptoms, or of the pathogenic noxa, but the achievement of a new and more effective dynamic balance in a person's vulnerable condition, modulating the intensity of troubling experiences, and making them less pervasive in order to facilitate the deciphering of their existential meanings.

This conception is certainly optimistic, but has the merit to promote a more balanced therapeutic perspective. The notion that patients are passively subdued by an illness can contribute to establish asymmetric relations, limiting our possibility of exchange with the other's perspective, mutilating our understanding of his/her world, and locking us into the dead-end of our limited sectoral perspective. On the contrary, a dynamic view can help establish a more balanced helping relationship, centred on the support given by the clinician to the patient's own efforts at self-healing based on self-understanding.

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The WPA Action Plan 2023-2026

Building on the Association's foundational activities, the WPA Action Plan 2023-2026 aspires to enhance the mental and physical well-being of psychiatric patients, psychiatric staff, and the broader public. The staggering statistic that one in every eight individuals globally grapples with a mental disorder[1] warrants continuous improvement in preventing and treating these disorders. Alarmingly, despite the magnitude of this issue, public expenditure on mental health remains disproportionately low[2,3], underscoring the urgent need for intervention and reform.

An umbrella review and meta-analytic evaluation of 102 meta-analyses, including 3,782 randomized controlled trials and 650,514 adult patients who received psychotherapies or pharmacotherapies for the treatment of the most prevalent psychiatric disorders, showed that the effect sizes of treatments appear to be low and have plateaued, hinting at a potential ceiling effect in current research modalities[4]. This calls for a paradigmatic shift in research methodologies as well as identifying new methods to improve mental health by treatment and prevention. However, finding, developing and getting approval for new treatments and preventive methods takes a long time. In the meantime, we must concentrate on implementing existing evidence-based treatments and preventive methods that show relatively good efficacy.

To accomplish this goal, the WPA Action Plan 2023-2026 prioritizes the following actions: implementation of evidence-based therapies, prevention and adoption of healthy lifestyles, research, and communication. Here we focus on implementation of evidence-based therapies, prevention and adoption of healthy lifestyles.

Evidence-based treatments are available for all psychiatric disorders. Some psychotherapies and pharmacotherapies, as well as their combinations with psychosocial measures, are proven to improve mental health of patients with various disorders. Research papers, while invaluable in advancing medical knowledge, often present a challenge for clinicians: their technical nature can make them inaccessible to those who are on the front lines of patient care and are pressed for time. It is imperative to bridge this gap between academic research and clinical practice. We must develop a system that consistently updates clinicians about the latest findings, enabling them to discern and adopt the best practices. Such a system would ensure that patients receive care based on the most recent and relevant evidence, enhancing the overall quality of care. To systematically implement these existing treatments, along with emerging ones, the WPA is introducing a "Specialist Corner: Advances of sciences and their application in clinical practice".

This Corner will serve as a hub to summarize advancements in clinical psychiatry, public mental health and ethics, while fostering diversity and inclusiveness. This platform, dedicated to clinicians, will feature online webinars where expert specialists present, in an accessible way, state-of-the-art treatments and best practices for daily psychiatric work. Within this Corner, insights on diagnosing, treating and rehabilitating patients with various mental disorders – including psychosis, affective disorders, substance use disorders, attention-deficit/hyperactivity disorder, autism, and eating disorders – will be presented. Topics such as mental health during crises, practical applications of digital psychiatry, and ethical considerations in everyday scenarios will also be covered.

The lead specialists for each mental disorder, responsible for each webinar or series of webinars, will appoint a group of colleagues from all continents to present the topic from different perspectives, showing gaps in research, availability of studies, and adaptation of existing materials to different cultural contexts. Outcomes from these webinars will be summarized for easy comprehension, intended as educational resources for patients, their families, and clinical staff. This approach aims to foster treatment adherence and the application of best practices. All webinars, along with their associated materials, will be available on the WPA website.

Preventing psychiatric disorders is essential for promoting mental well-being and reducing risk of relapses, and necessitates systematic implementation at both local and national levels[5]. Evidence-based preventive strategies, when adopted early in life, can significantly enhance mental health outcomes[6,7]. Through coordinated efforts, we can foster more resilient communities and reduce the overall burden of psychiatric disorders.

While there is evidence that healthy lifestyles boost general health, there is also growing proof of their impact on mental health across different populations. Activities such as physical exercise, a balanced diet, and consistent sleep hygiene all have positive effects on mental well-being[8-10]. Consistent sleep hygiene practices significantly enhance mental well-being by ensuring restorative rest and maintaining circadian rhythms[11]. Proper nutrition, characterized by a diet rich in essential nutrients, is crucial for brain health and overall mental wellness[9]. Engaging in regular physical activity has been consistently linked to improved mood, reduced anxiety, and cognitive benefits[8]. Integrating these healthy lifestyle practices can supplement and amplify the effects of existing pharmacotherapies and psychotherapies.

The public has increasingly recognized the importance of healthy living. A growing number of individuals now participate in regular physical activity and consciously strive to make healthier lifestyle choices. While the broader public acknowledges the benefits of a healthy lifestyle, its full potential in psychiatry remains untapped[12-15]. This disconnect often stems from patients' lack of knowledge about adopting and sustaining healthy habits. Many do not have tangible examples or role models from their homes or schools that illustrate the effective incorporation of physical activity, proper nutrition, and sleep hygiene into daily routines. Thus, the WPA Action Plan 2023-2026 is geared towards enhancing the emphasis on physical activity, nutrition, and sleep hygiene among psychiatric patients and staff.

Three videos have been produced to guide psychiatric staff and patients on the significance of daily physical activity and good nutrition habits. Developed at Karolinska Institutet in Stockholm, these videos provide guidelines and recommendations for incor-

porating exercises of varying intensity into daily routines for 3-5 min. Engaging both psychiatric staff and patients in joint physical activities can strengthen connections, promoting shared experiences, improved communication, increased empathy, reduced hierarchy, and overall enhanced physical and mental well-being.

The University of Campania in Naples has produced three videos on nutrition, specifically tailored for adolescents and young adults. They showcase dialogues that promote awareness of healthy dietary choices and include a 2-min summary offering advice on dietary habits that support mental well-being.

The videos produced will be hosted on the WPA website as part of a library on healthy lifestyles, making them accessible to colleagues worldwide. These resources can be downloaded for inspiration and application in daily psychiatric practice. We also encourage members from all continents to share short videos highlighting their initiatives in promoting healthy lifestyles among psychiatric patients. This initiative aims to enhance collaboration, cultural awareness, and inclusivity among all WPA Member Societies.

In 2015, the United Nations introduced the Sustainable Development Goals as a global blueprint to ensure prosperity, environmental sustainability, and peace by 2030. The WPA Action Plan 2023-2026 seeks to uplift the mental health of the global community by making significant strides in psychiatry and public mental health in the upcoming years. The Plan underscores the importance of integrating mental well-being across all fields of society, including education, clean water and sanitation, affordable and clean energy, good work environments, and reduced inequalities.

The WPA is determined to gain traction and lead the way to foster a worldwide community in which mental health advancements are not just limited to medical and psychiatric contexts, but are ingrained in the very fabric of society. The Association aims to inspire other sectors for intersectional collaboration, emphasizing the pivotal role of mental health as the foundation for harmonious relations, thriving communities, improved outcomes in all our endeavours, and a brighter future for all.

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One world, one profession: psychiatry

I am honored to assume the role of WPA Secretary General and excited to work even more closely alongside colleagues and friends whom I have come to know in my role as Chief Executive Officer (CEO) and Medical Director of the American Psychiatric Association (APA) over the last decade.

I am retiring from the APA in May 2024, but my passion and dedication to the work we do in support of our patients and profession and our shared goal of a more mentally healthy world remain as strong as ever. I can think of no better place to continue what has become my life's work than the WPA.

I am both humbled and excited to be able to play a direct role in helping WPA achieve its mission. During my time as CEO of APA, I have witnessed firsthand the incredible potential that robust investment in education and collaboration among psychiatric groups and our partner professions in mental health care can achieve. Mental health knows no borders, and the challenges we face are diverse and complex. However, armed with a comprehensive Action Plan[1,2], we are well-prepared to navigate these challenges and make a lasting impact on the field of psychiatry and mental health worldwide.

My vision for this role is simple: I want to build upon the great foundation of success that the WPA has achieved over the last 50 years, and continue to travel the path of bringing together psychiatric associations across the world to work collaboratively.

I see the WPA as a unifying force for our profession. Our collaborative network of members, partners and components around the world is truly incredible, and one of the great strengths of our Association. I am committed to fostering strong connections, facilitating meaningful discussions, and creating platforms that enable us to share knowledge, expertise and best practices. Through conferences, meetings and cutting-edge communication platforms, we will forge a united global network focused on promoting mental health.

Collaboration both within and outside our profession is key to our success. Partnerships with professional associations and nongovernmental organizations will enable us to deliver comprehensive care and support. By nurturing these relationships, we will foster the interdisciplinary approach to mental health care that is necessary to meet the challenges of our present and future. Collaboration also helps us maximize the impact of our resources and our expertise on a large scale.

We saw the great necessity for collaboration during the COVID-19 pandemic, where resources and personnel were strained to the breaking point even in high-income countries that typically are

not subject to the kind of scarcity that is a fact of life in middle- and low-income countries. This showed that countries such as the US can learn from our colleagues in lower-income countries, and that international collaboration is essential if our profession is to progress and make ourselves ready for the "next COVID".

At the WPA, we need to make sure that psychiatrists all over the world have the tools they need to succeed, and facilitate the exchange of knowledge, ideas and resources, that are the lifeblood of professional collaboration within our discipline. We must ensure that all WPA members have the opportunity and the means to travel to and participate in WPA meetings. It is at those events where lasting partnerships between psychiatrists from all over the world are forged. For some countries, travel to the World Congress is a hardship and, at times, a cost-prohibitive expense. The desire is there from these members, but the WPA needs to make sure that everyone who has the will also has the means to attend, use their vote, and make their mark on the Association.

I hope to start a discussion during my tenure as Secretary General about the value of WPA membership. Are we giving our members what they need and want? And at what cost? If we can answer these questions and demonstrate the great value of WPA membership, then I believe that we will see our Association grow, and become truly reflective of the diverse world we live in.

Committing to innovation in our meetings, publications and educational content is also key to enhancing the value of WPA membership and allowing the further growth of our Association. Education in particular is one of the cornerstones of our mission. The WPA has always done a great job ensuring that our educational materials are accessible, engaging and impactful for our members[3-5]. We can build upon that success by leveraging digital platforms to enhance the experience for our members and disseminate this knowledge on a wider scale.

As the unifier of world psychiatry, the WPA also serves as a vital hub for disseminating news, research and resources to mental health leaders across the globe. As Secretary General, I would like to see us elevate the work and voices of our colleagues in smaller and less well-resourced countries. Each day our colleagues across the globe confront unique challenges in their home communities and come up with innovative and novel ways to meet these challenges. We all have something to learn from one another, and ensuring that all of us have a platform to share what we have learned will only benefit our profession. Accuracy, organization, and ensuring that work is properly attributed is key to this effort and can really enhance the credibility of our published works.

As Secretary General, I believe it is my responsibility to act on the feedback of our members and see this work through to the benefit of the WPA, our Member Societies, and ultimately our patients and profession. I will always rely on the expertise and passion of our members, and I hope that they engage with me as I plan to engage all of them as we work to achieve our shared vision of a more mentally healthy world.

We come from different countries and cultures, but, by our nature, we psychiatrists are all driven to help humankind. Together, we have the resources, knowledge and skills to realize our shared goals. We are all part of one world and one profession, and, if psychiatry can come together and speak with one voice, there is no limit to what we can achieve.

Saul Levin
WPA Secretary General

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Action Plan of the WPA Secretary for Scientific Meetings (2023-2026)

It seems now an appropriate time to reflect upon all what the WPA has achieved regarding scientific meetings during the triennium 2020-2023. From the very beginning of that triennium, the COVID-19 pandemic has disrupted the organization of medical conferences across the entire world. However, the WPA has strived together and advanced in terms of holding high-quality scientific meetings[1,2].

Since 2021, the Association has built up a state-of-the-art platform of virtual scientific events to meet the needs of the global psychiatric community and provide cutting-edge information on recent advances in the mental health field. This has prompted Member Societies to network, continue to build bonds with each other, create new opportunities together, and allow thousands of psychiatrists and other mental health professionals to participate in scientific activities. The WPA has not succumbed to the "pandemic fatigue" and has not detoured its path, but has moved forward. While the world was opening up and the travel restrictions were gradually lifted around the globe, the Association has successfully re-started in-person meetings. We are proud of these accomplishments, and we could have not achieved them without the strong commitment of the organizers of all the events, including Member Societies and Scientific Sections. Also, we are profoundly grateful for the contributions made by the Standing Committee for Scientific Meetings and the Executive Committee in quickly reviewing and approving the proposed meetings, and we acknowledge the continuous, consistent and excellent support of the WPA Secretariat.

During the triennium 2020-2023, a total of 17 WPA scientific meetings have been organized, including four World Congresses (two in Asia/Oceania, one in the Americas, and one in Europe), five Regional Congresses (two in Europe, two in Asia/Oceania, and one in Africa/Middle East), and eight Thematic Congresses (three in Europe, two in Asia/Oceania, one in the Americas, and two in Africa/Middle East)[3,4].

The 2023 World Congress of Psychiatry, under the theme "Psychiatry: Current Knowledge and Perspectives for Action", was successfully held in Vienna, Austria from September 28 to October 1, 2023. The outstanding contributions made by Member Societies and colleagues from all continents helped us immensely to build up the program for the Congress. There was a wide selection of plenary sessions, panels, symposia, special sessions, project sessions, film sessions, and many more. Thousands of psychiatrists and other mental health professionals from across the world got together to witness cutting-edge research in the mental health field. Worldwide active participation in the 2023 World Congress made this a gratifying and memorable event. We most sincerely appreciate the partnership with the local WPA Member Society, the Austrian Society for Psychiatry, Psychotherapy and Psychosomatics.

The WPA is now calling for Member Societies to consider organizing a World Congress, Regional Congress or Thematic Congress in the triennium 2023-2026. All relevant information and documents can be downloaded directly from the WPA website (www.wpanet.org/contact-forms). Please feel free to get in touch with me or with the WPA Secretariat at wpasecretariat@wpanet.org for additional information, including how to plan and proceed with organizing a WPA scientific meeting.

For the triennium 2023-2026, the Action Plan of the WPA Secretary for Scientific Meetings includes: a) working with the Executive Committee and the Secretariat to oversee and coordinate all official WPA scientific meetings, and manage applications for WPA co-sponsored meetings; b) maintaining responsibility for the development of proposals to host the World Congresses of Psychiatry and other WPA scientific meetings in accordance with the Association's policies; c) assisting in all aspects of the organization of World Congresses and other WPA scientific meetings[4].

The WPA goals for scientific meetings in the triennium are: a) increasing the exchange of information between psychiatrists from different parts of the world, including networking, training and mentoring of early career psychiatrists; b) contributing to the education of all categories of mental health workers by providing up-to-date scientific information; c) increasing exchange and collaboration between psychiatrists and their community, professional, government and development partners in all parts of the world; c) boosting collaborative research by bringing together psychiatrists and others interested in research from various parts of the world; d) strengthening links between WPA Member Societies, as well as between the WPA and international and regional organizations in psychiatry; e) increasing the visibility of psychiatry nationally and internationally; f) contributing to WPA finances.

The WPA Standing Committee for Scientific Meetings will continue to implement and improve the tasks and functions of the WPA by: a) further upgrading the scientific quality of WPA scientific meetings with state-of-the-art presentations; b) working in close collaboration with the WPA Secretary for Education and Publications as well as with the WPA Secretary General to provide continuing medical education (CME) credits for WPA meetings; c) working in close collaboration with the WPA Secretary for Finances to improve the financial income and stability of the WPA; d) increasing the number of WPA co-sponsored meetings to involve all the four Regions and 18 Zones of the Association, reaching high-, middle- and low-income countries; e) disseminating WPA information, knowledge, educational programs and expertise to all the WPA Regions; f) focusing on evidence-based knowledge by research- and education-oriented presentations; g) addressing the mental health issues during the post-COVID-19 era.

In summary, as we look back to the past three years, we can state that the WPA has overcome the unprecedented challenges and obstacles of that period. For sure, the WPA will adjust to and enfold whatever the future normalcy/normality we will be facing during the "post-pandemic" era[5]. We trust that the future WPA scientific meetings will reinforce the unique bonds that hold our Member Societies together, and get all these Societies re-energized and re-engaged during the coming years. We are confident that, by embracing these opportunities, taking global action, and working closely together with international collaborations, we shall move forward to maintain our momentum into 2024 and beyond, to continue to define and shape the future in psychiatry[6-8].

Edmond H. Pi
WPA Secretary for Scientific Meetings

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WPA Section on Perinatal Psychiatry and Infant Mental Health: a report on recent activities

The field of perinatal psychiatry and infant mental health bridges adult, parent, infant and child psychiatry, and includes the growing area of developmental psychopathology[1,2]. Human infants are born with potentialities already visible at birth and during the peripartum, when a complex emotional communication takes place with their caregivers. Expanding epigenetic and nurture-nature interaction studies show the importance of intra-uterine gestational development and of what could be called the "second gestational period", i.e., the first postnatal nine months of life, during which an intense modeling of brain structure takes place. This period "delivers" a baby capable of secondary intersubjectivity, expressing emotions able to establish relationships based on the interactive foun-

dations and bricks provided by the environment.

Thus, by the end of the first year of life, attachment patterns are established which will both be built on, and influenced by, developmental milestones. It is therefore not surprising that numerous "environmental" insults, including toxic substances and stressors, can negatively impact both infant and interactive development. Among these negative adversities, chaotic, neglectful or distorted caregiving linked to parental psychopathology has consistently been shown to impinge on the capacity for sensitive coordinated regulation of the infant's stress. Consequently, negative and distorted interactions lacking mutuality and synchrony will lead to disorganized patterns of attachment, setting the stage for a high risk of mental health problems and negative emotional development in the offspring[3].

Unknown to many, the rates of mental health problems in young children are comparable to the 10 to 20% incidence among older children and adolescents[4]. Very early (from birth to 3 years) mental health problems too often go unrecognized and untreated. This lack of awareness is especially concerning as we know how rapid, but also how plastic and reversible, the impact of adverse events on infants' brains can be[5,6]. Effective treatments differ from those in older children, and must involve both the baby and the adult caregiver(s) within the community, which leads us to work jointly with child and adult clinicians, pediatricians, and other health and social services.

Illustrating this wide range of clinical topics, and in line with the WPA Action Plan 2020-2023[7-9], the WPA Section on Perinatal and Infant Mental Health has organized a series of intersectional symposia[10] to create a real dialogue within the wide domain of psychiatry, from infancy to adulthood.

During the COVID-19 pandemic, at the 2021 World Congress of Psychiatry, the Section co-organized with the World Association of Infant Mental Health an inter-organizational symposium entitled "Who is the patient: the complex interplay between parental and infant/toddler psychopathology". The presenters documented the importance of including parent, child and interactive components to understand, diagnose and treat mental health conditions during this period of life.

At the WPA Thematic Conference in Malta, in November 2022, the Section organized two intersectional symposia: one with the Section on Child and Adolescent Psychiatry about the impact of parental mental illnesses on the infant, the child and the adolescent, and the other with the Section on Women's Mental Health. In both symposia, early intervention for all people involved (women, parents, families and infants and children) was highlighted. The WPA President, A. Javed, who attended the symposia, proposed the development of a module about what adult psychiatrists need to know about infant psychiatry, to be made available on the Educational Portal of the WPA website[11]. This will hopefully be possible by 2024.

At the 2023 World Congress of Psychiatry in Vienna, two intersectional symposia have been organized by the Section with the World Association of Infant Mental Health and the WPA Section on Evolutionary Psychiatry.

In January 2023, following two years of "paralysis" due to the pandemic, we have renewed our Section with a growing list of members from around the globe. We hope to be joined by many more!

We wish to emphasize that the main goal of the Section is to allow the infant's voice to be heard by those psychiatrists who treat their parents, as well as by those child and adolescent psychiatrists who tend to believe that child psychiatry and early interventions should start at the age of 6 years. We call for a close collaboration between adult and child psychiatrists in order to better care for and potentially prevent or reduce the burden of mental illness for generations to come. The impact of adverse child events and the importance of perinatal and early infant mental health are our first and foremost target, emphasizing the need for a parent-infant, dyadic, triadic, multi-diadic psychiatric model allowing joint care and prevention for all.

We hope that WPA intersectional symposia will facilitate such a dialogue within and outside psychiatry. Tomorrow's children and future adults deserve that we all do better worldwide.

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Designing and delivering mental health literacy strategies in elite sport

At the 2005 World Congress of Psychiatry in Cairo, the WPA Executive Committee approved the establishment of a new Scientific Section dedicated to Exercise and Sport. This was the first truly global organized sports psychiatry organization, which was followed by the development of the International Society for Sports Psychiatry. In the subsequent twenty years, the attention to physical exercise as an essential component of lifestyle interventions in persons with mental health problems has remained constant

in the WPA[1-8]. At the same time, mental health symptoms and disorders affecting many individuals within elite sport – including athletes, coaches, staff, officials and fans – have been a major focus of the WPA Section on Exercise and Sports Psychiatry[9].

Mental health literacy has become an important strategy to help prevent and address mental health symptoms and disorders in this population. Traditionally, mental health literacy approaches have tried to provide individuals with accurate and up-to-date information to identify mental health symptoms and disorders as well as various forms of treatment; ways to understand, address and prevent personal and public stigma associated with mental health; and steps to shift attitudes and help individuals feel confident to seek mental health support.

Mental health literacy in this area has evolved in recent years, from a position where individuals would receive mental health information so that they could make specific decisions to improve their own health, to a position where sporting organizations need to enact reforms so that they can structure environments which may be conducive to promote mental health for all. This evolution of mental health literacy has meant that a more ecologically focused approach to mental health promotion has occurred, and that a collective spirit is needed for the sustained mental health of all individuals in elite sport. As mental health literacy strategies continue to evolve, it is necessary to understand that they are going to be designed in an evidence-based manner that is culturally competent and rooted in sound pedagogy[10].

Establishing evidence-based practice is a difficult, time consuming, and ever evolving process where constant updates are required. In order for mental health literacy strategies to be designed and delivered to the highest standards possible, they need to engage in a five-step process that helps establish evidence-based practice[11]: question formulation (e.g., what is the focus of the mental health literacy strategy?); information retrieval (e.g., where should mental health information be obtained?); information evaluation (e.g., what evidence should be used to inform the training?); prescription (e.g., how should information be delivered to participants?); and follow-up (e.g., what checks need to be in place to ensure that information was understood by participants?).

Establishing the focus of any mental health literacy strategy is vital to its success. Mental health literacy providers need to consider if the strategy is aimed at individuals within elite sports (e.g., athletes, coaches, officials, fans), medical professionals (e.g., sport psychologists, clinical psychologists, social workers, psychiatrists), or organizations (e.g., sports teams, leagues, federations).

Strategies that target individuals should be designed to provide appropriate and understandable information on mental health symptoms and disorders, known benefits and barriers to treatment, ways to shift negative attitudes to mental health symptoms and disorders as well as treatment, strategies to build confidence in help-seeking behaviours, and pathways to access care easily. Strategies for medical professionals can be designed to provide information on diagnosis (e.g., after on-the-field concussions), treatment options (e.g., psychotherapy, pharmacology, self-care), treatment access (e.g., ways to make appointments), treatment delivery (e.g., online, in-person), treatment goals (e.g., return to play, recovery, retirement), treatment assessment (e.g., adherence to treatment), and ways to work with groups that have been traditionally marginalized in sport (e.g., lesbian, gay, bisexual and transgender people). Strategies for organizations have an environmental focus on regulations and policies to ensure that information on and services for mental health symptoms and disorders are established, available, and easy to access. Additionally, the culture of the sport should be examined for ways to reduce stress as well as specific symptoms and disorders that may be prevalent in that environment.

Regardless of target audience, information presented to individuals must be of the highest quality, and strategies to enhance information retrieval and evaluation need to be considered. In essence, the best current and available information is often found within meta-analyses and systematic reviews. These are often based on randomized controlled trials and offer the highest level or gold standard of evidence. Scoping and narrative reviews may lack systematic protocols and therefore may present information in a biased manner. Quasi-experimental studies, cohort studies, case-controlled studies, case studies, editorials, expert opinions, and anecdotes offer progressively weaker evidence. Caution should be used when incorporating these forms of evidence, with limited research and quality expressed transparently to participants.

The delivery of content to participants is also of tremendous importance in any mental health literacy strategy, in order for information to be understood, retained, and ultimately used in the future[12]. Mental health literacy strategies in this area must be designed in a theoretically and pedagogically sound manner, where high-quality information is distilled, translated and ultimately disseminated. The content of any mental health literacy strategy must shift attitudes and strengthen self-efficacy, along with a host of other psychological learning factors to modify behaviours. Pedagogically, employing a constructivist approach allows participants to be active in their learning process as information is used to create knowledge that will be used to inform their practice. Materials used in mental health literacy strategies should be convenient, engaging, visually stimulating, and help reinforce the participants' purpose and objectives. Appropriate follow-up with participants is essential to examine how information was understood and used. Following up with participants provides further opportunities to modify mental health literacy strategies in the future.

As mental health literacy strategies in elite sport continue to evolve, so too must strategies that underpin their success. High-quality evidence, along with conceptual and theoretical models of appropriate information delivery, will need to be increasingly used in the future.

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WPA Volunteering Programme: lessons learnt so far

Capacity building has been one of the priorities of the WPA Action Plan 2020-2023[1-3]. In order for the Association's efforts to be more effective, Working Groups started formulating plans, and pilot projects were established[4-11]. The WPA Working Group on Volunteering was organized to share and enhance clinical knowledge and skills for improved patient care[12-14].

This Working Group is made up of psychiatrists with experience in organizing and running volunteer education activities, as well as a representative of families of persons with lived experience of mental health conditions. The Group has been established to enhance training opportunities for WPA Member Societies in countries that would like assistance from volunteer trainers from other Societies.

The WPA Volunteering Programme aims to link interested WPA Member Societies. Linking the expertise and experience of volunteer trainers can contribute to the development of skills, knowledge and confidence of those psychiatrists and their trainees. Also, mental health professionals who have less access to training opportunities and education can take part.

Although the WPA Volunteering Programme was originally expected to be implemented locally and in person, the circumstances surrounding the COVID-19 pandemic have significantly impacted these plans[12]. Therefore, the activities have focused on the implementation of volunteering work in various countries through support for online teaching. The Working Group members have now gained considerable experience in preparing and running online volunteer training programmes. Pilot projects have taken place in Mexico[13] and Pakistan[15]. Work is currently underway to prepare volunteer projects in Libya, Honduras and Guatemala[14]. Many useful lessons have been learnt from these pilot projects. One of these lessons is that transcultural psychiatry is a pleonasm: all psychiatry is transcultural.

Before starting a volunteering programme, it is important to identify and agree on the purpose and aims of the programme within the structure of psychiatry education in the host country. This can be done by establishing contact with stakeholders who will be involved in preparing and delivering the training. This process builds a training team as well as a partnership between host and volunteer professionals. Moreover, it delivers information about the cultural and educational background of the country.

Local resources and systems which will influence the impact and sustainability of a project include national mental health policy, current training resources and styles, and local collaborators. Support from senior colleagues and other stakeholders from the host country (top-down support) helps setting up the project and smooths the way through possible obstacles. It is also useful to know about the available international aid in teaching and service developments (e.g., World Health Organization, United Nations) which can be used in the programme.

Experience has shown that tailoring to the specific needs instead of offering off-the-shelf prepared lectures increases the interest of participants. Therefore, volunteers need to be able to organize a flexible training programme, be culturally aware, enjoy team work, be willing to give time to preparation and work with colleagues from different backgrounds. It is important to strike a balance between training that is directly useful in clinical practice and having an impact on improving the local quality/accessibility of mental health care. Trainers need to be prepared for the experience that volunteering can be challenging as well as rewarding.

Despite the seeming role of the volunteer as a leader in the Volunteering Programme, it is recommended that host country professionals actually lead the programme. They know what is needed and what might work within their culture and resources. Volunteers are invited guests. It is highly recommended to volunteers to be gracious and humble. Our aspiration is to have service users and carers involved in the project design and roll out. Language is critical in making training understandable and useful, both for practical and cultural reasons. Even if trainers speak in English, case discussions and role plays can be conducted in the local language. Proficiency in English is usually not equal amongst participants.

An interim assessment during the training, questioning which methods are successful and which are not, helps to adapt to local (cultural) specificities when needed. Interactive training is usually welcome, and there are numerous books, articles and manuals available online for participants to read (as suggested by trainers) before, between and after sessions. It is recommended that training offers a focus on human rights, lived experience involvement, and alternatives to coercion, in line with the global priorities and values of the WPA. It is preferable for the trainees to have supervision/mentoring.

Following the completion of the training, it is important to evaluate its positive and negative aspects. After a successful course, it is essential not to hesitate to review the training material and refresh courses for future work. A final evaluation of the course is important not only for the volunteer, but also for the host Society, to ensure sustainable benefits and ongoing plans.

Volunteering is a professional activity with the same demands of evidence-based practices: evaluations, feedback and courteous behaviour. Experience suggests that volunteering is a win-win endeavor, as all people involved learn, usually in many areas.

This includes clinical, academic and teaching skills. Some volunteers report that they had life changing experiences.

The WPA Volunteering platform is now available to all WPA Member Societies. Information is provided on the official WPA webpage (https://www.wpanet.org/wg-on-volunteering). Member Societies who would like to receive assistance with training in any area of psychiatry are welcome to submit a request for such assistance, discuss their needs, and understand how the Working Group can link them with suitable volunteer trainers. Member organizations with psychiatrists who would like to offer their skills and time on a voluntary basis are also invited to join the WPA Volunteering Programme.

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