World Psychiatry

OFFICIAL JOURNAL OF THE WORLD PSYCHIATRIC ASSOCIATION (WPA)

Volume 24, Number 1 *February 2025*

WILEY NO. 1 OF PSYCHIATRIC JOURNALS FOR IMPACT FACTOR ISSN 1723-8617

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World Psychiatry

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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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Promoting healthy digital device usage: recommendations for youth and parents

Young people's usage of digital devices is currently a central topic of interest for researchers, clinicians and the general public, particularly with regards to the impact of social media on adolescents' mental health. Notably, the duration of screen time is not the primary determinant of mental health outcomes[1,2]. Rather, the "quality" of an individual's device usage patterns, experiences and interactions online, and how they correlate with other lifestyle variables (e.g., sedentary time and sleep) appear to matter most[1,3,4].

Other than avoiding the more clear-cut "online harms" (e.g., addictive behaviors, cyberbullying, and online blackmail or exploitation), there is a lack of consensus on how youth can improve the "quality" of their online time. This is in part because the details of what constitutes "healthy" device usage are unclear, and likely differ with regards to sociodemographic factors[1]. Here we sought to produce a simplified set of recommended actions to promote adolescents' healthy digital device usage.

We assembled a multidisciplinary team of individuals with expertise across child and adolescent mental health, social media research, behavior change interventions, and public health. We then identified and reviewed recently published guideline/recommendation articles, online resources and reports from independent think tanks – particularly those that included feedback from young people themselves. We checked these resources for *directly actionable advice*, rather than general principles on healthy usage patterns. We then considered the recommended actions from such documents alongside the underlying scientific evidence and the team's experience, in order to put forward the *top three tips* for healthy device usage in adolescents. We also produced a further set of recommendations for parents who wish to implement such changes in their family units.

The *top three tips* for adolescents are the following:

- *Out of sight, out of mind*. The implementation of tech-free zones and times is featured consistently across existing guidelines/recommendations[4-6], empirical studies[7,8], and youth feedback[9]. The most common recommendation is aiming for at least *one hour of tech-free time before bed*, to mentally disconnect from the online world and promote adequate, restful sleep[4-6]. Designating bedrooms as tech-free zones at night and setting up device charging stations in other locations may help youngsters build these habits. Many sources also recommend keeping family mealtimes as tech-free zones[6,8]. The adoption of such breaks may improve mental health outcomes [2,8,9]. However, to increase the chance of success, they must be agreed upon and adhered to as a family, rather than imposed by parents[7].
- *Use device features to control usage*. Digital devices, particularly smartphones, increasingly offer a range of technological features for tracking and managing one's usage. There are specialist apps through which the user can customize restrictions around content access and usage durations. The default features in iOS and Android systems now readily enable screen time tracking, timing (with reminders), notification blocking, and privacy controls. So far, the use of screen time reminders alone appears to be ineffective, largely because the user can dismiss these easily when immersed in device usage[6,7]. Nonetheless, the "Do Not Disturb" setting (which blocks notifications unless they are specifically allowed from family or friends) is emerging as an effective technological strategy to reduce distraction overall[6,7], and "Notifications" settings can be used to tackle more specific bad habits by preventing alerts from individual apps[7]. Thus, users should become familiar with these features and learn to use them appropriately[5,7,9].
- *Replace rather than restrict*. One of the primary downsides of digital device usage is the extent to which online time can detract from healthy behaviors, such as regular physical activity, adequate sleep, and real-world socialization[1,4]. Efforts to reduce the use of devices during the day will be more acceptable, enjoyable and effective when the user focuses on replacing screen time with engaging, healthy activities[1,5,9], ideally performed with friends and/or family members to also enhance socio-emotional skill acquisition. Alongside this, the physical and mental health outcomes of device usage can be improved by replacing some of the time spent passively consuming social media with intentional engagement in "healthier" online activities. This might include sourcing out (or even creating) content on goal-based behaviors that are in keeping with the user's own interests, for example fitness or mindfulness, or interacting positively with supportive social networks of friends and associates online[1,2,4].

The recommendations for parents are the following:

- *Agree on a plan*. Many professional bodies and independent think tanks recommend that families discuss the best ways to manage digital device usage and put the results "in writing" as some form of agreement or plan[5,6,9]. Ideally, this text should encompass agreed tech-free times/zones, screen time replacement activities, boundaries on app/website usage, and plans for raising concerns or discussing experiences regarding adverse interactions or content in the online world[5,9]. For maximum acceptability, sustainability and effectiveness, the plan should: a) be created with youth input[4,5,9]; b) be reviewed regularly, with adherence barriers discussed openly and non-punitively; and c) remain fluid, to account for young people's development and new technologies or trends[2,4,6].
- *Become an example*. Parents who set a good example of healthy device usage form a central aspect of promoting these behaviors in youngsters[5,9]. Recent data suggest that healthy device usage among parents is strongly associated with positive out-

comes for their children's screen time use as well as mental health outcomes[2,8]. Although the exact rules agreed regarding adolescents' use of screens may not be directly applicable to their parents (e.g., due to home-office notebook usage), adherence to the agreed tech-free zones during family time will promote adoption of such habits, while also fostering opportunities for deeper interactions and conversations as a family[2,6]. Along with these benefits, the process of modelling these behaviors may incidentally improve parents' own device usage, time use, and consequently mental health and well-being[1].

- *Communicate often and openly*. Maintaining a non-judgemental frame and encouraging a two-way conversation about the content and quantity of online time is essential for: a) supporting the adoption of healthy device usage in young people[4,5], and b) creating well-functioning pathways for identifying and managing more serious threats that may arise, such as cyberbullying or online exploitation[6]. It should be noticed that, while some parental limit-setting is acceptable and beneficial to young people[8,9], adopting a strict, authoritarian approach may be damaging to family dynamics, reducing youth's well-being[6,9], and increasing the likelihood of media usage outside of agreed times and types[2].

As digital device usage has been increasing worldwide, the impact on youth mental health has emerged as a central concern. We sought to produce a set of best-practice approaches, on the basis of available evidence and guidelines, for adolescents and their parents looking to improve their device usage patterns. Ultimately, however, managing this issue at a societal level will require a whole system approach, involving partnerships between governments, social media companies, and health care organizations. To propel this, more high-quality research is urgently needed to determine what actions policy makers, clinicians and the public can take, including the perspectives of young people themselves.

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DOI:10.1002/wps.21261

Dispelling "pleasing myths" about the integration of ecological momentary assessment and intervention into clinical research and practice

There is a long and rich scientific and clinical history regarding the utility of ambulatory assessments – including relatively intensive strategies such as ecological momentary assessment (EMA) – to capture feelings, thoughts, behaviors, and context of everyday life[1,2].

EMA approaches can be beneficial in many ways, notably by providing a glimpse into everyday life that is missed in clinical appointments (i.e., ecological validity), characterizing processes that occur over time, providing information on the environments and contexts experienced by a patient, and reducing recall and reporting biases that can occur in clinic.

More recently, coupled with tremendous developments in mobile technology, there has been increasing attention on how to implement intervention approaches using ambulatory technology, particularly delivering micro-intervention content at moments of identified need (ecological momentary intervention, EMI)[3].

Enthusiasm for these approaches continues to increase. Yet, the actual evidence of significant benefit is still somewhat lacking. Herein we discuss several assumptions often held about EMA/EMI ("pleasing myths"), explaining why and how they need to be dispelled.

A first "pleasing myth" is that EMA will just "work" simply

through its application – that is, EMA will provide novel insight into characterizing patients' everyday experiences, as the methods are fancy, innovative and mobile. Unfortunately, the benefits of EMA do not emerge simply from the technology; rather, care must be taken to connect the design and implementation to the research and/or clinical goals. For example, there is no agreed upon "generic" assessment battery for EMA. The content of what is assessed must be derived from the most relevant constructs and contexts in a patient's everyday life, and reflect the relevant dynamic processes and mechanisms to be characterized and/or intervened upon.

A second "pleasing myth" is that EMI will produce benefit by providing the right help at the right moment. Actually, even presuming careful design of assessment content, there are many unanswered questions on the development and application of EMI (and subsequent approaches, such as just-in-time adaptive interventions[3,4]). EMIs are not "full" interventions, but brief, low-burden, micro-intervention elements/components in everyday life, often delivered through smartphones or other devices, and increasingly reflecting mechanisms-focused approaches (i.e., targeting mechanistic processes). Although there are examples of identifying personalized moments of risk, such as intense craving in the context of substance use, we know relatively little about what parameters we can reliably capture and which are psychologically or behaviorally relevant. Moreover, even when successful at identifying a risk moment (e.g., acute depressive symptoms, high interpersonal anger), we often lack an empirical basis regarding the best time point to intervene (e.g., is intervening at the highest risk moment appropriate, or is it preferable to intervene in advance and/or facilitate recovery processes?), as well as what (micro-) intervention content is most efficacious at improving the targeted process(es).

A third "pleasing myth" is that mobile applications ("apps") and mHealth are "cool" and engaging, so patients will love to use them. Unfortunately, the evidence suggests that just the opposite is true: most apps, including those targeting mental health and behavior change, are used infrequently and often abandoned within a few weeks or months. Given that most EMA/EMI approaches are reliant upon active reporting (e.g., responding to brief self-report items), efficiency in the design of assessment content is essential, as it relates strongly to patient burden and the capacity to obtain high-quality data and good compliance. That said, carefully designed EMA studies have demonstrated the capacity to retain patients with good reporting compliance over long periods of time (months for ongoing EMA studies, and even several years using episodic EMA sampling in measurement burst designs).

A fourth "pleasing myth" is that it is easy to implement EMA/EMI, as one can just get a student or hire someone to quickly program an app. Actually, although the tools and expertise for app development continue to improve, there are many challenges to developing and implementing a novel EMA/EMI app system. Most notably, if intended as part of clinical care and/or research, it is vital that the app has excellent user features, which requires careful development and testing (ideally including the target population). Apps have to be robust to implementation details, operating systems, and device characteristics. Moreover, these features of apps have to be maintained over time and respond to any relevant changes. Finally, when being used in clinical contexts, it is essential that the apps follow medical device law regulation (which may vary depending on the context of implementation). Although these issues are tractable (particularly through collaboration with academic/industry partners), they are not trivial and should be carefully considered prior to implementing EMA/EMI.

A fifth "pleasing myth" is that all we need is the EMA/EMI app to address all problems of an individual patient, and we can reduce or remove the need for clinical involvement. Here, too, the evidence does not support the premise: the use of an app by itself (e.g., for behavior change, or to address mental health needs) often does not result in significant and/or sustained improvements. Psychological and behavioral changes are difficult to achieve and sustain, and likely require comprehensive approaches that include integrated systems of care[5]. In such models, EMA/EMI approaches can be used as one element of care, with EMA helping to provide a real-life psycho-behavioral phenotype of each patient, and EMI helping to extend change/intervention processes into everyday life, facilitating the awareness and practice of applying such processes outside of the clinic.

We believe that persistent and incorrect assumptions ("pleasing myths") about EMA/EMI have hindered them from realizing their full potential. We need to dispel these myths and facilitate continued and expanded efforts to efficiently leverage the capabilities of patient-centered ambulatory assessment and intervention.

Considering the many benefits (real life, real time, help in the moment), we remain enthusiastic about integrating EMA/EMI into clinical research and practice[6]. Some particular areas in which EMA/EMI can help revolutionize treatment and research include the potential for treatment delivery plans to be dynamically adapted over time (e.g., in response to need, to identifying what works for a given person, to changes in clinical and/or experiential functioning); high scalability (although difficult to develop, once developed they can be widely disseminated at low cost as a supplemental/adjuvant treatment); inclusion of environmental sensors in care; and efficient provision of coherent summaries (e.g., visualizations) of real-world everyday life data to patients, providers and/or others, to facilitate care and promote well-being.

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DOI:10.1002/wps.21262

The current clinical approach to feeding and eating disorders aimed to increase personalization of management

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Feeding and eating disorders (FEDs) are a heterogeneous grouping of disorders at the mind-body interface, with typical onset from childhood into emerging adulthood. They occur along a spectrum of disordered eating and compensatory weight management behaviors, and from low to high body weight. Psychiatric comorbidities are the norm. In contrast to other major psychiatric disorders, first-line treatments for FEDs are mainly psychological and/or nutrition-focused, with medications playing a minor adjunctive role. Patients, carers and clinicians all have identified personalization of treatment as a priority. Yet, for all FEDs, the evidence base supporting this personalization is limited. Importantly, disordered eating and related behaviors can have serious physical consequences and may put the patient's life at risk. In these cases, immediate safety and risk management considerations may at least for a period need to be prioritized over other efforts at personalization of care. This paper systematically reviews several key domains that may be relevant to the characterization of the individual patient with a FED aimed at personalization of management. These domains include symptom profile, clinical subtypes, severity, clinical staging, physical complications and consequences, antecedent and concomitant psychiatric conditions, social functioning and quality of life, neurocognition, social cognition and emotion, dysfunctional cognitive schemata, personality traits, family history, early environmental exposures, recent environmental exposures, stigma, and protective factors. Where possible, validated assessment measures for use in clinical practice are identified. The limitations of the current evidence are pointed out, and possible directions for future research are highlighted. These also include novel and emerging approaches aimed at providing more fine-grained and sophisticated ways to personalize treatment of FEDs, such as those that utilize neurobiological markers. We additionally outline remote measurement technologies designed to delineate patients' illness and recovery trajectories and facilitate development of novel intervention approaches.

Key words: Feeding and eating disorders, clinical characterization, personalization of management, anorexia nervosa, bulimia nervosa, binge eating disorder, OSFED, ARFID, precision medicine

(World Psychiatry 2025;24:4–31)

Feeding and eating disorders (FEDs) are enshrined in both the ICD-11[1] and DSM-5[2] classifications as a single grouping, following the merger of two previously distinct sections, feeding disorders and eating disorders (EDs). This recognizes the expression of feeding and eating difficulties in a continuum across the lifespan.

The term FEDs encompasses a broad group of disorders with both distinct and shared phenomenological features, etiological factors and treatment responses[3-5]. They include anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED), other specified feeding or eating disorder (OSFED), avoidant restrictive food intake disorder (ARFID), rumination (or rumination-regurgitation) disorder, and pica[4].

These are common and disabling disorders occurring in people of all genders and cultures. Typical onset spans from childhood to early adulthood, a developmentally sensitive time, with around 15% of FEDs developing by age 14, around 50% by age 18, over 80% by age 25, and practically no new onsets occurring after the age of 30[6].

Core to all FEDs is a disturbance of eating behavior, often accompanied by various pathological compensatory behaviors (e.g., driven exercise, self-induced vomiting, misuse of medications to lose weight). These behavioral features are motivated by weight, shape and appearance concerns, or other (e.g., health-related) concerns about food, eating and weight.

Psychiatric comorbidities (e.g., mood and anxiety disorders) are common and contribute to adverse outcomes[3-5]. Mortality is raised, with AN having the highest mortality of all mental disorders[7]. A recent meta-analysis of years of potential life lost (YPLL) found that EDs have the second highest YPLL (16.64 years) of all psychiatric disorders[8]. Moreover, one in every two to three people with BN or BED are obese or will become obese, with potentially serious metabolic complications.

Much of the burden of FEDs has remained hidden for a long time. A recent extension of the Global Burden of Disease (GBD) study demonstrated that including BED and OSFED in the analysis, in addition to AN and BN, resulted in a revised estimate of the

disease burden, which more than doubled[9]. Burden for EDs – including BED and OSFED – has been estimated at 85.9 disability-adjusted life years (DALYs) per 100,000 person years[9]. This is around 5% of the DALYs per 100,000 person years for the twelve mental disorders considered by the GBD study in 2019[10]. These revised figures are still likely to be an underestimate, as ARFID, rumination disorder and pica were not included[11].

Numerous systematic reviews and meta-analyses have reported a substantial increase in ED symptoms in the general population[12], as well as significant increases in severity, distress, hospitalizations and demand for services across different FED diagnoses[13-16], during the COVID-19 pandemic.

In contrast to other severe psychiatric disorders, first-line treatments for FEDs are predominantly psychological. This means that a degree of personalization is typically built in via individual case formulations[17]. ED recovery rates are sub-optimal, with approximately 50% of patients recovering with best available evidence-based treatments, and 20-30% developing long-term treatment-refractory illnesses[18].

Personalization and precision medicine approaches may allow for improved outcomes, as has been found in other areas of mental health[19], but evidence related to FEDs remains limited. Notably, in studies of psychological therapies, possible mediators and mechanisms of treatments are not always defined or assessed in the same way across trials.

Patients, carers, clinicians and researchers are united in seeing the offer of personalized treatments and care as an important indicator of the quality of services for FEDs[20] and as a priority focus for future research[21]. We use Deisenhofer et al's definition of personalization[22], describing it as anything that a clinician does to "select, adapt or adjust treatment to the individual with the goal of improving outcomes". Precision approaches, which are "algorithmic, quantitative and empirically derived" are seen as a distinct part of personalization[22].

Advances in bio-technologies (e.g., neuroimaging, multi-omics) aim to facilitate personalized medicine and precision approaches to psychiatric disorders in general and FEDs specifically[23-25], via multimodal assessments of very large data sets and use of advances in computing, artificial intelligence and machine learning for data management and analysis[26]. Alternative approaches to personalization focusing on individually tailored person-specific models[27-29] are also emerging in FEDs. However, these advances are not mature yet for application in ordinary practice.

The present paper aims to review systematically the key domains that are usually considered when personalizing treatment for mental disorders[30-33], describing their current status as far as FEDs are concerned. Gaps in current knowledge are highlighted, and potential directions for the future of personalization are outlined.

We cover FEDs across the entire age spectrum. As appropriate, we mention issues around race, culture, gender and social disadvantages. The relevant evidence base is much larger for AN, BN, BED and OSFED, compared to ARFID, pica and rumination disorder. Therefore, in many sections of this paper, the term EDs has been retained to reflect that the available evidence focuses on these disorders rather than covering the broad group of FEDs.

SYMPTOM PROFILES

FEDs are characterized by cognitive, behavioral and physical symptoms that cut across diagnostic categories and can be conceptualized as occurring on a continuum.

Cognitive symptoms include over-evaluation of eating, weight and shape as well as their control (basing one's self-worth primarily or entirely on these domains), fear of weight gain or fatness, and more general body image disturbances. The latter may include body image distortion (e.g., seeing oneself as larger than objective size) and body image concerns (wanting to be of a different shape or size). These symptoms can present in all ED diagnoses and may occur at less extreme levels in individuals without EDs.

In cognitive-behavioral models, over-evaluation of eating, weight and shape is seen as the "core psychopathology" of EDs[34]. In later stages of illness, chronic stress from starvation and social isolation may lead to depression, neuroadaptation and neuroprogression. This is described in the cognitive-interpersonal model of AN[35], which includes the inter- and intra-personal consequences of isolation and stress that can accumulate with enduring illness[36].

Behavioral FED symptoms include dietary restraint (efforts to eat less or follow dietary rules), dietary restriction (actual under-eating), fasting, both objective and subjective binge eating (feeling out of control of one's eating with/without eating an objectively large amount of food), purging (self-induced vomiting or misuse of laxatives or medications, including insulin in those with type 1 diabetes mellitus), and excessive or compulsive exercise. Physical manifestations of these symptoms can include weight loss (with or without objective underweight), weight fluctuations or gain, and a range of physical health problems associated with undernutrition, binge eating and purging.

Cognitive and behavioral symptoms are heterogeneous within and across FED diagnoses. Latent class and trajectory analyses have identified clusters of FED symptoms which partially map onto current diagnostic categories. These clusters include individuals who are underweight and report fear of weight gain; who are underweight and do not report fear of weight gain; who have binge eating without purging (often co-occurring with overweight/obesity); who have binge eating and purging together; and who have dietary restriction and body image concerns without being underweight[37-39]. Binge eating and purging commonly cluster alongside depressive symptoms, deliberate self-harm, and/or substance misuse[40].

Symptom clusters may vary by developmental stage, and interconnectivity between symptoms may increase with age and illness duration[41]. Thus, personalized care may be supported by considering developmental and illness stage alongside careful assessment of the specific cognitive and behavioral FED symptoms that the individual is presenting.

There is some preliminary evidence that targeting treatment at an individual's particular constellation of symptoms is associated with good outcomes[29], suggesting that this may be a prom-

ising model for personalization of management. Work in this area is beginning to use idiographic network analysis[28,29] and causal discovery analysis[27] to assess an individual's real time data – e.g., obtained via ecological momentary assessment. However, the clinical utility of these approaches remains to be established, and some authors have suggested that, in order to achieve truly person-centred clinical care, these precision approaches need to be supplemented with additional "ecosocial" components including developmental, cultural, social and experiential dimensions[26].

At present, clinicians can be encouraged to carefully assess individual symptom profiles in order to try and personalize available evidence-based treatments. Indeed, treatments such as cognitive behavioral therapy (CBT-ED, sometimes also referred to as enhanced CBT, CBT-E) and the Maudsley model of anorexia nervosa treatment for adults (MANTRA) already recommend a personalized formulation to guide application of the treatment protocol. It is also worth emphasizing that, across different FED diagnoses and treatments, early response to treatment, within 4-6 sessions, is the most robust predictor of overall treatment outcome[42]. Thus, regular monitoring of symptoms may help with designing and tailoring treatment and lead to improved outcomes.

The Eating Disorder Examination (EDE)[43] is a semi-structured interview assessing cognitive and behavioral FED symptoms over the past 28 days. It generates four subscale scores with a rating from 0 to 6: restraint, eating concern, weight concern, and shape concern. It has been adapted for use in children aged 6 and over (Child EDE). It is available in English, Chinese, Croatian, Dutch, Finnish, German, Hebrew, Italian, Japanese, Korean, Malay, Norwegian, Persian, Portuguese, Spanish and Swedish. A 28-item self-report questionnaire (EDE-Q)[43], adapted from the EDE and generating the same subscales, has been validated for use in adults and adolescents, and is available in the same languages.

The Eating Pathology Symptoms Inventory - Clinician Rated Version (EPSI-CRV)[44] is a semi-structured interview assessing cognitive and behavioral FED symptoms over the past three months. It generates eight subscale scores: body dissatisfaction, binge eating, cognitive restraint, excessive exercise, restricting, purging, muscle building, and negative attitudes towards obesity. A 45-item self-report version (EPSI) is also available in English and Chinese.

Detection of FEDs in cisgender men, as well as in gay and bisexual men, can be hindered by assessment models being developed in relation to cisgender women. The EPSI is an example of a measure that performs comparably across cisgender men and women, as well as in gay and bisexual men. In fact, it includes subscales focused on excessive exercise, muscle building and negative attitudes towards obesity, as well as the more typical areas of body dissatisfaction, dietary restraint, binge eating, and purging.

The EDE/EDE-Q and the EPSI/EPSI-CRV are less well suited to assessing symptoms of ARFID, while the Nine Item Avoidant/Restrictive Food Intake Disorder Screen (NIAS)[45] can be used for this purpose. The NIAS has three subscales (picky eating, low appetite, fear of eating) and is able to distinguish between individuals with ARFID, with other FEDs, and without ED symptoms.

CLINICAL SUBTYPES

In both the ICD-11 and DSM-5, the FED grouping includes AN, BN, BED, OSFED, ARFID, pica, and rumination disorder. The DSM-5 identifies five OSFED sub-categories: atypical AN, sub-threshold BN and BED, purging disorder (PD), and night eating syndrome. These diagnoses can be made using the already mentioned EDE and EPSI interviews, as well as the Eating Disorder Assessment for DSM-5 (EDA-5)[46], a semi-structured interview which generates DSM-5 diagnoses but no subscale scores. Movement between FED diagnoses is common, particularly from AN to BN and between these diagnoses and OSFED[18]. Movement from BED to atypical AN may occur with bariatric surgery and weight loss medications.

AN is historically recognized by its hallmark features of someone with an emaciated body who eats very little but does not think she/he is thin (or thin enough) nor perceives any risk related to her/his physical condition. The diagnosis of AN has been broadened in current classifications by: a) "relaxing" the definition of low weight, b) excluding the requirement of amenorrhoea, and c) expanding the criteria "fear of weight gain/excessive preoccupation with weight and shape".

A significantly low body weight for height, age, sex, developmental stage or weight history is required by the DSM-5 and ICD-11 for a diagnosis of AN. The assessment of weight status by body mass index (BMI) has shown some limitations[47]. Nevertheless, according to the ICD-11[1], a significantly low body weight means a BMI lower than 18.5 kg/m^2 for adults and a BMI-for-age lower than the 5th percentile for children and adolescents. Importantly, children and adolescents above the 5th BMI percentile may be considered underweight if failing to maintain their personal growth trajectory. Rate of weight loss is also relevant, and can substitute the underweight level if it occurs rapidly (e.g., >20% of total body weight within 6 months).

Fear of weight gain and drive for thinness are considered the "core" features of AN that sustain eating and weight-related behaviors. However, they are not always explicitly stated by the patients. Current classifications allow for indirect manifestations of these cognitive features based on collateral reporting (by family members/carers) or the presence of behaviors such as dieting, calorie counting, or body checking. The above-mentioned semi-structured interview or questionnaire measures can help with thoroughly exploring such behaviors.

AN specifiers have been kept in the DSM-5 and ICD-11. They include the restricting pattern/type and the binge-purge pattern/type (in which regular binge eating and/or purging are present alongside restrictive eating). Significant crossover with progression of the disorder (especially from the restricting type to the binge-purge type or to BN) limits the predictive validity of these specifiers in terms of course and outcome[48,49].

International treatment guidelines for AN[50,51] emphasize the importance of multidisciplinary care (e.g., medical, nutritional, psychological); weight restoration; psychoeducation; and the involvement of family members/carers when appropriate. In adults, several outpatient psychological therapies are recommended as

first-line interventions: CBT-ED, MANTRA, specialist supportive clinical management (SSCM), and focal psychodynamic therapy (FPT). Outcomes across these different treatments seem to be similar[52] and there is limited evidence on how to choose between them.

Each of these treatments is protocolized but also personalized. CBT-ED and MANTRA are guided by a personalized formulation, whereas SSCM encourages personalized assessment of "key problems" and psychoeducation, and FPT is guided by patient-centred focal hypotheses regarding the individual's AN. Clinicians need to use their judgement and patient input to make personalization choices, but there has been little research on how these decisions are made and how they relate to treatment outcomes. In contrast, "therapist drift" (i.e., clinicians failing to deliver evidence-based treatments despite having the necessary tools) is recognized as common in the management of FEDs[53]. Until further data are available to guide precision medicine approaches, personalization within evidence-based treatment guidelines is an important principle for all FEDs ("flexibility within fidelity").

For children and young people (<18 years) with AN, AN-focused family therapy (FT-AN, sometimes also referred to as family-based therapy, FBT) is recommended as the first-line outpatient option. This can be delivered as a single-family or multi-family intervention, and with children/young people seen with or separately to their family members/carers. Briefer formats of FBT seem to work well for most, except for single-parent families or if the patient has obsessive-compulsive disorder (OCD) symptoms[54].

In families with high expressed emotion – defined as hostility, criticism and emotional overinvolvement – outcomes are likely to be poorer, and separate therapy for parents and patients or adjunctive parental emotion coaching may be helpful[55,56]. Expressed emotion can be measured in clinical contexts using the Levels of Expressed Emotion Scale[57].

If FT-AN is not acceptable or effective, alternative outpatient therapies include CBT-ED or adolescent-focused psychotherapy for AN. Both are guided by a personalized formulation and encourage family involvement calibrated to the individual and their family.

While outpatient psychological therapy is recommended as the first-line treatment approach for AN, some individuals will require more intensive treatment. Decisions about when to step up to day-service, inpatient or residential care should be guided by medical and psychiatric risk, and whether outpatient therapy is effective over the first 4-6 weeks of treatment. Thus, again, regular symptom monitoring is an important component of personalizing care. There is limited evidence to support psychotropic medications in the treatment of AN, although atypical antipsychotics such as olanzapine are sometimes used to facilitate weight gain.

In BN, the characteristic behavioral features are regular binge eating combined with inappropriate compensatory behaviors to prevent weight gain. In the DSM-5, binge eating is defined by: a) eating an amount of food, within a limited time period (e.g., two hours), that is larger than most people would eat under the same circumstances; and b) a sense of loss of control over eating. This definition of "objective" binge eating can be distinguished from "subjective" binges, which involve loss of control but not an objectively large amount of food.

In the ICD-11, binge eating is defined as loss of control over eating and eating notably more or differently than usual, and so may include eating normal portions of foods that are usually avoided. This represents a major difference in the definition of BN (and BED) amongst current classifications: objectively large binges are required by the DSM-5, while either objective or subjective binges are accepted in the ICD-11. In practice, both types of binges are reported by people with BN and BED, and similar levels of eating and general psychopathology are found across individuals reporting objective and subjective binges[58,59].

As in AN, BN involves excessive preoccupation with body weight and/or shape and an undue influence of these aspects on self-evaluation. This is linked to recurrent inappropriate weight-control methods to (try and) compensate for binge eating. Compensatory behaviors may vary or be combined, but self-induced vomiting is the most common. Both purging and non-purging methods can contribute to a BN diagnosis, with non-purging behaviors including fasting, extreme dietary restriction, and extreme exercise. Unlike the DSM-5, the ICD-11 requires "marked distress" related to the binge-purge cycle as an essential feature of BN.

Frequencies for binge eating and compensatory methods have been reduced to a minimum of once a week over three months in the DSM-5 (over one month in the ICD-11), versus twice a week in earlier classifications. The once-weekly frequency shows clinical validity[60,61], and has reduced the number of individuals given an unspecified/other diagnosis. BN is distinguished from AN-binge/purge subtype as underweight is not present[1]. BN occurs across healthy weight, overweight and obesity ranges, although premorbid overweight/obesity and weight suppression have been found to increase risk[62-65].

Treatment guidelines recommend guided self-help as the first-line treatment for BN in adults. This typically involves brief supportive sessions with a therapist "coach" to facilitate application of CBT self-help material. The self-help material may be digital or book-based, and supportive sessions may be in person, online or via telephone.

If this approach is unacceptable, contraindicated or does not result in symptom reduction in the first 4 weeks, individual or group CBT-ED should be considered, guided by a personalized formulation. Fluoxetine continues to be recommended by the American Psychiatric Association (APA)'s guidelines[50] in combination with CBT-ED, and may improve outcomes from CBT-ED.

For children and young people with BN, BN-focused family therapy (FT-BN) is recommended as the first-line outpatient option. If unacceptable, contraindicated or ineffective, CBT-ED can be offered, and would again be guided by a personalized formulation and family involvement calibrated to the individual and her/his family.

Interpersonal therapy and dialectical behavior therapy have also been used successfully in BN[50], although with less overall evidence for support than CBT-ED. Intensive treatment is less common for BN than AN, but may be appropriate in cases of high medical or psychiatric risk or lack of response to outpatient therapy.

Ten-session CBT for EDs, "CBT-T", is not yet recommended in ED treatment guidelines, but has been steadily growing in evidence[66]. Intended for use with all non-underweight EDs, it is modelled on CBT-ED but emphasizes rapid behavioral change and greater use of experiential techniques. It seems to be most effective in those with high motivation to change[67]. Unlike CBT-ED, CBT-T is not guided by a personalized formulation, but the approach recommends applying the protocol in a way that is tailored to individual needs (e.g., in terms of which treatment sections to include and in what order). Although no direct comparison between CBT-T and CBT-ED has as yet been conducted, outcomes in CBT-T appear to be comparable to those in CBT-ED, albeit with half the number of sessions, so CBT-T is increasingly used in clinical services[68].

After decades of research, BED was recognized as a new FED category in the DSM-5 and ICD-11. The introduction of BED has enhanced the diagnostic consistency and accuracy of FEDs[69-72] and reduced reliance on unspecified ED categories[72,73].

As in BN, BED is characterized by recurrent binge eating at least once per week for three months, associated with marked distress or functional impairment, and not resulting from another health condition or use of medication/substance. Unlike BN, binge eating is not regularly accompanied by inappropriate compensatory behaviors. Body weight or shape over-concern may be present in BED, but are not considered essential for the diagnosis. Nevertheless, together with marked distress, these features might reflect severity of BED[74-76].

The DSM-5 also requires ≥3 additional indicators of binge eating, such as: eating much more rapidly than usual, eating until uncomfortably full, eating large amounts when not physically hungry, eating alone due to embarrassment around eating; and feeling disgusted, depressed or very guilty after eating[2]. These requirements have resulted in lower BED prevalence when applying the DSM-5 compared to ICD-11 criteria[77].

It has been estimated that 65-70% of people with BED present with high BMI (e.g., ≥30 kg/m^2), but BED is seen across the healthy and overweight/obesity weight ranges[76]. Whilst not covered within DSM/ICD criteria, clinically it may be appropriate to focus on loss of control over eating rather than binge eating in younger children, as defining objectively large amounts of food in the context of developmental shifts in nutritional needs is difficult, and younger children tend to have less access to foods in private[78].

Treatment recommendations for BED are similar to those for BN: cognitive behavioral guided self-help, group CBT-ED, and individual CBT-ED. Interpersonal therapy and dialectical behavior therapy are alternative options. There is less specific guidance on applying family-based interventions to BED in children and young people. In adults, antidepressants (e.g., fluoxetine) and stimulants (e.g., lisdexamfetamine) have been used successfully alongside psychological therapies, although stimulants have mostly been used in individuals with BED who are obese[2]. Use of weight loss medications by individuals with BED who are obese is being explored, but research into the impact of these drugs on ED symptoms is in its infancy[79].

OSFED is a heterogeneous category that has been studied as a single entity and with consideration of DSM-5 sub-categories. Overall, individuals with OSFED are highly similar to those with AN, BN and BED when considering ED and general psychopathology, psychosocial functioning, and response to treatment[80-82].

Within the OSFED category, PD is defined by recurrent purging in the absence of binge eating in individuals who are not underweight[2]. PD is similar to BN in terms of risk factors, symptom profiles and response to treatment, but may be associated with higher premorbid BMI and greater gastrointestinal distress (e.g., nausea) after eating[83].

Atypical AN is defined by all criteria for AN being met except that, despite significant weight loss, weight is within or above the normal range[2]. "Significant weight loss" is not operationalized, and it is noteworthy that the ICD-11 allows the diagnosis of AN to be applied when someone has lost >20% of her/his body weight but is not yet significantly underweight.

Individuals with atypical AN are more likely to be male and non-White than those with AN, and to have higher premorbid BMI, but show comparable or higher rates of ED psychopathology, comparable rates of general psychopathology, and comparable or slightly lower rates of medical complications[84].

There are not yet discrete treatment recommendations for those with OSFED. Most guidelines suggest that recommendations for the closest specific FED (e.g., AN, BN or BED) are applied. CBT-ED and CBT-T have been successfully used with a range of OSFED sub-categories. Of note, two versions of CBT-ED are available and may help personalization: a large trial found that, for OSFED patients with greater complexity (i.e., high levels of distress, perfectionism, low self-esteem, and interpersonal problems), a broad form of CBT-ED which encompassed these topics had better outcomes than a focused form, targeting mainly ED cognitions and behaviors. For patients without these complexities, the reverse was true[85]. Perfectionism can be measured in a clinical context by the Frost Multidimensional Perfectionism Scale[86]. Self-esteem can be measured by the Rosenberg Self-Esteem Scale[87], and interpersonal problems by the Inventory of Interpersonal Problems[88].

ARFID involves severe restriction or avoidance of foods, with underweight and/or nutrition deficiency, without marked body image concerns (although individuals may express concern about low weight). It commonly develops in childhood and adolescence, and has high comorbidity with autism[89,90]. Under-eating in ARFID may be linked to sensory concerns (smells, textures or appearance), apparent lack of appetite or interest in food, and/or fear of adverse consequences (e.g., choking, nausea). ARFID patients are often younger than those with AN and BN, with a higher proportion of males and of medical comorbidities[89].

Treatment of ARFID may be CBT-based (individually or involving the family) or consist of family-based or parenting interventions. Research in this area is still evolving, and there is no compelling evidence at present for one psychological treatment over another. Dietetic, medical and wider multi-disciplinary care (e.g., speech and language therapy) may be helpful, and higher-intensity treatment may be required in cases with very low weight or other medical complications. There are calls for further research on the effective treatment of ARFID, and recommenda-

tions for personalized management are not yet available[91,92].

There is insufficient research on rumination disorder and pica to address these categories in detail. Rumination disorder is characterized by intentional and repeated regurgitation (bringing previously swallowed food back up into the mouth), which may be accompanied by rumination (re-chewing and re-swallowing food) or the food being spat out. The regurgitation needs to occur at least several times per week over at least several weeks. Pica is defined as recurrent intake of non-nutritive, non-food substances for at least one month. Recent population-based findings suggest over-representation of pica in children with autism and developmental delay, and reductions in prevalence from age 3 years onwards[93]. Behavioral interventions may be helpful, e.g., by reducing access to the non-food substance and providing an appropriate substitute, and dietetic input can support nutritional improvements where needed[94].

Previously, FEDs were considered largely as Western culture-bound syndromes, occurring mainly in women. Increasingly, there is now recognition that they are a growing public health problem in many non-Western cultures, e.g. in many Asian countries[95]. Internationally, many individuals with FEDs never receive treatment. Men, those from minoritized ethnic groups; and lesbian, gay, bisexual, transgender, queer or questioning (LGBTQ+) individuals are particularly under-represented in clinical services, even though FED prevalence rates are rising in these groups.

There is emerging evidence that racial discrimination may increase risk for BED[96]. Gender identity and sexual orientation intersect with race/ethnicity to influence ED symptoms in ways that are only starting to be understood[97]. Clinicians should consider culture and ethnicity, subjective experiences of racial discrimination and cultural identity, gender identity, and sexuality as part of their assessment of FEDs.

The prevalence of underweight is greater in Asian than Western countries. For example, 20-24% of young Japanese women are underweight (i.e., with a BMI <18.5 kg/m^2)[98]. This may influence detection of AN, and makes BMI a poor marker of FED presence or severity. Culturally tailored severity classifications for AN might be needed for treatment optimization. There are also well-documented presentations of underweight AN-like patients in Hong Kong, Japan and India in whom fear of fatness is not present[99], suggesting that culture may exert a pathoplastic effect on FED symptoms. As most research on AN without fear of fatness was conducted prior to the release of the DSM-5, these patients may over time move to being diagnosed with ARFID.

In Arab, Middle Eastern and African countries there are relatively few studies on FEDs. Prevalence rates are thought to have increased over time[100,101], but with scarce historical data. Restricted food intake may be attributed to somatic complaints, rather than body image concerns, to a greater degree than in Western samples[102], which may change the emphasis of assessment and treatment. Exposure to Western culture and higher socioeconomic status have been linked to ED symptoms in some but not all studies.

In the US, young Black/African American women and Hispanic/Latina women report higher rates of binge eating, dieting and purging than their White and Asian American counterparts[103,104]. Black/African American and Hispanic/Latino men also report higher rates of binge eating than White and Asian American men[104]. For diagnosed FEDs, some studies have found higher rates of BN or BED amongst Black American, Hispanic and Latin American groups, compared to White Americans, but results are inconsistent[105-107]. Similarly, race moderated response to ED treatment in some studies, while in others outcomes appear similar across Black, Hispanic and/or Latin American groups and their White counterparts[97]. However, treatment use may be lower amongst Black and Hispanic/Latin American than White American groups[106], which complicates interpretation of cultural differences.

There has been little research on FEDs in Indigenous populations, but emerging research from Australia, New Zealand, the US and Canada suggests that risk for disordered eating may be higher among Indigenous groups compared to the White ethnic group[108]. There are calls for research to specifically explore FEDs in Indigenous people and for culturally sensitive approaches to assessing and understanding FEDs in these populations. This will require collaboration and co-production with local Indigenous communities.

Despite being under-represented in clinical services, transgender, non-binary and gender expansive individuals appear to be at higher risk for EDs than their cisgender counterparts[97,109]. This may stem from the additional psychosocial stress experienced by individuals in these groups, together with body image concerns specific to gender and sexual diversity, including gender dysphoria[109].

Most studies of FED treatments have been conducted with samples of (presumed cisgender) women, but there is growing attention, particularly in the US, to providing care that is gender and sexuality affirming, weight inclusive, anti-racist and trauma-informed.

SEVERITY

The assessment of severity is a valuable tool to guide treatment decisions and inform expected outcomes and prognosis in FEDs. As there are no available biomarkers, a definite conception of FED severity remains a matter of debate. Severity specifiers for FEDs were introduced in the DSM-5 and ICD-11.

In the DSM-5, severity levels are based on BMI in AN; on the frequency of compensatory behaviors in BN; and on the frequency of binge eating in BED. Four severity grades are described for each disorder: for AN, "mild" (≥17 kg/m^2), "moderate" (16-16.99 kg/m^2), "severe" (15-15.99 kg/m^2), and "extreme" (<15 kg/m^2) BMI; for BN and BED, "mild" (1-3 episodes/week), "moderate" (4-7 episodes/week), "severe" (8-13 episodes/week), and "extreme" (14 or more episodes/week).

The ICD-11 only describes a severity specifier for AN, with BMI being the driving characteristic. Two ICD-11 underweight subcategories are proposed: AN with significantly low body weight (BMI 14-18.5 kg/m^2 for adults, or 0.3rd-5th percentile BMI-for-

age in children/adolescents) and AN with dangerously low body weight (BMI <14.0 kg/m^2 in adults, or <0.3rd percentile BMI-for-age in children/adolescents). A third category, "AN in recovery with normal body weight", applies to individuals who restored weight to normal but still experience core cognitive and behavioral symptoms of the disorder.

The conception and grading of severity specifiers of the DSM-5 and ICD-11 can be considered somewhat arbitrary, and research into their validity and utility is only partially supportive[110]. For instance, inpatient treatment was found to be positively associated with DSM-5 AN severity sub-categories[75], but psychiatric morbidity, distress and cognitive impairment were not[110-114]. In BN, a meta-analysis of seven studies found ED psychopathology increasing with the frequency of compensatory behaviors[110], whilst measures of impairment, psychiatric comorbidities, cognitive functioning and distress differed between BN severity categories in some but not all studies[75,110,114]. For BED, a meta-analysis of five studies found higher ED psychopathology in more severe categories[111], while varied results were reported for other measures, such as general psychopathology, cognitive functioning, and quality of life[111,113,114]. There is very limited research on potential severity markers in ARFID, pica and rumination disorder.

Alternative severity indices have been proposed to reflect the transdiagnostic features of EDs, rather than the current disorder-specific markers[75,115]. There is some evidence for the clinical utility of a severity index based on low or high over-evaluation of weight and shape or drive for thinness[75,116], or duration of the disorder[114]. However, conclusions are limited by methodological differences across studies, and there is little evidence for any severity markers reliably predicting differential response to particular treatment approaches[117,118].

It is recommended that the DSM-5 and ICD-11 severity categories be used as general guidance, but levels of severity be considered in relation to overall psychopathological status, physical risk, and functional impairment.

In addition to markers of severity, motivation to change is often considered when assessing FEDs. It is common for motivation to fluctuate over time and to vary across FED symptoms[119]. For example, someone may be motivated to reduce her/his preoccupation with eating, weight and shape or stop binge eating, but not to cease dietary restraint or increase her/his weight. Self-reported motivation does not always correlate with behavioral change, and motivation to change typically increases with effective ED treatment[119]. For these reasons, low self-reported motivation to change should not be a reason to withhold or stop treatment. However, exploring motivation may support collaborative treatment planning.

CLINICAL STAGING

In EDs, the rationale for a staging framework stems from various sources of evidence. Much clinical research has indicated that outcomes are best in children and young people, i.e., where illness duration is typically short, suggesting that intervening early in the course of an ED may prevent a more chronic illness[18]. A very large network analysis of people with EDs (N=6,850) attempted to identify central symptoms, comparing networks across duration of illness[120]. Cognitive symptoms were found to be more central in the shorter duration of illness subgroups, whereas behavioral symptoms were more central in the medium-to-longer duration of illness subgroups. These findings provide important pointers towards stage-matched interventions, suggesting that targeting cognitive ED symptoms such as the over-evaluation of weight and shape may be more effective for treating early-stage EDs than for those with a longer illness duration.

Development and maintenance of an ED is associated with complex changes to brain morphology[121] and functioning[25]. As in other psychiatric disorders[122,123], the brain changes resulting from neuroprogression – i.e., reduced neurogenesis and neuroplasticity – have been postulated to drive clinical progression of EDs[124,125]. It is also important to consider that, over time, there are profound impacts of EDs on physical health that are not always reversible, such as impaired dental and bone health.

Several staging models for EDs have been developed[126]. Most of them focus mainly on AN, except one which focuses on binge-type EDs[127]. Criteria for stage differentiation are mostly based on combinations of cognitive, behavioral and physical features, and illness duration.

Treasure et al[124] proposed a four-stage model for EDs, based on that of McGorry et al[128] for psychosis, i.e., ranging from incipient/high-risk stages to persistent forms of illness. The model also suggested stage-matched interventions. Aspects of this model were tested in a sample of 187 AN patients treated in outpatient services and followed up for one year[129]. Despite similar baseline BMIs, early-stage AN patients had much better BMI outcomes and improvements in work and social adjustment at 12 months, and were less likely to need day- or inpatient treatment over the 12-month period.

Other authors have focused on testing stage-appropriate interventions for particular populations, in particular early-stage and severe enduring illness. For example, a service model for early-stage illness – targeted at young people (age 16 to 25) with a recent (≤3 years) onset ED – is the First Episode Rapid Early Intervention for Eating Disorders (FREED) model[130]. This model offers rapid access to youth-friendly evidence-based intervention tailored to illness stage (i.e., emphasizing biological malleability and need for early nutritional change), together with developmentally appropriate adaptations to interventions (focusing on identity development and "adulting", using parental support as appropriate), to promote full recovery and prevent chronic illness. Compared to usual care, FREED has been shown to shorten duration of untreated illness (time from onset to first evidence-based treatment), substantially improve clinical outcomes, lead to cost savings[130-133], and be highly acceptable to patients[134].

With a focus on AN, others have operationalized the severe and enduring illness stage, with a proposed set of empirically testable criteria (illness duration >3 years and at least two unsuccessful evidence-based treatments appropriately delivered)[135]. A Cochrane review[136] identified one RCT of psychological interventions

(CBT and SSCM) adapted for this chronic population, with no differences in outcomes between them.

In conclusion, staging models for FEDs are promising, but still in their infancy, with few agreed definitions. Current stage characterizations focus mainly on clinical features, but will ultimately be able to truly transform clinical care only if they can be extended to include genetic, neurobiological and other physical markers of illness risk, treatment outcome and prognosis[25].

PHYSICAL COMPLICATIONS AND CONSEQUENCES

Physical sequelae of FEDs can affect any organ system. They mostly arise either from self-starvation and low weight (as in AN, ARFID or atypical AN) or from purging (as in binge-purge AN, BN or PD), or are related to persistent binge eating and overweight/obesity (as found most commonly in BED). The risk of serious physical health consequences, including death, is typically highest when self-starvation and purging occur together. An overview of starvation- and purging-related complications is provided in Table 1.

The mortality from both medical morbidity and suicide is high for all EDs[137], with standardized mortality ratios of 5.86 for AN, 1.93 for BN, and 1.92 for OSFED. One in five of AN deaths result from suicide. Large national register studies confirm these findings[138], with some pointing to a gender difference, i.e., with higher mortality in men than women with AN or BN[139]. For BED, the standardized mortality ratio is 1.50 to 1.77[5].

In a longitudinal hospital register cohort of 5,169 women, AN was associated with death from suicide (hazard ratio, HR=4.90, 95% CI: 1.93-12.46), pulmonary diseases (HR=3.49, 95% CI: 1.77-6.89), diabetes mellitus and other endocrine diseases (HR=7.58, 95% CI: 1.89-30.42), liver and other gastrointestinal diseases (HR=3.27, 95% CI: 1.33-8.06), and shock and organ failure (HR=3.59,

Table 1 Physical complications of malnutrition and purging behaviors

	Malnutrition		Purging	
	Pathological findings	**Symptoms**	**Pathological findings**	**Symptoms**
Central nervous system	Decrease in the volume of grey and white matter and functional alterations in the brain	Cognitive impairment	Swollen brain cells (e.g., due to low plasma sodium)	Epileptic seizures
Endocrine system and reproductive function	Hypogonadotropic hypogonadism, growth hormone resistance, low levels of IGF-1; low levels of TSH, T3 and T4; hypercortisolaemia, hypercholesterolaemia, hypotestosteronism in males	Amenorrhoea, hypoglycaemia, growth delay in children and adolescents		
Cardiovascular system	Low blood pressure, bradycardia, hypokalaemia and QT prolongation	Asthenia, syncope, cardiac arrhythmia	Hypokalaemia, acid-base disorders and QT prolongation	Cardiac arrythmia
Teeth and parotid glands	Dental damage	Dental caries	Erosion of lingual dental surface, parotid glands hypertrophy	Irreversible dental caries, parotid glands inflammation
Gastrointestinal (GI) tract	Impaired gastric emptying, low GI motility, altered gut microbiota	Constipation, early fullness	Oesophagus and pharynx mucosal laceration, low colon motility, hyperamylasaemia	Cough and dysphagia, episodes of epistaxis, diarrhea/constipation, nausea, abdominal pain
Urinary tract	Hypokalaemia, hypochloraemia, metabolic alkalosis	Kidney damage	Hypokalaemia, hypochloraemia, hyponatraemia, metabolic alkalosis, hyperaldosteronism	Kidney failure, edema
Respiratory system			Intrathoracic pressure increase	Pneumomediastinum and aspiration pneumonia
Haematological and immune system	Reduced bone marrow cell production, hypoproteinaemia	Anaemia, susceptibility to bacterial infections, compromised immune function, edema		
Bone	Osteopenia, osteoporosis	Bone fractures		
Muscle	Myopathy	Impaired muscle strength (e.g., leading to inability to get up from a squat)	Decreased muscle blood flow	Muscle cramps
Skin	Dystrophic and dry skin, lanugo hair	Fragile and fulling hair, acrocyanosis	Russell's sign (calluses on the knuckles or back of the hand due to repeated self-induced vomiting)	

IGF-1 – insulin-like growth factor 1, TSH – thyroid stimulating hormone, T3 – triiodothyronine, T4 – thyroxine

95% CI: 1.23-10.49). Among pulmonary causes, AN was most strongly associated with death due to pneumonia (HR=8.19, 95% CI: 2.78-24.14)[140].

The APA[50] and the UK National Institute for Health and Care Excellence (NICE)[51] guidelines recommend that, in addition to a careful mental health and physical history, the initial physical examination of a patient with a possible FED includes assessment of vital signs (i.e., temperature, resting heart rate, blood pressure, orthostatic pulse and blood pressure); height, weight and BMI; and signs of malnutrition and purging. These guidelines also recommend a complete blood count and a comprehensive metabolic panel, including electrolytes, liver enzymes, and renal function tests. An electrocardiogram should be obtained in patients with a restrictive ED, in those with severe purging behavior, and in those taking medications known to prolong QTc[50]. Weight measurements will typically be recorded on a session-by-session basis during treatment, with other examinations (including height in children) and investigations recommended at regular intervals, depending on medical risk, presence and severity of physical comorbidities, and treatment response. Guidance on the recognition and management of medical emergencies in EDs has been provided by the UK Royal College of Psychiatrists[141].

Most physical consequences of starvation are reversible with weight regain and normalization of eating. An exception are the effects on bone density. NICE guidelines[51] recommend that a bone mineral density scan is considered after one year of low weight in children and adolescents and after two years in adults, or earlier if there are bone pain or fractures. Patients with a persistently low weight can suffer an annual loss in bone density of up to 10%[142,143]. The best treatment is reaching and maintaining a healthy BMI for age. Oral oestrogens, calcium-vitamin D3 preparations and bisphosphonates are unlikely to halt or improve the reduction in bone density whilst low weight persists. More recent studies point to the usefulness of transdermal oestrogen application in adolescents and of bisphosphonates in adult patients with persistent AN[144]. However, bisphosphonates have potentially teratogenic effects that need to be explained to patients, so they can weigh up risks and benefits.

Bone marrow suppression may lead to anaemia and leukopenia, both of which normalize with weight gain[145]. Liver damage, as reflected in raised transaminases, is highly correlated with low BMI and again quickly normalizes with weight gain[146].

In patients with AN and ARFID, a wide range of upper and lower gastrointestinal symptoms are common in the underweight state, with constipation, nausea and abdominal pain the most common in AN[147]. These often improve during or after nutritional rehabilitation[148]. The gut microbiome may be involved in the pathophysiology of gastrointestinal symptoms in AN, as it is affected by alterations in energy intake and dietary composition. In some cases, probiotics have shown therapeutic effects[149]. As research in this area continues to progress, there may be new opportunities for personalizing care, including either direct changes to gut microbes (via probiotics or faecal microbial transplants) and/or changes to the microbial environment (prebiotics, diet)[150,151].

AN also leads to endocrine changes, such as hypothalamic amenorrhea, low triiodothyronine (T3) and thyroxine (T4), low levels of insulin-like growth factor 1 (IGF-1), relative hypercortisolaemia; decreases in leptin, insulin, amylin and incretins; and increases in ghrelin, peptide YY and adiponectin[152]. Correction of thyroid hormones is not advised, given the potential for misuse of these hormones to aid weight loss. Most of these changes are adaptive and reversible with weight restoration, although a degree of growth stunting may persist and for some patients there is Cushingoid truncal weight gain during re-feeding[152].

Purging can lead to many physical consequences, that vary according to the type and frequency of purging behaviors. The most dangerous and life-threatening medical complications are cardiac arrythmias and QT prolongation due to electrolyte imbalance, especially hypokalaemia and acid-base disorders[153]. Severe hypokalaemia can also promote renal failure. Vomiting and diuretic abuse are associated with the development of hypokalaemia, hypochloraemia, and metabolic alkalosis; laxative abuse can present with hypokalaemia and hypochloraemia[154]. Hyponatraemia can occur as a consequence of all purging behaviors[154]. Assessment and regular monitoring of serum electrolyte disturbances and electrocardiogram evaluation must be considered essential steps in the management of patients with purging behaviors. Potassium depletion not lower than 2.5 mmol/L without symptoms or electrocardiographic changes can be treated with oral potassium supplementation and correction of volume depletion, while intravenous repletion of potassium is required at <2.5 mmol/L levels[155].

In addition to the above life-threatening complications, stimulant laxative abuse can cause reduction of gastrointestinal motility, and patients may present with chronic diarrhoea, constipation, nausea, or abdominal pain[156]. It is debated if stimulant laxative abuse can cause loss of colon motility ("cathartic colon"); thus, osmotic laxatives are preferable for managing constipation.

Erosion of dental enamel through gastric acid is common in those who self-induce vomiting on a regular basis. In these cases, NICE guidelines[51] encourage avoidance of brushing teeth immediately after vomiting, using non-acid mouthwash after vomiting, and avoiding highly acidic foods and drinks. Regular dental reviews are also encouraged. The stomach acid-induced erosion of oral mucosa and the pharynx can be associated with cough and dysphagia[157], while gastric acid in the oesophagus can induce reflux disease and rare mucosal laceration with episodes of hematemesis[158]. Delaying, reducing or stopping self-induced vomiting, together with medications to suppress acid production, are indicated in the presence of these symptoms.

Further complications associated with violent retching are subconjunctival haemorrhages and episodes of epistaxis. Indeed, recurrent epistaxis in young women without other medical causes may be a sign of covert BN, as well as hypokalaemia without ascertained causes[159]. Rarely, vomiting may increase intrathoracic pressure causing pneumomediastinum, or may promote aspiration pneumonia. Of note, both vomiting and cessation of vomiting may cause parotid gland hypertrophy: sialagogues and anti-inflammatory drugs are indicated in this case.

Persistent binge eating and BED are commonly associated with

or lead to higher body weight or obesity. Individuals with BED in the general population report a variety of gastrointestinal symptoms, including dysphagia, acid reflux, bloating, abdominal pain, diarrhoea and constipation. In addition, respiratory (30%) and musculoskeletal (21%) problems are significantly increased in people with BED.

Individuals with BED – particularly due to obesity and increased risk of type 2 diabetes mellitus – have multiple risk factors for cancers. Other health concerns in these people include urinary incontinence and polycystic ovary syndrome. The latter is associated with insulin resistance and increased risk of infertility. Up to 23% of patients with this syndrome meet BED criteria[5].

In a nationally representative study of US adults, the mean BMI of people with BED was 33.9 kg/m^2. Thus, health conditions commonly associated with BED include hypertension (31%), various heart conditions (17%), arthritis (24%), elevated cholesterol (27%) and triglycerides (15%), diabetes mellitus (14%), sleep problems (29%), general poor health, and metabolic syndrome[160].

All these findings highlight the need for a close monitoring of physical health in patients with EDs, who should be provided with full information about the consequences of starvation and purging and the ways to minimize risks.

ANTECEDENT AND CONCOMITANT PSYCHIATRIC CONDITIONS

Antecedent and concomitant mental disorders are exceedingly common in FEDs, but vary within and across clinical subtypes. This psychopathological complexity is influenced by biological and environmental factors[5,161,162]. For example, genome-wide association studies (GWAS) in AN have found positive genetic correlations with OCD, major depression and anxiety disorders[162,163]. These comorbid psychiatric conditions may influence treatment response of the ED. Meta-analyses show poorer treatment outcomes, and higher dropout rates, for ED patients with greater comorbid psychopathology[117].

Premorbidly, having a greater number of internalizing and externalizing behaviors in childhood has been linked to greater risk of developing an ED[164]. Common premorbid psychiatric conditions are anxiety disorders, OCD, major depression, impulse control disorders, and obsessive-compulsive personality traits[5,165-167], with the three years following onset of the first psychiatric disorder suggested as a key risk window for subsequent development of an ED[166,167].

According to several systematic and meta-analytic reviews and specific comorbidity studies[166-169], the most common current and lifetime psychiatric comorbidities in AN are anxiety disorders (55-59%), major depression (65-81%), OCD and personality disorders (namely obsessive-compulsive and borderline personality disorder, the latter often associated with the presence of self-harm)[170,171]. There is also notable co-occurrence of AN and ARFID with autism[172], with approximately 1 in 5 people with AN showing high autistic traits[173], and high food selectivity being very common in autistic children and adults[174].

Autistic patients with EDs have been found to have higher ED psychopathology, longer hospital stays, and increased depression and anxiety than non-autistic ones[175], showing that this is a vulnerable population in need of appropriately tailored support. Assessment tools for autism are known to have poor sensitivity in girls and women, meaning that rates of autism in FEDs are likely to be underestimated.

The few studies reporting on comorbidities in men with AN have described similar findings as in females. However, in males there appears to be a higher prevalence of neurodevelopmental disorders – e.g., attention deficit hyperactivity disorder (ADHD) and autism – and substance use disorders compared to females[176].

Mood, anxiety and OCD symptoms may persist after recovery from an ED. For example, one study found that a quarter of patients who had recovered from AN met criteria for an anxiety or depressive disorder[177].

In BN, major depression is the most frequent comorbid psychiatric condition (72-84%)[166], followed by anxiety disorders (56%), post-traumatic stress disorder (PTSD), OCD, substance use disorders[178], and personality disorders (particularly borderline personality disorder)[170].

BED has a very similar profile of psychiatric comorbidity to BN, often being associated with lifetime comorbid mood disorders (70%), anxiety disorders, PTSD, substance abuse, personality disorders (mainly borderline personality disorder) and ADHD[5,179].

The concomitance of behavioral addictions is higher in BN and BED compared with restrictive-type EDs, with compulsive buying (19%), kleptomania (18%) and pathological Internet use (12%) as the most frequently observed[170]. In terms of gender, gambling is the most common behavioral addiction among men (16% of cases), while compulsive buying is the most common among women (17% of cases)[167].

Although there is limited evidence, "other" and subthreshold EDs (e.g., OSFED) have shown high levels of general psychopathology, and the most commonly described comorbidities are mood/anxiety disorders and substance misuse[166,170].

Rates of lifetime non-suicidal self-injurious behavior and suicide attempts are higher in those with EDs than in other psychiatric disorders and in healthy controls[180]. The former has been described in 27% of ED cases, and is more common in BN than in AN (33% and 22%, respectively)[181]. Suicide attempts appear equally present (about 22%) across ED subtypes[182].

The presence of psychiatric comorbidity in EDs is often associated with greater severity of ED symptoms, more general psychopathology, maladaptive personality traits, greater cognitive impairment, longer duration of ED, and poorer prognosis[18,183-186]. Systematic reviews and meta-analyses have found that psychiatric comorbidity is a significant predictor of relapse or treatment dropout[18,185,187].

Screening for common psychiatric comorbidities can be done by the Psychiatric Diagnostic Screening Questionnaire (PDSQ)[188]. For autism, the Autism Spectrum Quotient (AQ-10) can be used as a screening tool[189]. A careful psychiatric history will help establish the time course and potential interdependence of any comorbid disorders.

A protocol for how to best address co-occurring mental health conditions in the treatment of EDs has been developed[190]. This proposes that, where the comorbid condition appears to be a consequence of the ED, treatment can exclusively focus on the ED. For example, it has been clearly documented in starvation studies that low weight *per se* leads to low mood, anxiety and increased obsessionality[191]. Thus, in people with AN, weight restoration is likely to improve many of these symptoms. Specific intervention is advisable if a comorbid disorder is likely to impede engagement with ED therapy.

The most challenging cases are those in which the comorbid condition interacts with the ED and this impedes progress. In these cases, it may be possible to employ either concurrent or integrated interventions (e.g., modular approaches, or those that target transdiagnostic processes).

The Pathway for Eating disorders and Autism developed from Clinical Experience (PEACE)[192] is an example of how ED care may be tailored to take into account co-occurring presenting features, in this case autism, with good results.

SOCIAL FUNCTIONING AND QUALITY OF LIFE

People with EDs often show impairment in interpersonal relationships, family function, work, finances, and social and private leisure activities[193]. Early clinical and community-based cross-sectional studies reported poor social adjustment in people with EDs[194], and associations between lower adaptive function and greater illness severity[195]. In the clinical context, assessment and monitoring of FED patients' overall social functioning and quality of life, and the specific life domains affected by the disorder, may help them reflect on their values, improve motivation to change, and help refine treatment goals. It may also be a useful way of monitoring broad-based progress over time.

Subjective generic measures, such as the WHO Brief Quality of Life Assessment Scale (WHOQOL-BREF)[196], assessing quality of life as it relates to social interaction and perceptions of well-being, are being increasingly applied to the assessment of EDs, particularly in recovery definitions[197,198].

Health-related quality of life measures assess people's appraisal of the impact of disease and treatment on their physical, psychological, social and somatic functioning and well-being, and the relationships between severity of illness, functional status and disability[199,200]. They have been argued to be the "primary endpoint" in clinical settings[201]. Generic instruments – such as the 12-Item Short Form Survey (SF-12)[202] and the EQ-5D-5L[203] – can be utilized across diagnostic groups, but several ED specific instruments are also now widely used – e.g., the Clinical Impairment Assessment scale (CIA)[204] and the Eating Disorder Quality of Life Scale[205,206]. These specific tools may be more sensitive at identifying differences between people with different levels of ED severity and/or different forms of an ED[207], and have greater convergence with ED symptoms[208].

An emerging field of assessment is the use of measures that allow individuals to report their person-specific outcomes and unique concerns, such as the Psychological Outcome Profiles (PSYCHLOPS)[209]. Such instruments resonate with the broader conceptualization of recovery to encompass a personal perspective beyond symptom severity[198].

It has been observed that quality of life findings for people with AN may appear inconsistent, with a discrepancy between assessor (clinician) ratings of function and individual's symptom-related quality of life[210]. This has been ascribed to the ego-syntonic nature of symptoms, such that an individual's sense of well-being may be improved with the heightened sense of control and validation of successful weight loss in a society with high endorsement of the thin ideal. Nevertheless, using either generic or specific measures, a significant impairment of health-related quality of life has been documented for all main EDs[211]. Further, poor quality of life has been reported in representative population studies of people with sub-categories of OSFED, such as night eating syndrome[212,213], and in meta-analyses of people with atypical AN[214] and with ARFID[215,216].

Empirical measurement is consistent with the lived experience of EDs as captured in qualitative research. In a qualitative meta-synthesis of "severe and enduring" AN, functional impairment was reported as a "global impoverishment of self" in interpersonal relationships, physical health, mental health and socio-economic functioning[217]. This involved a series of losses, including intimacy and work/life functionality, which result in individuals living very lonely and isolated lives. Such experiences are not confined to AN, but occur to varying degrees across all EDs[218].

Research has also shown a wider impact of FEDs beyond the individual. Family and carer mental health impact and stress are amongst the highest for any psychiatric disorder[219]. Three measures assessing caregiver burden, which can be easily applied in the clinical context, are the Experience of Caregiving Inventory[220], the Eating Disorders Symptom Impact Scale (EDSIS)[221], and the Accommodation and Enabling Scale for Eating Disorders (AESED)[222]. The EDSIS assesses carer social isolation, guilt, ability to manage nutrition in the family and cope with dysregulated behavior in the patient. The AESED evaluates how carers adapt to the illness.

One of the best-known efforts to develop carer interventions to address these issues are the Maudsley Eating Disorders Collaborative Care Skills Workshops[223], which use key elements of motivational interviewing and CBT to reduce caregiver distress and improve their skills in supporting their loved one. This model was developed originally for carers of adults with EDs and was found to be efficacious in reducing carer burden and expressed emotion (frequency of critical comments), and in improving self-efficacy, skills and knowledge[224]. However, the approach also works well in families of adolescents with AN[225,226].

NEUROCOGNITION

Several cognitive processes have been shown to be altered in people with EDs and are relevant to specific psychological and behavioral disturbances: reward processing, inhibitory control and

decision-making. Some processes (attention, working memory) have been found to be affected in ways that are largely attributable to starvation[227]. Several studies have found that cognitive impairment is a predictor of poor therapy response[228], and might be reversible after ED recovery[229].

Reward processes include hedonic value, motivational salience, and a set of learning processes in which the receipt of reward shapes behavior (reinforcement learning). The maladaptive behaviors that characterize EDs have been related to each of the above processes. People with AN, for example, have been shown to assign lower value to food, in general, compared with healthy peers – though whether this is a cause or a consequence of illness is unclear. People with BN or BED have been shown to have higher expectation of reward from food, but then to report decreased subjective experience of reward with receipt of food[230].

Individuals with AN have been shown to be slower in learning from reward outcomes in laboratory tasks (reinforcement learning deficits) and to show abnormal brain responses to expected and unexpected reward outcomes[231]. Some studies have found that reward learning differences between patients with AN and healthy peers have significance in clinical course[228,229]. Both behavior and brain research in AN suggest decreased reward properties of food and abnormalities in the processing of food value (which contributes to decision-making) and abnormalities in dopamine functioning (dopamine is central to reward learning). The literature among patients with BN and BED is more limited, yet it does point to some differences in reward value in anticipation and receipt of food that may contribute to binge eating phenomena[5,232-234]. Interestingly, patients with BED also show deficits in reinforcement learning (specifically, limited use of goal directed learning).

Cognitive control is a higher-order executive function comprised of numerous cognitive functions. Components of cognitive control include inhibitory control, cognitive flexibility, and attentional control. This broad area has drawn a lot of attention in EDs because of the plausibility of a connection between cognitive control and eating behavior. Restrictive eating is likely reflective of an extreme inhibitory control. Restrictive eating also occurs in non-binge meals for individuals with BN. At the same time, BN has also been associated with higher levels of impulsivity, which can be approached as a distinct neurocognitive process and is related to deficiencies in cognitive control.

Classic findings among people with AN include increased cognitive control during neuropsychological tasks, such as difficulty with set shifting (that is, changing response patterns when environmental contingencies change). Findings among patients with BN are more commonly suggestive of impaired inhibitory control – the inability to prevent a particular response[230].

Decision-making has been studied using monetary or food outcomes. The most commonly employed monetary tasks probe delay discounting, where participants choose between an amount of money available sooner or a larger amount available later. This complex task includes several sub-components, and tends to identify that people with AN favour the larger-later amount and patients with binge eating disorders tend to favour the smaller-sooner[235]. In one set of food choice tasks, participants provide subjective ratings (healthiness and tastiness) as well as choice. This paradigm has identified differences in neural mechanisms of food choice between patients and controls, whereby people with AN show greater choice-related activation in the anterior caudate and dorsal fronto-striatal systems. While caution is warranted in making inferences about behavior based on brain activation patterns, these data are broadly consistent with habit-centred models of AN[236].

Assessment of neurocognitive impairments using task-based measures is not typically feasible in clinical practice, due to their time-consuming nature. Self-report questionnaire measures exist for some of these constructs, e.g. cognitive flexibility, but with little or no correlation between questionnaire and task-based measures[237]. Nonetheless, each of the neurocognitive domains reviewed has clinical implications in terms of identifying potentially new treatment targets. The reward deficits among patients with AN may make it more challenging to use learning in psychotherapy to change behavior in the service of health[238]. Novel psychological treatment approaches, such as positive affect treatment, aim to enhance attention to and appreciation of experience of reward to change behavior and are showing clinical promise in AN[239]. Further clarifying the ways in which people with AN have challenges in the reward and reward learning domains will help the development of these treatments.

Habit strength of illness-related routines, e.g. in relation to eating, in AN is related to greater illness duration and severity[240], and multimodal interventions targeting habits have shown promise and are the subject of further investigation[241,242]. Treatment designed to directly target neurocognition (e.g., cognitive set-shifting weakness and overly detail-focused thinking), namely cognitive remediation therapy for AN, has not as yet shown any clear advantages over different control treatments in improving neurocognition or other outcomes. However, it may reduce dropout[243,244].

Among individuals with BN, psychotherapy may need to specifically focus on enhancing inhibitory control. Neurocognitive trainings with this target have indeed shown promise[245-247], and are being explored with some success also in BED[248,249]. Computational psychiatry has potential to provide a more granular evaluation of these neurocognitive processes, and to identify latent variables (i.e., aspects of decision-making that are not directly observable) that will be useful for personalization of treatment[250].

SOCIAL COGNITION AND EMOTION

Most research on social cognition has been conducted in people with AN[251,252]. The findings indicate impairments across a range of domains[251-255], including communication; affiliation-related outcomes, as reflected by self-reported insecure attachment[251]; and a tendency towards negative interpretation of social scenes[252]. People with AN have also shown deficits in emotion processing, including alterations in retrieval of emotions, startle response, pleasure ratings to affective touch, and emotional expression[251,252,255].

Impairments in domains related to the evaluation of (emotional/cognitive) states of others have been expressed in (facial) emotion recognition difficulties[251-254]. Theory of Mind (ToM)

impairments in people with AN were reported in earlier meta-analyses[251,253], but more recent evidence is inconsistent[255]. ToM outcomes in AN seem to be influenced by the task used, and previous studies mainly relied on a single task which might assess emotion recognition rather than ToM[255].

There has been less research on social cognition and emotion in BN and BED, rendering it difficult to draw conclusions about these disorders[251,252,256]. Studies have centred on emotion-related domains, resulting in some evidence for difficulties in emotion processing among patients with BN, and self-reported emotion regulation difficulties among patients with BN or BED[252,253]. Recent meta-analytic data outline the transdiagnostic character of emotion regulation difficulties, indicating strong relationships between maladaptive emotion regulation strategies such as rumination, avoidance or suppression of emotions and ED symptom severity[257].

Whilst task-based measures of social cognition are too cumbersome for use in clinical practice, brief questionnaire-based measures exist that tap into emotion (dys)regulation. Two widely used tools are the Emotion Regulation Questionnaire (ERQ)[258], which assesses cognitive reappraisal and expressive suppression, and the Difficulties in Emotion Regulation Scale (DERS)[259], which assesses a broader range of facets of emotion (dys)regulation.

In terms of clinical implications, the cognitive-interpersonal maintenance model of AN posits that deficits in socio-emotional functioning contribute to development and persistence of illness, and existing data from patients are largely consistent with this model[35,260]. The MANTRA approach is derived from this maintenance model[35,260] and includes interventions to address the emotional and social life of patients and work with close others to strengthen interpersonal functioning.

For binge-like EDs, despite the sparsity of mechanism research, disease models and treatment approaches are increasing. Current efficacy data for BED treatment match very well with the evidence on socio-emotional deficits, as interpersonal psychotherapy and dialectical behavior therapy have shown efficacy in randomized controlled trials alongside CBT-ED[5]. Interpersonal psychotherapy specifically focuses on interpersonal functioning, communication and relationships, while dialectical behavior therapy predominantly addresses emotion regulation skills, and has a focus on interpersonal issues.

Finally, the reported abnormalities in the social brain networks in people with EDs[256] suggest that neuromodulatory approaches may have potential, with a putative treatment focus on improving social functioning and emotion regulation by targeting associated brain areas by neurofeedback approaches or non-invasive brain stimulation[261].

DYSFUNCTIONAL COGNITIVE SCHEMATA

Cognitive theories propose that the development and maintenance of psychopathology can be partially attributed to processing disorder-salient stimuli preferentially above other information types[262]. Attention bias refers to the preferential processing of salient stimuli such that the focus of attention influences responses [263]. Techniques targeting attentional bias (e.g., dot-probe, Stroop, free recall, eye-tracking) aim to manipulate selective attention for disorder-salient information. Various cognitive models share the premise that biased patterns of basic information processing, operating early within the cognitive system and at a low level, play a central causal role in vulnerability to experience intense emotional symptoms[264].

Evidence suggests that people with EDs experience greater bias away from food stimuli, and bias towards body-related stimuli, compared to healthy controls[264]. The Stroop task is the most widely used measure of attentional bias in EDs, with results suggesting that attention bias to food stimuli is comparable in people with AN and restrained eaters, but greatest in those with BN[265] and BED[266].

Patients with EDs are more likely to attribute negative body interpretations to ambiguous sentences and scenarios compared to healthy individuals[264]. Attentional, interpretation and memory biases for stimuli pertaining to negative self-worth have been implicated in the development and maintenance of EDs. People with EDs experience elevated sensitivity hypothesized to be triggered by a negative interpretation bias, the tendency to interpret ambiguous social situations negatively and to anticipate negative endings[267].

Cognitive bias modification (CBM) refers to a class of interventions targeting cognitive processes considered key in the etiology and maintenance of different psychopathologies. Research has focused primarily on two types of CBM: attention bias modification (ABM) and cognitive bias modification for interpretation (CBM-I). Bias modification trains participants to attend to neutral or positive stimuli in preference to negative, threatening stimuli. There is weak evidence of the efficacy of ABM for appetitive behaviors[268], with reduced attentional avoidance of food stimuli and a reduction in ED symptoms[245].

CBM strategies have targeted many aspects of ED psychopathology, including concerns about appearance and self-worth, with moderate-to-large reductions in bias, though with smaller and less consistent effects on symptomatology[262]. CBM has also been shown to decrease negative interpretation bias towards ambiguous social situations, with strong effects in women with AN and BN[269,270]. CBM could provide a useful treatment enhancement by increasing sensitivity to positive social feedback and reducing sensitivity to social criticism from family and peers. The online nature of the training may appeal to younger populations. It is possible that in future these strategies offer the potential to augment treatment-as-usual strategies.

Early maladaptive schemata are broad, pervasive and dysfunctional belief systems regarding oneself, others and the world, which develop during childhood and impact functioning. They can be assessed by the Young Schema Questionnaire[271], which includes eighteen such schemata across five domains: disconnection/rejection, impaired autonomy/performance, impaired limits, other directedness, and over-vigilance/inhibition. Compared to healthy controls and other clinical populations, individuals with EDs score higher on most schemata[272].

Schema therapy was developed to address the causes of early maladaptive schemata and the impact of these on present-day functioning. A recent systematic review of schema therapy in EDs[273] found four articles (including one RCT[274]) with 151 participants that met inclusion criteria. In the RCT, schema therapy performed comparably to CBT and appetite-focused CBT for people with binge-eating[274]. Given the small number of studies, few firm conclusions can be drawn.

PERSONALITY TRAITS

Recent studies report similarities in personality traits across ED diagnoses. For example, a comprehensive review suggested that perfectionism, neuroticism and avoidance motivation are elevated, while extraversion and self-directness are reduced, in AN, BN and BED[275]. Despite these similarities, some ED diagnostic differences did emerge across certain personality traits. For example, there was considerable evidence that impulsivity was higher in BN than in AN, but further analysis of AN subtypes revealed that individuals with AN who binge and purge showed levels of impulsivity that are roughly equal to BN, and notably higher than in the restricting AN subtype.

Cluster analytic studies and latent structure models have been used to try and identify personality-based groups within ED diagnoses[276-279]. Using a variety of personality measures, and different statistical approaches, three personality-based subtypes were identified across studies for AN and BN: under-controlled, over-controlled, and low psychopathology[280]. When these groups were compared, they showed significant and clinically relevant differences in patterns of treatment utilization and response, psychosocial functioning, and history of various etiological factors[278,281].

Another important area of study is the longitudinal predictive value of personality traits in the clinical course of an ED. Studies which have assessed personality functioning at baseline, and used it to predict disorder course and outcome, suggest that elevations in emotion dysregulation and impulsivity predict a negative ED outcome[282,283]. However, there has also been evidence suggesting that ED symptoms are correlated with elevations in personality traits, and that personality trait elevations subside as ED symptoms improve[284,285].

When personality traits and ED status are both assessed repeatedly in longitudinal studies, findings are mixed. One study found that personality functioning had no significant influence on ED outcomes over a five-year time frame in individuals with BN[286], while a 17-year follow-up of a transdiagnostic sample of ED individuals found that elevated borderline personality scores at baseline predicted a more negative ED course, but that changes in personality traits or ED symptoms did not significantly influence the other condition[287]. Thus, the longitudinal relationship between personality traits and ED symptoms remains relatively unclear, and more robust, prospective longitudinal studies are needed to test this relationship.

It is important to consider whether personality traits may moderate the effectiveness of ED treatments. Studies in this domain are relatively limited and have revealed a pattern of inconsistent findings, depending on the ED diagnosis in the study and the types of treatment implemented. A literature review which included seven RCTs and four treatment-related naturalistic follow-up studies concluded that personality traits typically had some type of impact on treatment outcomes, but this varied across studies[288]. For example, treatment outcomes for BN did not seem to be significantly impacted by the level of impulsive or emotionally dysregulated personality traits[289,290], whereas heightened avoidance and inhibition personality traits displayed a negative impact on outcomes for BED treatment and also an increased likelihood of attrition in AN studies[183].

Integrative cognitive affective therapy (ICAT) has been evaluated as an emotionally-focused ED treatment, and may be helpful for individuals with personality disorder features. In a comparison of ICAT and CBT-ED for BN, the two treatments did not differ overall in their impact on bulimic symptoms, depression and anxiety[291]. However, when specific personality traits were included in the statistical model to examine differential efficacy of each treatment for different personality types, there were differences. Specifically, individuals higher in stimulus seeking had greater reductions in bulimic behavior and ED psychopathology when receiving ICAT than when treated with CBT-ED, whereas individuals lower in stimulus seeking had greater reductions in bulimic behavior with CBT-ED than ICAT. Additionally, individuals with higher affect dysregulation had greater reductions in ED psychopathology in the ICAT than in the CBT-ED condition[292].

For clinicians wishing to evaluate personality, brief assessment tools for ICD-11 and DSM-5 personality trait domains include the 17-item Personality Assessment Questionnaire for ICD-11 (PAQ-11)[293] and the Personality Inventory for DSM-5-Brief Format (PID-5-BF)[294], respectively.

FAMILY HISTORY

There is substantial evidence that EDs run in families. Ascertaining family history is therefore an important element of clinical assessment.

Family and twin studies show that heritability estimates are high across EDs, with variable estimates depending on the disorder[295]. Twin-based heritability estimates are highest for AN (0.28-0.74)[296-298]; intermediate (0.55-0.62) for BN[297,299,300]; and lower for BED (0.39-0.45)[301-303]. A high twin-based heritability of a broad ARFID phenotype (0.79) has also been identified[304].

The risk of EDs in first-degree relatives of individuals with EDs is about 7-10-fold higher compared to the general population[305]. An investigation of whole population samples in Denmark and Sweden estimates heritability of diagnosed AN at 0.36 and BN at 0.39. This study also found that having a parent with AN is associated with a 3-fold increased risk of being diagnosed with AN[306]. Family history of other psychiatric disorders, such as anxiety and depression, is also higher in individuals with EDs[307].

Ascertaining parental ED and other psychiatric morbidity might be helpful in aiding treatment in children and adolescents

(as that morbidity might impact on treatment), but also in identifying potential traits contributing to individual clinical presentations (e.g., in the case of autism spectrum disorder or anxiety) and formulation, as well as aiding individual understanding of the disorder itself.

The last ten years have seen an exponential growth in our understanding of genetic risk for EDs (particularly AN). Two GWAS have been carried out for AN[308,309], providing insights into the genetic etiology of AN and its genetic overlap with other psychiatric disorders (e.g., OCD, schizophrenia, anxiety) and anthropometric/metabolic factors (e.g., BMI, insulin levels, diabetes mellitus).

Whilst quantifying genetic risk (in the form of polygenic risk scores) is not yet useful in clinical practice, naming the contribution of genetic factors to the development of EDs in a clinical setting may be helpful. Clarification of the role of genes as well as environment during a diagnostic assessment might allow not only moving away from the dichotomy of individual responsibility in illness development (which often manifests as guilt in adult individuals and in caregivers) vs. genetic determinism, but can also help defining treatment targets and adherence to treatment[310-312].

ENVIRONMENTAL EXPOSURES

Most EDs emerge before the age of 25 years. Of these, 40% emerge in adolescence and 49% in early adulthood[313]. When considering environmental exposures, the notions of intersectionality and developmental sensitivity are critical. For example, genetic influences and non-shared environmental influences impacting on the emergence of disordered eating increase significantly over puberty, while shared environmental influences decrease and become negligible[314]. In other words, there is dynamic interplay between multiple genetic and non-shared environmental risk factors over the critical developmental span where EDs emerge.

Therefore, none of the early or recent environmental exposures discussed in this section should be viewed as silos, but rather as part of a rich and complex tapestry of risk and maintaining factors. A comprehensive assessment of relevant environmental exposures in practice should consider these interactions and the unique constellations of factors for each patient. It is notable that the vast majority of studies on environmental exposures is focused on general ED pathology or BN, and to a lesser extent AN and BED. Relatively little is known about risk factors for other FEDs, including ARFID, pica and rumination disorder.

Early environmental exposures

A range of early environmental exposures have been investigated in relation to EDs, and have been found to contribute to their development, although much of the research relies on retrospective studies, potentially impacting the reliability of the evidence generated.

Available evidence from large studies on the role of pregnancy, obstetric and perinatal factors points to higher risk related to prematurity, lower birth-weight, and small for gestational age for AN, higher birth weight/large for gestational age for BED, and pregnancy smoking and prematurity for BN[163,315]. Although few studies are available in ARFID, initial findings suggest higher prevalence of preterm birth, postnatal complications and invasive procedures (involving the gastrointestinal or respiratory tract) postnatally in children with this condition[316]. This matches clinical observations and has relevance for guiding treatment in ARFID.

Enquiring about obstetric complications in the context of EDs may not impact on treatment planning or prognosis of the individual. However, where women with an ED are planning to get pregnant, it is important to provide them with information on reducing ED behaviors during pregnancy, as this may improve outcomes for their unborn child and decrease the risk of intergenerational perpetuation of the ED. In ARFID, obtaining a detailed history of perinatal complications is essential, as the sequelae of obstetric factors and/or early postnatal invasive procedures may have impacted on oral sensitivity and/or led to food aversion(s) and therefore may require a specific focus in treatment[316,317].

The literature supports an association between childhood maltreatment and EDs. An umbrella review[318] found associations between childhood sexual abuse and BN, and between appearance-related teasing and any ED, based on meta-analyses pooling longitudinal observational studies. These findings corroborate the role of early traumatic experiences as risk factors for EDs and add to previous evidence of higher prevalence of childhood maltreatment in EDs compared to both healthy controls and individuals with other psychiatric disorders[319].

Compared to patients without a history of maltreatment, those with such a history have a more severe clinical presentation, earlier onset, higher rates of comorbidity[319] and poorer treatment response[320,321]. Putative mediators of the association between childhood maltreatment and EDs have been investigated through different methodologies[322,323], but results are not conclusive[324]. Preliminary experimental evidence suggests that childhood maltreatment may lead to a heightened sensitivity to social stress in adulthood[325].

Overall, early trauma may be considered an important diagnostic specifier that can alter treatment response, and the evaluation of childhood maltreatment history should be part of clinical routine assessment. The Childhood Trauma Questionnaire[326] is a self-report tool commonly used to assess childhood maltreatment in terms of emotional abuse and neglect, physical abuse and neglect, and sexual abuse. However, it does not provide information about timing, severity or duration of maltreatment exposure and relies on the individual's recall. Bearing in mind these possible biases, this instrument can be considered for use in clinical practice.

There is preliminary evidence for the use of schema therapy[274] and cognitive analytical therapy (CAT)[327] in the treatment of EDs, and established evidence for dialectical behavior therapy in the treatment of BED[5]. These treatment models consider early trauma experiences and may provide alternative options for patients who have not been helped by first-line ED treatments (e.g., CBT-ED, MANTRA). However, first-line evidence-based treatments should always be tried first, and these can be tailored to ensure that care

is trauma-informed and considers comorbidities, including PTSD, if present[190].

Early adverse experiences also include insecure attachment bonds. Disrupted interactions with early caregivers promote the development of maladaptive schemata about the perception of self and others[328]. Insecure attachment is more common in individuals with EDs compared to community controls, and meta-analytic evidence of this association points to medium-to-high effect size, despite some limitations[251,329]. Maladaptive emotion regulation and depressive symptoms were the strongest mediators of this relationship[330]. However, given a lack of longitudinal and experimental studies, these findings are not exhaustive. Moreover, preliminary data suggest a possible reciprocal interaction between insecure attachment and childhood maltreatment[331,332].

Of note, insecure attachment can affect treatment outcome via its effect on the development of the therapeutic alliance[329]. Several self-report measures have been developed to assess attachment style/relationships, including the Experience in Close Relationship[333] and the Attachment Style Questionnaire (ASQ)[334]. Focal psychodynamic therapy[335] is an evidence-based treatment option for AN which targets attachment-related issues.

Recent environmental exposures

The role of stressful life events in precipitating ED onset is well established, with interpersonal and sexual-type events being of particular significance[336]. There is also some evidence from qualitative and quantitative studies that negative life events are implicated in ED relapse and poorer treatment outcome, whereas positive life events may facilitate recovery[336].

The wide range of interview and questionnaire measures to assess life events and difficulties have been previously reviewed in this journal[30-33]. A novel electronic, structured approach for obtaining and graphically representing data on life stresses and their impact on mental health is provided via the Tulsa Life Chart (TLC)[337]. This tool covers distinct life epochs (birth to elementary school, elementary school, middle school, high school, young adulthood, age 25 to 35, 35 to 45, etc.) and assesses negative and positive life events, and epoch- and event-related mood ratings, in the broader context of factors such as school attendance, hobbies, jobs, social support, substance use, mental health treatment, and family structure changes. As yet, this is an interview-based tool, but self-report versions are planned.

The importance of stress in the onset and course of EDs has been highlighted by the significant increases in ED presentations at treatment facilities around the world since the advent of the COVID-19 pandemic[338]. Young people seemed particularly affected. Multiple acute and chronic stressors were identified as contributing to worsen the mental health of young people during the pandemic, such as social isolation, excessive screen time and social media use, parental stress, poor parent-child relationship, low socioeconomic status, pre-existing mental health conditions and/or disabilities[339,340]. It can be helpful for clinicians to enquire about how FED symptoms were impacted by, or developed alongside, the COVID-19 pandemic, in order to understand any precipitating or maintaining factors relevant to treatment.

Strong evidence exists to implicate appearance pressures in the development of EDs[341,342], and preventive programmes targeting thin ideal internalization have been shown to reduce incidence of EDs[343]. A longitudinal study of risk factors for the emergence of disordered eating in adolescent females showed that weight-related peer teasing significantly strengthened genetic risk for the development of disordered eating, a gene-environment interaction[344]. A meta-analysis of experimental evidence showed that exposure to social media appearance-ideal images had a moderate negative effect on body image in the short term, although longer-term impacts of naturalistic use of social media are less clear[345,346].

Given the significant pressures around appearance on many patients with EDs, enquiring about appearance ideals as well as patient's social media use is an essential part of the clinical assessment. The Sociocultural Attitudes Towards Appearance Questionnaire-4-Revised (SATAQ-4R)[347] is a widely used measure of appearance pressures, but is relatively long to use in routine clinical practice.

As mentioned earlier in this paper, EDs affect certain minoritized groups at elevated rates. These include people with a second-generation migration background[348]; LGBTQ+ individuals[349], as well as people at higher body weight. There are consistent correlations between experiences of discrimination (racial, sexual, ethnic, weight-based) and disordered eating symptoms, suggesting that minority-stress factors may partially explain this higher prevalence[350]. Individuals with BN and BED are two to three times more likely to have been bullied or teased about their appearance compared to those without EDs[351].

A short measure of everyday discrimination which is able to accommodate different minoritized characteristics, asking people if they are being discriminated in their daily life (e.g., whether they are treated with less courtesy or respect or whether they are given a poorer service) and how often this happens, may offer a useful way of starting a conversation about the topic of minority stress[352].

Income level and employment status do not predict the development of ED[342]. However, there is some evidence that socioeconomic status can be associated with the type of ED behaviors: low socioeconomic levels may predict binge-purging behaviors, while higher education may be associated with food restriction[353]. More recent work has shown that intersectionality is important here, with some evidence of increased likelihood of a positive ED screen in groups with *lower* socioeconomic status, particularly those from Hispanic/Latinx and sexual minority backgrounds[97]. Food insecurity may be one factor driving EDs in groups with lower socioeconomic status, potentially via a "feast and famine" cycle of food availability.

Nascent evidence shows that bulimic-type difficulties (binge eating and compensatory behaviors) are more common in adults (but not necessarily adolescents) who are food insecure[354,355]. Moreover, experience of childhood food insecurity is associated with binge eating behaviors[355]. Importantly, low socioeconomic status is a barrier to early access to specialist treatment for EDs[161].

The US Department of Agriculture offers a suite of measures to

assess food security in adolescents, adults and households, with a brief, 6-item screening tool typically being most suitable for use in clinical practice[356]. It is important that, where food insecurity is identified, the individual's lack of financial resources is taken into account in meal planning and other aspects of treatment (e.g., travel).

STIGMA

Stigma is consistently found to have a major and adverse impact on people's well-being, and their ability to access and engage in appropriate treatment for their ED. For people with an ED, stigma occurs across many levels and is multifaceted. It is experienced regarding the presence of a mental disorder, the presence of an ED, and the presence of high or low weight. It may be expressed in cognitive (e.g., stereotypic beliefs that people with AN should "just eat"), emotional (e.g., disgust towards people who vomit after eating), and behavioral (e.g., not providing appropriate care for someone who is of "adequate" weight) terms[357]. Stigma is also typically suffused with moral connotations, i.e. labelling ED symptoms and behaviors as "sinful or selfish" and arising from "vanity" or "greed", or being "wasteful of food".

The experience of stigma may subsequently be internalized. A negative association was found between self-stigmatization and effective help-seeking[358], and it was observed that this may be a stronger phenomenon for men than women with EDs[359]. However, a meta-synthesis of 29 papers[358] also highlighted people's capacity to utilize "resistive" strategies to challenge stigma, e.g. seeking validation through peers, and reported that such strategies are associated with better outcomes.

A large body of literature has affirmed the association between stigma and inadequate treatment, although this mostly lies in the qualitative research space[360]. Many investigations have described a fear of exposure and an anticipated or actual negative response from health professionals when seeking treatment, albeit in one meta-analysis there was a suggestion that the role of stigma may have been overstated as a barrier to care[361].

Stigma and beliefs that EDs are not serious or impactful may have contributed to their under-recognition and neglect from policy makers and funders of mental health training, research and treatment[362,363].

The modified Weight Bias Internalization scale (WBI-M)[364] can be used by patients across different body sizes to assess their weight-related self-stigmatization. The patient-rated Scale for Treatment-Based Experiences of Weight Stigma (STEW)[365] may help assess whether individual therapists, treatment teams, or peers engage in stigmatizing beliefs or actions in relation to people with EDs at higher body weight.

At a population level, improved health literacy and understanding should reduce stigma. However, this is difficult to achieve. Training of health practitioners to reduce bias and combat/disrupt the impact of stigma and shame around help-seeking is also needed. The importance of moving research forward has been emphasized[357], not least as it is the vulnerable (young and socio-economically impoverished people) who experience most of the negative impacts of stigma.

PROTECTIVE FACTORS

Potential protective factors – which may reduce ED risk, mitigate the noxious influences of recent and early environmental exposures, and support recovery – include some ED-specific factors (such as learning to appreciate or accept one's body, challenging unrealistic appearance ideals, minimizing exposure to appearance-focused material in social media, learning to enjoy a healthy diet) and some broader factors (such as enhancing self-compassion to offset the self-criticism that can be a consequence of unfavorable comparisons, and strengthening social connection).

Body appreciation is defined as accepting, holding positive attitudes toward, and valuing the body. A meta-analysis of 240 studies found that body appreciation was inversely associated with several indices of eating and body image disturbances, as well as general psychopathology (depression, anxiety), and positively associated with several well-being constructs (such as self-esteem and self-compassion)[366]. A longitudinal study of 3,039 women found that body appreciation was associated with lower levels of eating pathology eight months later[367]. The Body Appreciation Scale-2 (BAS-2)[368] is a widely used 10-item measure to capture body appreciation in adults, and a recent 2-item version offers a brief measure that may be particularly practical for clinical use[369].

There is current debate in the literature about positive body image (an individual's ability to conceptualize her/his body with love, respect and appreciation)[370] versus body neutrality (a neutral and mindful attitude toward the body, with self-worth being broadly defined and not dominated by appearance)[371]. Future research is required that examines meaningful differences and impacts of the two concepts. Currently, body-image focused treatment components or adjuncts to treatment for FEDs, such as mirror or virtual reality-based exposure treatments[372], tend to focus more on reducing body dissatisfaction and achieving a neutral or accepting stance to one's body rather than increasing appreciation.

Approaches that enhance individual critical appraisal of appearance ideals are effective at protecting against or reducing body image concerns and, to some extent, in helping FED treatment. These include enhancing media literacy (the ability to critically engage with and evaluate media content), as well as directly challenging thin ideal internalization using cognitive dissonance-based exercises. These approaches support individuals in being able to critically consider the credibility of media sources, the veracity of images, and the values and intentions that underpin media content creation, thus minimizing internalization of appearance ideals and engagement in social comparisons[373].

Public health approaches to tackle unhelpful media content are an important element. However, attempts made to minimize the negative impact of media content, via strategies such as disclaimers on images (e.g., highlighting when digital manipulation

has been applied), have consistently been shown to be ineffective[374].

Self-compassion is increasingly recognized as a factor aiding ED recovery. It involves treating oneself with kindness and encouragement rather than self-criticism when facing challenges. It has been hypothesized to be protective by providing an adaptive process to manage negative emotions, self-criticism and self-critical perfectionism which might otherwise trigger/exacerbate ED behaviors[375].

A meta-analysis found that self-compassion is associated with lower eating pathology, and that self-compassion interventions are effective at reducing ED symptoms[376]. In the clinical context, the Self-Compassion Scale[377] is useful as a brief assessment tool. Most empirically-supported ED treatments, with the exception of MANTRA[378], do not directly target improving self-compassion. Compassion-focused therapy may be particularly useful for patients with a trauma history[379].

High levels of loneliness and disordered eating have been shown to be mutually reinforcing[380], suggesting that building positive social connection may be a key protective approach. Analysis of the National Longitudinal Study of Adolescent to Adult Health found that both mother- and father-connectedness is associated with lower odds of onset of a range of ED symptoms six years later in girls (but not in boys)[381]. Parents can also build a protective home environment by supporting regular family meals and engaging in conversations around food that do not focus on dieting or weight[342].

Relatively little is known about the protective role of positive social connection to peers, but there is some evidence that a strong sense of social support from friends may buffer against the development of body image concerns and disordered eating[382]. Importantly, positive social support is also the most prominent facilitator to engaging in help-seeking for FEDs[360].

Loneliness can be measured directly (i.e., by asking "how often do you feel lonely?") or indirectly (i.e., by asking about emotions associated with loneliness). The 3-item UCLA Loneliness Scale is the most widely used measure of loneliness, assessing relational connectedness, social connectedness, and self-perceived isolation[383]. The 10-item Significant Others Scale (SOS)[384] allows differentiation between actually received and ideal level of emotional and practical social support from others. The 19-item Medical Outcomes Study Social Support Survey[385] distinguishes between emotional, tangible and affectionate support and positive social interaction with others.

Given the evidence that dieting is a risk factor for EDs[341], it seems likely that good nutrition may protect against the development of or relapse from an ED. Whilst most Western countries have published official guides for healthy eating, only the Australian REAL Food Guide is tailored to the specific needs and beliefs of people with FEDs, and includes a user-friendly food pyramid[386].

A thorough clinical assessment should include evaluation of ED-specific and broader protective factors that may support improvements or recovery from an ED. In addition to covering the areas described above, it will be helpful to ask patients to complete the VIA Assessment Suite for Adults[387], to help them attend to those strengths that may have become neglected or side-lined during their illness, and those that they might not recognize as having the potential for supporting their recovery.

DISCUSSION

This paper has attempted to systematically describe some of the key clinical domains that should be considered when trying to personalize the management of FEDs, along with relevant measurement tools. For most of the domains presented here, it is currently not known how to prioritize, combine or sequence these considerations in order to improve patient outcomes, except for the need to prioritize high medical risk when determining treatment setting and intensity.

At the heart of FED management is psychological treatment. A generic three-dimensional conceptual framework of personalization of psychological therapies has been proposed[388]. This framework includes the timing at which personalization decisions are made in a patient's treatment pathway – e.g., at initial assessment, throughout the course of treatment, or at the end of it (such as to determine need for and type of relapse prevention). Secondly, it considers the level, type and intensity of treatment, choice, combination and sequencing of techniques, or style of delivery. Lastly, it deals with what the authors call "structure", i.e., the method of personalization that is used. The latter is on a continuum from informal idiosyncratic personalization, based on clinician "intuition" and/or patient choice, through to theory- and data-informed integrative or matching approaches and other adaptations of standard treatments for particular populations, up to data-driven actuarial approaches to enhance treatment decisions. Evidence-based clinical guidelines lie somewhere in the middle of the "structure" spectrum. Whilst this framework was designed specifically with psychological therapies in mind, it can readily be applied more broadly to other treatment and clinical management decisions.

Across the EDs, there are very few replicable baseline predictors of outcome[117]. A recent meta-analysis[18] found that children and adolescents (i.e., those with typically shorter illness duration) had more favorable outcomes than adults, and those with self-harm had poorer outcomes than those without. These data support the principles of illness staging and emphasize the importance of early detection and easily accessible early intervention with developmentally and illness stage appropriate treatments. The data also highlight the need to take comorbidities into account when personalizing treatment for FEDs.

A key finding is that, across different evidence-based treatments and all EDs, early treatment response (i.e., reliable symptom improvement during the first four sessions) is a solid predictor of recovery[42]. In AN, trajectory studies based on BMI during early treatment sessions found that there were broadly three groups in terms of outcomes: "hares", "tortoises" and non-responders[389,390]. These studies confirm that those with the most rapid early change do best in the longer term ("hares"), but also identified a class of patients that after a slower start did well in the longer term ("tortoises"), together with another group that dete-

riorated or was unchanged.

Thinking about types and levels of interventions in different populations, for those at the milder end of illness severity or with fewer comorbidities and complexities, there is growing interest in programme-led, focused interventions[391] and single-session interventions[392], which may increase access to treatment, reduce waiting times, and allow treatment to be provided in more flexible and personalized ways (including online and digital solutions). Conversely, there is a need for further research on intensive treatment programmes for EDs and how to optimally use these for patients who require higher levels of support and do not benefit from standard outpatient care[393].

Personalization through adaptation of Western evidence-based treatments to different cultures – e.g., East Asia[394] – or to minoritized ethnic/racial groups[395] is also an area of growing interest, but with limited research. It is also important to hold in mind that, in the case of these groups, minority status is often intersectional with other indicators of disadvantage which may need to be considered. It has been posited that current measures may not adequately capture eating pathology in marginalized groups, given the different drivers of pathology in such groups (e.g., dietary restraint due to food insecurity rather than to weight/shape concerns). Biased measurement may contribute to sub-optimal diagnostic screening, prevention and outcome measurement[396].

Personalization based on age fits with the traditional divide into child/adolescent and adult services, and some staging approaches. However, emerging evidence suggests that family-focused and individual therapies, previously recommended for young people aged below 18 years or adults respectively, can be effectively developmentally adapted to fit older or younger age groups[17,397], by including more or less intensive family involvement and support from others (partners, friends), whilst also acknowledging the young person's need to become an independent adult.

Advances in personalization through patient stratification and prediction of clinical outcomes are likely to come from large-scale real-world data, including genomic and deeply phenotyped clinical information, together with comorbidity and treatment outcome data[398]. In FEDs, the newly established Eating Disorders Clinical Research Network (ED-CRN) (www.kcl.ac.uk/research/eating-disorders-clinical-research-network) aims to capture such data across the full range of ED patients presenting to services across the UK. In addition, studies are needed that integrate information from real-time deeply phenotyped longitudinal data, using remote measurement technology with active and passive sensing, to provide better delineation of biological and psychological components of different illness and recovery trajectories across FEDs. A number of studies on this topic are in progress, with the ultimately aim of using characteristic data signatures to aid improved illness staging and the development of protocols for just-in-time interventions[28,399-401].

An emerging novel precision approach to personalizing psychological treatments, which is not for particular subgroups or clusters of patients, but truly individualized, is via the use of idiographic (one person) network models of ecological momentary assessment symptom data to individually match participants to evidence-based modules of treatment[29,402]. In an open case series, this approach was found to be highly acceptable and feasible. A clinical trial is now in progress to assess whether this approach improves outcomes compared to standard psychological treatments for FEDs[403].

Beyond the realms of personalized psychotherapies, novel brain-targeted treatments (e.g., brain stimulation approaches) are also emerging as safe and acceptable precision treatments for FEDs[404]. These tools allow neuroimaging-guided targeting of specific brain circuits underpinning specific symptoms, such as low mood, anxiety or emotion regulation, with additional methods of personalizing this approach via individuals' brain connectivity or EEG patterns or other physiological parameters[405].

Advances in precision nutrition-based interventions for obesity are emerging[406], with clear relevance to FEDs. Such precision nutrition takes into account both individual-level and environmental characteristics, such as genetic predisposition, circadian rhythms, physical activity and sedentary behavior, metabolomics, the gut microbiome, and behavioral and socio-economic characteristics[406]. Data for the application of such an approach to FEDs are as yet lacking.

In light of these more recent developments, one challenge for the field is that the most widely used evidence-based treatments – CBT-ED and FBT – are based on manuals that are more than 20 years old. These (and other) evidence-based treatments need to be adapted in light of new insights into comorbidities and major sociocultural shifts, including consideration of under-served groups, in order to personalize treatment and improve clinical practice[407].

One key recommendation[407] is providing patients (and families) with up-to-date personalized psychoeducation. Examples of this include the psychoeducational resources for young people with early-stage EDs on the FREED website, which highlight the malleability of brain and other biological changes in the early illness stages (www.FREEDfromED.co.uk). Such malleability narratives have been found to increase patients' hope and recovery expectations[408].

Ultimately, the holy grail is the development of precision approaches to personalization of ED care. To drive this field forward, several factors need to be considered. Even if one accepts the utility of measurement-based precision approaches to personalizing psychological treatments, their implementation is complex. A generic framework for implementing these approaches has been established, giving consideration to evidence supporting them, as well as facilitators and barriers. Demonstrating the value of such approaches to patients and clinicians and getting their "buy-in" is crucial[22].

Moreover, the current disparity in research funding (for example, per-person research funding for schizophrenia in the US and Australia is 69 and 84 times larger than for EDs, even though these disorders are comparable in terms of YPLL[8]) needs to be remedied urgently, to drive the field forward and obtain the improved understanding of underlying neurobiological, genetic, environmental, nutritional and psychosocial drivers of FEDs that is

needed for optimal personalization of prevention, treatment and care.

Finally, to achieve truly personalized care, people with lived experience of FEDs and their carers need to be involved in co-production of new research, treatment and service initiatives designed to address this issue[409], from their inception and throughout.

ACKNOWLEDGEMENTS

U.H. Schmidt receives salary support from the UK National Institute of Health Research (NIHR) Biomedical Research Centre (BRC) at the South London and Maudsley NHS Foundation Trust and King's College London. K.L. Allen is supported by the Medical Research Council (grant no. MR/X030539/1); H. Sharpe by UK Research and Innovation, the National Institute for Health and Care Research, and the Medical Research Foundation (grant no. MR/X03058X/1); F. Fernández-Aranda by the Instituto de Salud Carlos III, the AGAUR-Generalitat de Catalunya, and the European Union's Horizon 2020 Research and Innovation Program; N. Micali by a Novo Nordisk Foundation Laureate award (NNF22OC0071010); T.D. Wade by the Australian National Medical and Health Research Council (grant no. 2025665); S. Wonderlich by the US National Institutes of Health (grant no. P20 GM134969). U.H. Schmidt, K.L. Allen and H. Sharpe are also supported by the Medical Research Council/Arts and Humanities Research Council/Economic and Social Research Council Adolescence, Mental Health and the Developing Mind initiative as part of the EDIFY programme (grant no. MR/W002418/1). The views expressed herein are those of the authors and not necessarily those of the supporting institutions. K.L. Allen and H. Sharpe are joint last authors of this paper.

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DOI:10.1002/wps.21263

The lived experience of postpartum depression and psychosis in women: a bottom-up review co-written by experts by experience and academics

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This is the first bottom-up review of the lived experience of postpartum depression and psychosis in women. The study has been co-designed, co-conducted and co-written by experts by experience and academics, drawing on first-person accounts within and outside the medical field. The material initially identified was shared with all participants in a cloud-based system, discussed across the research team, and enriched by phenomenological insights. The subjective world of postpartum depression is characterized by a sudden onset ("being hit with a ton of bricks"), unbearable loneliness and sadness that are often suffered in silence, inability to feel positive emotions, grieving over the loss of self, feelings of being bad mothers (haunted by a suffocating burden of guilt due to that), inability to concentrate, lack of control of thoughts ("feeling like a tightrope walker without control over thoughts and emotions"), insecurity (up to needing to be nurtured and mothered themselves), and thoughts of death ("contemplating death as a glimmer of hope to escape the living nightmare"). In addition to these themes, the subjective world of postpartum psychosis is characterized by difficulty in articulating thoughts ("feeling the brain in a centrifuge"); perceptual abnormalities and unusual beliefs disrupting the sense of personal unity (with, in a few cases, thoughts of harming themselves or their baby, so that women may feel that they are "sinking in the depths of hell"); losing trust ("ploughing through the fog and losing trust and safety"), and stripping down relationships. Much of the isolation, guilt and disorientation experienced in these conditions relates to sociocultural and family environments, especially a gulf between how women feel and a web of norms and expectations surrounding motherhood. In most cases, stigma is related to a lack of knowledge of what postpartum depression or psychosis are. Stigma and lack of knowledge are core drivers impacting health care in terms of seeking professional help, accessing mental health services, and receiving pharmacological or psychological treatments. The narratives described in this paper should inform clinical practice, research and public health education. This study brings voice to the unspoken and unheard, and fosters relational connections within which different mothering experiences may be expressed and understood. This is vital to challenging negative sociocultural attitudes towards postpartum depression and psychosis, and providing the most supportive care to women experiencing such pervasive psychiatric disorders at a critical, fragile time in their lives.

Key words: Postpartum depression, postpartum psychosis, lived experience, first-person accounts, mood disorders, psychotic disorders, mental health care, recovery

(World Psychiatry 2025;24:32–45)

Perinatal (i.e., occurring during the pregnancy or in the first twelve postnatal months) mental disorders represent a significant clinical and public health concern[1], being associated with substantial personal burden, impact on bonding with the baby; later physical, cognitive, emotional, behavioral and social developmental outcomes in the offspring; complex treatment challenges, high economic costs, and – in the most severe cases – increased risk of maternal suicide[2-4] and of the very rare outcome of infanticide[5].

Alterations of mental health in the perinatal period range from mild and self-limiting depressive features (i.e., "baby or maternity blues"), that are highly frequent (up to 40-50%)[6] but represent physiological adaptations, to clinically significant and impairing depressive or psychotic disorders.

Globally, about one in four women experience perinatal depression. The prevalence is higher in low- and middle-income countries[7], in women who experienced intimate partner violence, and in those with a previous history of mental disorders[8].

Perinatal psychosis is considered a rare disease[9], with only about two in a thousand women affected globally. The prevalence is higher in women with a previous history of mood disorders[10]. Notably, psychotic symptoms may present as extreme features in postpartum depression, and these episodes may be the initial presentation of a psychotic bipolar disorder[11,12].

As the risk of developing these disorders peaks in the first few weeks after delivery[13] (e.g., the relative risk for the first onset of affective psychosis is 23 times higher during postpartum than in any other period[9]), they are also termed "postpartum" depression and psychosis. Because of the risk and high impact on the mother-baby dyad (postpartum psychosis is considered a psychiatric emergency[1]), screening women for these conditions and preventive interventions are clinically recommended[14-16].

Yet, postpartum depression and psychosis remain poorly managed globally. This is partly due to the poor understanding of the qualitative nature of these experiences, as they are typically siloed

in academic investigations lacking first-person perspectives or, on the other hand, in autobiographical accounts lacking in-depth analyses.

To the best of our knowledge, this is the first bottom-up review of the lived experience of postpartum depression and psychosis. Experts by experience co-designed, co-conducted and co-wrote the study, leveraging an established methodological template developed by our group to investigate the lived experience of psychosis, depression, and mental disorders in adolescents[17-19].

Experts by experience of different ages and ethnicities, from multiple continents (Europe, Asia and Africa), were invited to participate through the Global Mental Health Peer Network (https://www.gmhpn.org). The Web of Science, PubMed and EBSCO were searched from inception until February 2024, using the terms (postpartum* psychosis OR postpartum* depression) AND (qualitative OR etnograph* OR phenomenol* OR "lived experience").

We included qualitative studies providing first-person accounts that involved women with a diagnosis of postpartum depressive or psychotic disorder (postpartum psychosis generally refers to a manic, mixed or major depressive episode with psychotic features, a brief psychotic disorder, or a psychotic disorder not otherwise specified[20]), as operationalized by each individual paper. Notably, the nosological status of these disorders remains contentious, partly because of the "mercurial nature"[21] of their symptoms, which vary widely and have rapid fluctuations. While the ICD-11 includes a distinct diagnostic category, the DSM-5 recognizes them as specifiers of depression or psychosis. We did not include baby or maternity blues, and mental disorders occurring in men transitioning to fatherhood (e.g., postpartum depression in fathers)[22].

Researchers produced a thematic synthesis of selected papers and generated a preliminary list of descriptive themes and subthemes. Further sources external to the medical domain, including autobiographical books (see Table 1), websites, blogs, and social media material written by experts by experience were also considered within the synthesis.

We stratified the material across four overarching descriptive sections (each including themes and sub-themes): "The subjective experience of postpartum depression", "The subjective experience of postpartum psychosis", "The lived experience of women with postpartum depression or psychosis in the wider society", and "The lived experience of women with postpartum depression or psychosis in receiving mental health care".

Experts by experience and academics collectively interacted to draft and review the manuscript via a shared Google Drive platform, and enriched it with phenomenologically informed perspectives[30-46]. All experts by experience actively participating in the manuscript elaboration were offered reimbursement for their time, adhering to available guidelines[47], and were invited to be co-authors. As in previous papers of this series[17-19], first-hand quotes are cited and reproduced verbatim in italics. Commentaries from co-author experts by experience are anonymized as "personal communications".

While this study outlines the most paradigmatic ways by which postpartum depression and psychosis manifest, we neither assume that the reported experiences are exhaustive nor that they are systematically applicable to all women. On the contrary, we acknowledge the fluctuating presentation and kaleidoscopic variability[12] of the lived experiences reported.

Table 1 Selection of publications on the lived experience of postpartum depression and psychosis considered for this review

Hanzak EA. *Eyes without sparkle: a journey through postnatal illness*[23]
Munday A. *Day nine: a postpartum depression memoir*[24]
Redhouse N. *Unlike the heart: a memoir of brain and mind*[25]
Aiken C, Brockington IF. *Surviving post-natal depression: at home, no one hears you scream*[26]
Osmond M, Wilkie M, Moore J. *Behind the smile: my journey out of postpartum depression*[27]
Wight J. *Rattled: overcoming postpartum psychosis*[28]
Shields B. *Down came the rain: my journey through postpartum depression*[29]

THE SUBJECTIVE EXPERIENCE OF POSTPARTUM DEPRESSION

In this section, we describe the subjective experience of postpartum depression across several characteristic themes.

Being hit with a ton of bricks

Many women feel that postpartum depression emerges suddenly out of the blue, and hits their lives with unprecedented violence: "*It hit me like a ton of bricks. I never would have imagined that could have all happened so suddenly*"[30]. As most of them never experienced a severe mental health problem, they typically have no idea of what is happening and cannot understand what they are going through: "*You are normal and then the next thing, you know, you're crazy*"[30]. This experience is particularly shocking in those women who tend to be neat and precise in their management of interpersonal relations and life events[31,32]: "*I've planned everything in my life, I've been used to doing it this way forever*"[33].

Women often try to describe the sudden and profound change in their mental status by referring to darkness ("*I was in the total dark the whole time*"[30]) or suddenly being in a cold place ("*My living nightmare put me in a very cold place*"[30]). Images of water, waves and the sea – like they are drowning and no one is rescuing them, leaving them in the depths of a dark and cold ocean – are sometimes used: "*I felt like I was in the middle of the sea and no one was able to understand*"[30].

Being enveloped in unbearable loneliness and sadness that are suffered in silence

Most women with postpartum depression report an unbearable loneliness: "*It is just a very lonely illness*"[30]; "*The emptiness, the endless loneliness*"[27]; "*One thing you're not prepared for is the feeling of loneliness*"[34]. This experience may relate to both the depressive symptoms themselves and the associated personal or so-

cial situation. It typically peaks during the night: "*I felt totally alone. If the whole world were in my front room, I would still have felt this terrible isolation. The loneliness was even more evident at night*"[26].

Common feelings are an immense sadness ("*I couldn't stop crying, and I was just feeling this overwhelming sadness*"[35]), which is different from previous transient experiences of low mood ("*This was a sadness of a shockingly different magnitude. It felt as if it would never go away*"[29]), and a profound despair ("*I would get up in the morning and… this awful feeling of loneliness and sadness and doom and gloom would come over me. I would just get worse as the day went on*"[36]).

Central to these women's experience is a sense that their negative feelings are unspeakable[36,37]. No words can explain the contrast between their feelings and the new motherhood: "*Where do you find the words to explain that you can hold a new life in your arms and still feel no hope for the future?*"[27]. Most women suffer in silence, because they feel that no one can understand: "*I didn't have anyone to talk to and no one actually knew about me being diagnosed with postnatal depression, my mum or anyone, no one knew, not even my partner*"[38]. Consequently, a common experience is the mismatch between their inner suffering and their apparent smiling façade: "*My smile is like a two-way mirror. I can see out, but no one can see in. No one sees what is going on behind the smile*"[27].

Those who have migrated away from their families, friends and communities into a new foreign country, where they have no established social network, may be particularly vulnerable to loneliness and silent suffering following the birth of their child: "*Have got nobody to help*"[39]; "*No one was nearby to assist. I had no one to turn to. I think I had no security, no sense of safety*"[40]. However, feelings of loneliness are commonly reported by women with available social and emotional support, as they feel that their experiences are intrinsically uncommunicable, or that most of their attempts to share their suffering with their family members remain unsuccessful[41]. This profound loneliness may amplify feelings of disconnection regarding the self, the baby, and the social and material world (see below).

Feeling like mechanical robots stripped of all positive feelings

Women with postpartum depression typically report being unable to feel positive emotions: "*I cannot see anything that makes me happy. People talk about how happy I am to be a mother, but I do not feel anything*"[42]; "*I always pictured being happier with the baby, and now I don't really feel anything*"[43].

They also describe a lack of enjoyment in their usual interests or hobbies, which become unimportant to them: "*Having zero enjoyment for life, as it was dark, it was a dark space… Nothing made me smile, and nothing made me happy, nothing made me enjoy anything*"[44]. They feel that nothing makes sense anymore, not even the little things that usually made them happy: "*It is like you are sitting in a dark bubble*" (*personal communication*). For example, they may no longer desire to have sexual relationships with their partners, or feel angry towards them: "*I wanted nothing to do with sex. I just wanted him to leave me alone and not touch me*"[41]; "*No intimacy. We did not have any sexual relations*"[45].

In some cases, women with postpartum depression feel neither positive nor negative emotions. This experience is described as the "feeling of not feeling"[46], a profound and pervasive sense of the absence of feelings that should be there. The lack of any emotion can be extreme to the point that they may feel psychologically dead: "*Please, someone come in and confirm I'm still alive*"[24].

This is particularly distressing because women experience a profound disconnect to the emotions regarded as "normal", such as feeling joy or love when cuddling, feeding or bathing their newborn baby. They may feel like mechanical robots stripped of any emotional feelings as they are caring for their newborn: "*It was like a withdrawal of emotions. I didn't feel real… I went through the motions of my life without any of the joy*"[41].

These experiences are associated with a profound desire to escape from their body and a sense of discomfort with how their body has changed: "*I want to escape my body. I don't recognize it anymore. I have lost any resemblance to my former self*"[27], which is frequently amplified by feelings of disconnection and depersonalization, and a profound sense of loss of self (see below). Women may feel deprived of their previous emotional repertoire in relation to the new focus and demands posed by the baby, as well as all the changes in their body, and may have the impression of only being a "*walking womb*" or a "*baby carrier*"[48].

However, it is important to note that other women still experience intense love for their baby, although this may involve a deeply felt mix of responsibility, inadequacy, vulnerability, isolation and guilt.

Grieving over the loss of self

Although the birth of a child always evokes an identity shift, this process is much exaggerated in women with postpartum depression: "*Why was I now a shadow of my former self?*"[23]. They lose their sense of self and feel like strangers or aliens: "*I wasn't myself anymore. I became a stranger, an alien. I lost myself*"[30].

Women may feel that they are not the same person they were before the depression hit ("*I know me, I know the 'me' in me. So I have never been like that since I had my baby*"[49]), and they are scared that they cannot offer their true self to their baby: "*It's very scary. You are afraid you are not the same person. You are afraid your child isn't going to have you for a mother*"[30].

They feel that they will never recover their old selves (something that is also often reported in the context of bereavement[39]), and grieve for this loss: "*There's this photo of me shrinking back with dead eyes, looking around not talking to people. Totally, this was not like me. Where was I?*"[30]; "*I did go through a period of feeling like I was mourning the loss of my old life*"[50]. They are frequently frightened that their lives will never be normal again and that happiness is gone forever: "*My big fear was that I wasn't going to get better… that I never would quite get over it*"[41].

At the same time, there appears to be no prospect of consolidating a new identity either (you can't be who you were and you

can't be someone new)[51]: "*I feel incapable, I wish I could go back and reset everything. I wish this child had never been born, it would have been better for everyone*"[33]. The loss of self is exacerbated by a sense of grief surrounding their uncooperative or defiant body (e.g., because they are unable to breastfeed or to wake up to the baby's cries, or unable to stand for long periods with the baby), which is felt as not doing enough to take care of the baby's development: "*I felt like my body just wasn't doing what it was meant to be doing*"[35].

These experiences may ultimately lead to pervasive feelings of depersonalization, like being unreal or in a dream ("*not with it*"[52] or "*out of the self*"[52]), and of detachment from their own life: "*As being in a daze, feeling distant, seeming as if a cloud descended on me, everything looking cloudy and distorted*"[53]. Women frame their experience as feeling alien to their core, internal or authentic selves, as if "*a large part of it doesn't feel real. It's like the baby's here and I'm taking care of him, but it's like I'm numb*"[43].

Haunted by a suffocating burden of guilt for being bad mothers

Women with postpartum depression frequently experience a suffocating burden of guilt over being unable to give their babies the love or care needed, because of the overpowering sadness and despair: "*I'm overwhelmed with guilt*"[24]; "*I feel the guilt of not being able to feel love for my daughter*"[33]; "*I feel only one guilt. I can't feel love for him. I am an asshole. I feel nothing for this child*"[33]; "*To give birth to a child and not be able to take care of it, what kind of person am I then?*"[45]; "*What's wrong with me? Am I going crazy? Why can't I enjoy being with my baby? Will I ever be normal again?*"[41].

These thoughts typically stem from the gap between their expectation of being mothers (i.e., internalized images of "the perfect mother") and the reality of motherhood with depression: "*I thought… I wanted this baby; I'm going to be so happy; everything is going to be perfect. I'll be baking cookies and making soups, and the baby will be sleeping, and I'll nurse him… I had this image that everything would be perfect. When it wasn't, I was shocked*"[36].

A woman with postpartum depression may feel like she "*has no maternal instinct*" and "*can't even take care of herself, let alone a baby*"[27]. For example, she feels unable to bond with her baby ("*Why couldn't I bond with my baby?*"[26]) or feels "*desperate to breastfeed*"[54] her baby to comply with her moral expectations: "*I felt as if I had some moral obligation as a mother and if I didn't breastfeed him I was badly letting him down*"[54]. The inability to breastfeed the baby becomes an inconsolable source of guilt[55]: "*I cried inconsolably many times because of the pressure of breastfeeding*"[42]; "*I am consumed with sadness at the idea of having to forgo breastfeeding. Society places such a high premium on it*"[28].

Similarly, women may feel incapable of comforting their newborn ("*When my son was crying, I wanted to leave him alone in the room, lock the door and walk away*"[56]), because they already struggle to survive ("*I found I had nothing left to give to the ones who needed me the most. I had to stop and save myself*"[27]). These experiences are sometimes associated with fears of psychologically harming their infant ("*I knew I couldn't take care of him, but… I didn't want him to suffer. The guilt made it even worse and the fact I couldn't love him normally made it even worse*"[41]), and the conviction that they could cause depressive features in the baby ("*I think the baby also felt the sadness because you don't pay attention at the time the child needs it*"[57]).

As the notion that mothers "should" be able to take care of children transcends cultures[36], women are reluctant to admit that they are "*drowning in [their] own mind in the happiest time ever*"[58] and that they cannot reach the "relaxing and happy" moral standards of mothering[56]. Because of this dichotomy between expectations and reality[59], they are unlikely to admit these experiences and ask for help, and instead mask their difficulties to maintain their role: "*I gave the impression that things were really great and I was so happy and everything was going fine. And that's what they saw when they came to see us, a lovely baby and a nice house*"[60]. This inevitably places further pressure on themselves and amplifies the contradiction with their poor image, fostering further stress, sadness, guilt, poor self-esteem and self-worth: "*I wasn't worth anything, just like garbage*"[30].

In fact, women frequently experience heartrending feelings of being horrible mothers and failures: "*I was too terrified to hold my baby and I cried even more than he did*" (*personal communication*). These feelings are experienced as physically exhausting ("*The language of postnatal depression was corporeal… a failing of my body*"[25]). They may long for some rest during the night, but sleep is frequently disrupted ("*A very restless night again*"[23]) and their minds keep racing[41] ("*I would lie awake at night having a lot of obsessive thinking*"[41]).

Shrouded in fogginess and unable to concentrate

Women with postpartum depression typically describe intense ruminations and an associated inability to concentrate and think clearly, referred to as "*the fogginess and fatigue [that] would set in*"[41]. They feel that their mind is filled with cobwebs, uncontrollable thoughts and emotions that decrease their concentration: "*I felt like I had cobwebs in my brain. I wished I could put a broom in there and brush away the cobwebs*"[30].

Feeling disorganized and unable to make decisions is also commonly reported: "*I felt like there was just confusion in my head… I was overwhelmed by the simplest thing so easily*"[50]. This severely limits their ability to perform ordinary activities: "*It was difficult to manage daily tasks*"[50]; "*If I went grocery shopping… I would do it, but it would take me four hours to unload the bags and put them away. It was as if I just wasn't efficient at anything. Everything was a big, big deal to do*"[41].

Being a tightrope walker without control over thoughts and emotions

Some women report feeling like a tightrope walker with no safety net below: "*Each day when I was deep into my depression,*

I felt like I was walking a tightrope trying not to fall off and lose my mind"[30]. This feeling of being on edge may resemble "*a see-saw balancing act*"[61]. The experience is related to a loss of control over ruminative and intrusive thoughts and negative emotions ("*I could not control my emotion and behavior*"[62]), which may emerge suddenly ("*Sometimes this losing control just suddenly comes over you no matter what. You never know when it's going to come*"[30]).

Women may feel trapped ("*I had no control and that was a scary thing. I felt trapped. I felt like there was absolutely no way out of this hell. These horrible feelings weren't going to leave no matter how hard I tried*"[41]), and these experiences may amplify their feelings of guilt ("*You are a bad person because you've got something you can't control*"[30]) or of being defective ("*You think you're defective. Something is terribly wrong with me*"[59]).

Sadness may be periodically shattered by uncontrollable and unexpected panic attacks, during which women may feel like they are losing their minds, along with bodily experiences such as tingling hands, difficulty in breathing, digestive problems, sweating, palpitations, and chest pain. These experiences can be so intense that they feel on the edge of dying: "*It's terrible. It's like the worst thing you can imagine. Think of how you would feel if your husband or child had been hit by a car and killed*"[41].

Being besieged with insecurity and needing to be nurtured and mothered themselves

Because of the experiences described above, women typically perceive intense feelings of insecurity, fragility, vulnerability, helplessness and dependency, and of no longer being able to relate to the social world: "*I felt totally insecure. I'm a basket case. I felt like I needed all the help I could get*"[30]. The responsibility of motherhood is overwhelming: "*The responsibility seemed absolutely enormous*"[41]. As they feel unable to control their thoughts and feelings or restore their previous self, they cannot rely on themselves to care for another tiny and helpless human being: "*Don't wake up. Don't wake up. I can't cope with you on my own*"[28].

At times, women with postpartum depression may themselves seem to revert to an earlier stage of development, to a place in time where they felt safe and could depend on a caretaker[52]: "*I just wanted to be looked after*"[63]. They may need to be nurtured themselves, frequently by their own mother ("*I was like an infant. I had to be with my mother all the time*"[41]). These experiences may cause profound feelings of devaluation, amplifying an inner sense of failure and intensifying the perception of a corroded sense of autonomy: "*I was like a baby because I had to be taken care of and couldn't be left alone*"[41].

As women become very dependent on others, they may identify with their baby, to the point that he/she becomes an extension of themselves and they have difficulty in separating their emotions from the baby's perceived ones: "*I feel that my feelings are directly related to him because if he has a good day, then I have a better day*"[64].

Contemplating death as a glimmer of hope to escape the living nightmare

The profound and disruptive experiences of postpartum depression described above amount to a "*living nightmare*"[41]. A subset of women may experience thoughts of ending their lives and leaving this nightmare, as if death is the only escape: "*I've never been that low where I just thought death was the way to go*"[30]; "*It was terrifying. I felt there was absolutely no way out of it. I was very suicidal. I loved my baby, but I thought if this was the quality of life that I was going to have, there was no way. No way anybody can endure the kind of pain I was going through*"[41]; "*I think that the worst part of my entire depression was that it locked me [in]. I wanted to crawl into a hole and die*"[30].

For a few of these women with postpartum depression, a further dreadful feeling is an extreme and unspeakable irritability ("*It's like a rage, it's all-consuming, like a fury, like a volcano*"[65]), associated with thoughts, frequently of obsessive nature, of harming their baby ("*After a while, my sadness became aggression*"[45]; "*I could have strangled him at times*"[65]). Thoughts of infanticide can accompany suicidal thoughts: "*I had been tempted to jump out of the window, taking the baby with me*"[62]. This may be related to feelings of a distorted and abnormal sense of responsibility toward the baby: "*I felt that it wasn't fair on [the baby] to have a terrible mother, but it also wasn't fair on him not to have a mother. And so, to take him with me was the only option*"[65]; "*I believed that he was my responsibility and he would be disadvantaged by not having a mother, so it was better to take him with me*"[65].

Mothers typically feel horrified that they could harbor such feelings ("*It is shocking really, wishing he was dead*"[66]), and are physically and mentally consumed with guilt ("*I felt such tremendous guilt that I just wanted to hurt myself*"[41]). However, most of them do not tell any health professional about their thoughts of infanticide, because they are concerned that their baby would be taken away: "*You don't come straight out with it to your GP or your psychiatrist*"[65].

THE SUBJECTIVE EXPERIENCE OF POSTPARTUM PSYCHOSIS

Because of the substantial clinical overlap between postpartum depression and psychosis, most of the experiences described in the previous section also apply to postpartum psychosis. The current section focuses on additional aspects of the lived experience of this latter condition.

Feeling the brain in a centrifuge

Many women with postpartum psychosis experience a sudden and severe escalation in their mood state, and a rapid fluctuation of mental states[11], typically shifting from depressive to euphoric feelings ("*It was a nice experience… and immediately rang my husband to tell him!*"[21]), with racing thoughts and flying ideas that are

difficult to control, and profound disorientation ("*For ten days I was filled with sorrow. Then suddenly, as if someone had thrown a switch, I was wildly agitated, full of ideas, all of them pressing to be written down*"[21]; "*Without any warning sign, suddenly, my thoughts were unstoppable and flew around. My brain was in a centrifuge*"[66]).

Racing thoughts are typically associated with hyper-talkativeness and hyperactivity ("*I was speaking really, really fast and just trying to do everything, clean the house and just do everything at once and be super mum*"[67]) and grandiose feelings ("*I feel connected with all people in the world via invisible wires. I became God*"[66]). The surroundings may appear uncanny and bear obscure meanings ("*I can move and talk, but the environment feels strange. Something I have never felt before, an almighty feeling*"[66]).

Some women may attempt to write notes to themselves to keep track of their racing thoughts: "*I felt if it wasn't all written down, I would forget it, as my mind was switching from one subject to another every minute*"[21]. Several women report that the manic shifts were preceded by lack of sleep ("*I was very awake and alert at night even just in the maternity ward*"[67]), even for a prolonged period ("*11 days after he came home that was 11 days of zero sleep*"[67]).

Feeling trapped in a split mind

These manic experiences are frequently associated with perceptual abnormalities: "*I had to breastfeed him with no eyes, just large black eye sockets. I would hear voices through the baby monitors*"[21]. At the same time, women may start noticing unusual connections in their environment or life, which becomes self-referential ("*I thought everyone on the TV or radio was talking to me and everything had hidden meanings. I became obsessed with colors and each color would mean something to me*"[21]), eventually leading to delusional beliefs, such as persecutory ideas ("*They were coming for me. They were watching and they knew. Knew what? I don't know*"[21]; "*They are going to euthanize me there [at the mother-baby unit], aren't they?*"[21]; "*I was certain that my husband… was out to get me and take our child*"[68]; "*I thought the house was bugged, and people were listening*"[67].

The storm of hallucinations and delusions has a "*knock-on effect*"[69], disrupting and fragmenting the sense of personal unity so that the women may feel trapped in a split mind and a dying self: "*Your whole being, how you see yourself, the kind of person you are, and your whole sense of identity is completely devastated really*"[70].

Hallucinations and delusions are unprecedented experiences to many of these women ("*If I'd known about [psychosis] it would have helped to understand a little*"[71]), extremely challenging to explain ("*It's very difficult to get your head around that*"[72]) because there is typically no insight ("*At the time, it felt that those things were really happening*"[72]).

Sinking in the depths of hell

In a few cases, postpartum hallucinations or delusions plague women and sink their minds into a psychological hell: "*In the depths of hell*"[21]; "*I thought I was on my way to hell on earth*"[68]; "*Going to the gates of hell*"[41]. They may feel that something horrible resides in their mind, because voices tell them to harm themselves ("*Inside me is a dark force. A dark shadow that looks like me outside of me. If I kill myself, will the shadow go away?*"[66]) or their baby[66].

In postpartum psychosis, infanticidal thoughts are usually secondary to psychotic symptoms and are thus at higher risk of being acted out than in postpartum depression: "*Intrusive thoughts and a voice… telling me to [harm my baby] were what plagued me every time*"[21]. As a consequence of such terrifying experiences, some women may have intense depersonalization feelings ("*I stood outside myself looking in, detached but present*"[21]) or feel mentally drained ("*I lay powerless, helpless, tense, terrified, exhausted*"[21]).

Ploughing through the fog and losing trust and safety

Many women experience psychotic symptoms as an extreme deviation from their usual self, likening their feeling of lost identity to "*ploughing through the fog*"[72]. This feeling may be accompanied by the loss of trust in others, including professionals and family members: "*I didn't trust anybody. I felt like people were just playing games with me, nurses, police*"[69]. This lack of trust leads to women keeping things to themselves, afraid to reach out to others around them: "*I would never have reached out; it's like you've entered a different world, nothing is safe, and you can't trust anyone*"[69].

Stripping down relationships

The above experiences substantially impact how women relate to their family members. Some of them report an increase in conflictual interactions ("*We fought a lot when I was raging with psychosis*"[69]) and reduced communication ("*During psychosis… we didn't have normal chats like we would've done… that was really missing*"[69]).

Psychotic symptoms are critical challenges to interpersonal relationships ("*It kind of strips down your relationships*"[69]), possibly leading to their dissolution. However, in some cases, women may seek reassurance and physical touch: "*I'd want him to hold me, hold my hand, constantly reassure me. Like I was when I was a kid. To help with feelings of paranoia, fear, safety*"[69].

Stigmatizing experiences are frequently reported, and may even be more disruptive than those occurring in postpartum depression: "*Not only the stigma of being mentally ill, you have got the stigma of being a mentally ill mother, a bad mum*"[71]. Some women whose friendships are affected detrimentally perceive this as a mixture of fear and ignorance: "*I felt a bit stifled with my friends*"[73].

Attempting to reassemble a fragmented self

Soon after the acute psychotic episode, women may self-reflect and experience a shattered sense of themselves or their identity as a couple: "*What is going on? What on earth just happened?… It*

was more a sense of shock, like what on earth?"[69]. The shock is often "*followed by a really bad depression*"[69] ("*The depression afterward, the deep, deep depression afterward, was just such a blow*"[70]). In this context, recovery is often experienced as a problematic journey characterized by an up-and-down transition towards feeling better, feeling that they have missed out on what has been lost through their condition[74], and taking years to return to a recognizable version of themselves: "*It took a long time to rationalize what had happened to me*"[70].

The recovery process is a non-linear trajectory that requires collecting up the pieces of the fragmented self, making sense of it and integrating the experience[75]: "*I knew that things had to change so I didn't get ill again… being more aware of what I need. I'm easier on myself now, and I have a healthier lifestyle. Exercise and sleep are really important*"[69].

Several women reflect on how the experience of postpartum psychosis influences their decision-making regarding personal choices: "*The experience lives with you… for a long time*"[72]. At the same time, mothers often report that the baby was intrinsic to their recovery ("*He was the key reason, he was the reason I wanted to get better*"[76]; "*It made me continue my life*"[76]). On the other hand, many women report that separation from the baby would have been detrimental to recovery: "*I think if I had my baby taken away at that stage, then I would not have recovered*"[76].

THE LIVED EXPERIENCE OF WOMEN WITH POSTPARTUM DEPRESSION OR PSYCHOSIS IN THE WIDER SOCIETY

The experience of postpartum depression and psychosis in the family

The experience of these disorders is shaped in significant ways by the responses of partners, family, friends, and health care professionals. Many women report uncaring and "*disempowering*"[72] relationships with the partner ("*I wanted my husband to take care of me. I felt very alone*"[40]), who did not provide the emotional support they needed ("*I felt he didn't give me a lot of emotional support*"[36]).

Women can feel invalidated when family members deny the existence of mental problems: "*In my house, people don't accept the fact that depression exists*"[77]; "*I told my husband that I might be suffering from postpartum depression, but he didn't believe me*"[42]. In some cases, women even experience stigma from their husband: "*He never comforts me, only blames [me]*"[78]; "*[My husband] says that I am not a good mother and I am hurt by that*"[78]).

In other cases, women find that their mother or mother-in-law attributes their depressive symptoms to external causes that can be fixed: "*My mother also can't understand. She thinks that because my parents-in-law are helping me with my baby, I don't have the pressure of looking after the child*"[79].

Intergenerational differences in values and beliefs may exacerbate these experiences: "*This is the battle you can never win. Grandparents represent the tradition that cannot be adjusted*"[56]. For example, in the early postpartum period, women may be expected to devote themselves to meeting certain traditional mothering values of their mother and mother-in-law[56], leading to constant and exhausting arguments over childcare authority. They may experience stigmatizing attitudes from their parents or family members ("*They… believe that the baby will inherit this disease*"[42]) and fear their blame ("*In my town, if a new mother became [mentally unwell] after giving birth, she would be blamed by her family*"[42]).

However, several other women report that their family provided the main social and emotional support, including their husband[80] ("*[My husband] never blamed me. I cannot imagine how to go through the darkest time without my man*"[56]; "*[My partner] helped build my confidence with the baby and going out and about to see people, talking me through situations*"[69]), grandparents and mother ("*I talked to my grandma and my mom… I told them I felt depressed and they helped me*"[81]) and mother-in-law ("*My husband… his mother, my mother-in-law, were doing so much*"[72]).

The experience of postpartum depression and psychosis in the social and cultural context

The profound sociocultural differences in experiences of motherhood (e.g., a month's rest for the mother post-birth: "*In my country, after childbirth, we rest for 40 days*"[40]) are reflected in varying experiences of postpartum depression or psychosis[82].

In several cultures, women and their family members are likely to not recognize these conditions. For example, in some areas in India, postpartum psychosis is termed as a religious fate (*Devva hididide*, possessed by a ghost; *Devaru bandeti*, possessed by god[83]). A core belief shared by different cultures is that perinatal depression and psychosis are not specific and diagnosable mental disorders: "*I didn't think that this thing was a disease, but here [in Canada], the doctors are saying it is a disease*"[40].

Women may instead feel that their mental problems are due to external factors such as financial difficulties, relational problems, lack of sleep, perceived negative changes in their physical appearance, feeling overwhelmed by multiple responsibilities, overthinking, stress, or lack of a supportive community[49,84,85]. However, a chemical imbalance within their body related to pregnancy is sometimes considered: "*I think, perhaps it is some sort of chemical hormone or imbalance*"[86].

In some US regions (e.g., Northern California), predominantly Black women may experience postpartum mental disorders as a manifestation of weakness that may be cured through prayer: "*You have to stay strong… Whatever emotions you have, you push them away because you don't want to seem weak. And just pray about it*"[87]. This view is associated with high expectations that mothers handle their mental health problems on their own: "*In African-American culture, the idea is of being able to handle your own problems and Black women being strong… and no time to talk about being depressed*"[40]. According to traditional gender roles, women are expected to take up the multiple responsibilities of household work, nurturing the children, and attending to family social relations, without complaining of the pain or discomfort[36]:

"*You bring the baby home. You need to eat; the family needs to eat; you have to clean the house; you have to wash the children, take them to school, take them to Arabic reading [classes]*"[40].

In some Asian countries (e.g., China), mothers may be ashamed of asking their husband to share the housework or take care of babies, because of the traditional roles of men and women: "*He has no time to share housework with me. I feel exhausted and usually upset*"[42]. In some US regions, Latina women also perceive high family expectations that they are responsible for all parenting duties and cannot take time out for their mental health[87], while White and Asian mothers may experience shame induced by social media portraying "perfect mommies": "*The kind of social media… perfect mommy scenario where you feel like it's normal to get everything done*"[88].

In some cultures, postpartum mental disorders may be perceived as a personal deficit or failure as a mother. For example, women in Hong Kong are expected to fulfil their social role "with grace and dignity". Failure to meet the traditional maternal role may be experienced as motherhood betrayal: "*loss of face and shame*"[89].

In Western countries, ethnic minorities of women with postpartum depression or psychosis may experience additional multiple layers of challenges[40], such as low social support resulting from migrating away from their extended family, dissolution of their partner relationship, or significant life histories of trauma and poverty, which exacerbate their symptoms[87].

THE LIVED EXPERIENCE OF WOMEN WITH POSTPARTUM DEPRESSION OR PSYCHOSIS IN RECEIVING MENTAL HEALTH CARE

The lived experience of undergoing screening

Many women feel reluctant to undergo mental health screening for postpartum depression or psychosis, due to their lack of knowledge of these conditions or because they struggle to identify or put into words their experiences ("*I don't know what it is supposed to be, how you're supposed to feel, look or whatever, I don't know. I have no idea*"[40]), or are concerned about stigma ("*I'm very much aware that Black people are more likely to be labelled as having psychiatric problems. Therefore, I don't want people labeling me*"[40]).

Other women express dissatisfaction with the use of "tick box" screening questionaries ("*I was told to fill in a paper. The nurse looked at the paper and said that it showed that I was depressed, no more response*"[45]), because they do not take into consideration the need for interpersonal bonding ("*I'd rather have a coffee and a chat with someone than put circles round numbers while the baby's crying*"[89]). Other women feel that their health care providers' attitude during screening is unsupportive since it overemphasizes physical over mental health problems: "*Many doctors… don't tell you anything beyond physical examination*"[79].

Women may also identify room for improvement in how clinicians discuss and manage the diagnosis of postpartum depression or psychosis[87]. However, these experiences are highly variable, and many other women express trust in their mental health screening program to promptly identify and treat their emotional problems.

The lived experience of accessing mental health support and receiving care

Women with postpartum depression or psychosis can experience various individual, interpersonal, institutional or socioeconomic barriers which interfere with seeking help and accessing mental health care.

Regarding individual barriers, many women do not proactively seek help due to not recognizing their mental health needs or not understanding the treatment processes: "*I just was in such denial that I didn't really know that it was postpartum depression*"[87]. Often, it is not until symptoms worsen to a severe level that they, or their surrounding social network, become aware of the need for mental health support[87]. For example, in some cultures, traditional healing practices such as chanting, fasting or prayer are frequently used for the treatment of postpartum psychosis, depending on local beliefs[83].

As to interpersonal barriers, many women experience a lack of education and knowledge of postpartum depression or psychosis in their family, which is perceived as a critical obstacle to the recognition and acceptance of their problems: "*If you teach him some knowledge about post-partum depression outside of the hospital, then he will believe me in the future*"[42].

Concerning institutional barriers, several women struggle to get attentive health care support: "*I was frustrated, and the doctors wouldn't listen, so I pushed them. I admitted myself to the psych unit at the hospital*"[36]. Multiple mothers recount challenging instances in which health care professionals misdiagnosed their psychotic symptoms: "*People often think it's just postnatal depression, and they don't understand it at all*"[71].

Socioeconomic barriers are particularly relevant in low- and middle-income countries, where women may face high health care costs or social discrimination: "*We are sometimes not able to come back for medication because we lack the money*"[90]. Another common barrier is lack of time due to infant care and other responsibilities, finding the multi-step process of engaging in mental health care unfeasible[87]: "*It's not very convenient [to go to the doctor], [we] have to take care of the children*"[79].

However, the most pervasive barrier to mental health access is the fear of losing their baby: "*My biggest concern is that people will think that I'm not normal and… that I'm not able to take care of my child and then they're going to take my child from me. That's the biggest reason why I didn't go and seek help*"[40].

Finally, stigma is experienced as a core barrier to accessing mental health services: "*I think there's a huge stigma about postnatal depression*"[89]; "*I would feel ashamed… I don't want people to know I'm mentally ill*"[79]. As noted above, stigma may be associated with prevailing societal norms involving the expectation that mothers be happy and strong: "*You grow up with traditions, the customs that tell you you're not to express so much. It's hard to go to counsellors even if you believe they could help you*"[40].

Nonetheless, several other women with postpartum depression or psychosis regard their family environment as a core facilitator of their help-seeking behaviors and access to health care ("*I think having the support network is probably an important part of the recovery*"[69]), and of treatment adherence ("*My family said I wasn't well and that I needed to take tablets*"[70]). At times, mothers may resist help-seeking suggestions made by family members: "*The moment he [partner] said, do you think you need to go talk to somebody or try some medication, I was so offended*"[91]. In these cases, they may perceive the expression of concern or offer of care as a confirmation of their failure as mothers: "*I was obstinate and awkward when help was offered as I took it as another indication of my failure*"[23].

For those women eventually accessing health care, the system and associated care pathways are often experienced as fragmented ("*There were so many people involved, and they just all said different things*"[92]), particularly in low- and middle-income countries ("*The doctors did not attend to me well, and they made me feel so bad… she just took the baby and rushed with her to the nursery*"[84]), or at times dismissive of their needs ("*I think they could have at least listened*"[86]).

Hospitalization, when occurring, may be experienced as terrifying: "*It was atrocious*"[92]. Contributing factors include the sense of isolation (e.g., not seeing partner or family for several days; being cut off from the baby, which increases the subjective suffering and guilt); the misrecognition of postpartum psychosis ("*They kept treating me like I was just depressed… but it was something more than that*"[92]), and the facilities feeling like "*scary*"[93], "*horrible*"[92] or "*jail-like*"[93] places. These feelings are further intensified in women who are compulsorily admitted to hospital because of psychotic symptoms: "*The shocking departure out of my own home with police and ambulance and the whole street out… it's very traumatic to process… if you have been quite well functioning up until now*"[72].

On the contrary, many women feel that mother-baby mental health units are "*amazing facilities*"[93], "*so beautiful… like a spa*"[93], "*better at communicating… and much more organized*"[92]. These units are ultimately experienced as providing a safe respite from mental pain: "*I looked at it as a retreat that might be a miracle*"[94].

The lived experience of receiving pharmacological treatments

Many women may fear pharmacological treatment, primarily due to stigma ("*I wasn't comfortable with accepting medication because I didn't want it to be in my medical record*"[87]), poor knowledge of the medications ("*My concern is that I will just get addicted and it will change my personality*"[86]), fear of side effects (e.g., impacting breastfeeding[93]), and beliefs that the problems can be self-managed ("*I don't want to take tablets. I want to cope with it myself*"[95]).

In addition, several mothers experience pharmacological treatment as a confirmation that they are unsuccessful at coping: "*I remember going on that and feeling like… I'm on an antidepressant; there's such a stigma attached to it. I like to think that I'm stronger, that I don't need something like that*"[91]. However, other women report more nuanced views of medications, and may express acceptance or hope ("*I felt pretty hopeful and excited at the potential of feeling better*"[91]; "*Maybe the medication will stop the feeling that [my baby] and I are going to die*"[24]), especially if psychotherapy was not effective ("*I am extremely open to going on medication [after I give birth], because I would love to do anything that I can in order not to have a postpartum depression again*"[87]).

Several women experience relief from their symptoms with medications ("*Since taking the medicine, I can sleep well and eat well. I now think less about my worries. I suddenly feel good. I have a good appetite and I can eat well. I also do not worry about my children like before. The thoughts do not stick in my mind for too long*"[78]; "*When I take the medicine, I feel better. I can laugh… now. Before I took medicine, I couldn't*"[78]), to the point that they may be reluctant to discontinue them ("*I'm too scared to come off them*"[95]). The rapid effect of medicines may be particularly appreciated: "*When it comes to a situation like… postpartum depression, postpartum psychosis, whatever it may be, time is very critical*"[94].

The variability of these experiences is primarily modulated by negative beliefs of the family about medications ("*He [partner] doesn't have a good view on antidepressants… He thinks that they're unneeded or unwarranted*"[91]) and by the quality of the therapeutic relationship and the connectedness with health personnel ("*My first [clinician] treated me like a statistic, a number… but my second one has been so great. She listens, she is very understanding, and she makes me feel the communication is open*"[87]). Furthermore, several women experience a beneficial effect of combining physical exercise with medications: "*You feel tired, so you don't want to exercise. I think it's when you do start to exercise that you realize it actually gives you more energy and makes you feel more positive*"[96].

The lived experience of receiving psychological treatments

Women also describe a diverse range of experiences with psychotherapy. Several of them report positive nurturing experiences [87], such as the possibility of sharing their silent suffering with a therapist and opening up ("*She was so understanding and easy to talk to and willing to listen, that I actually opened up, otherwise I wouldn't have done*"[38]), and the feeling of being supported ("*She was so helpful and thoughtful. She wasn't hard on me like I am on myself and really made me stop and think about how I treat myself*"[97]). They may experience enhanced self-esteem, feel more proactive, manage stress more effectively, and embrace and adopt a positive view of life: "*I am more relaxed and confident. Earlier, I could not speak or even go out of my house; now I go out with my friends*"[38].

However, other women report negative experiences of psychotherapy, driven by concerns about self-disclosure, lack of individual attention, fear of not being understood or taken seriously. They may also encounter structural hurdles in the health care system, such as limited therapist availability[87] and financial constraints,

particularly in low-income countries. Sometimes, women feel that a good therapeutic relationship cannot be established, or that their therapist lacks the appropriate competence or necessary personal qualities, or is not flexible, or that their feelings and beliefs are not valued[38]. Internalized stigma for seeing a therapist may also be present (*personal communication*).

Other drivers of poor treatment adherence or low satisfaction with psychological interventions may include excessive day-to-day responsibilities that are incompatible with rigid psychotherapeutic routines ("*I find it hard to put anything into practice with others around*"[98]; "*I tried, but I could not do that much*"[38]), or finding the sessions too short or unfocused to be helpful ("*I thought the sessions went by too quickly and not enough*"[38]).

The lived experience of peer support

Peer support groups involving other women with similar experiences and problems are frequently welcomed, as they foster the sense of feeling understood and accepted: "*Being able to attend a support group and meet other moms who are experiencing the same thing, it was really helpful knowing that I wasn't alone*"[87]. Participants also appreciate that other women are willing to reciprocate and share their thoughts and feelings: "*I realized they are interested knowing how many children I have, and they will ask things about me too. So, when I start to share with them my personal story like with depression, they are ready to tell me more about their children*"[99]. Peer support helps overcome the sense of loneliness and provides opportunities for interpersonal connection and bonding: "*The thing I looked most for was something that allowed me to meet people, just get out of the house and meet others, like new mothers, people that I could speak to*"[40].

Providing peer support is particularly empowering, because women's confidence and self-esteem are boosted once they become a source of help for others, particularly in low-income countries where access to other sources of support can be limited: "*When you help someone, then you feel happy that you can be a source of support for this depression, I've been there, I experienced it myself*"[99]. Overcoming the sense of grief and loss of postpartum depression or psychosis often involves a personal transformation and the consolidation of a new identity relying on social resources. Peer support can help these women reframe their identity, deriving insights and learnings from their past suffering to help others, assigning positive meaning to previous negative experiences, and promoting self-acceptance: "*You can recover from this illness… Postpartum psychosis has made me a stronger, more resilient person. I am alive, and I love my children now more than ever*"[21].

DISCUSSION

Becoming a mother is always a major "life-changing experience", involving physical, hormonal and psychological changes. It is foremost a life condition that entails deconstruction and reorganization of one's sense of identity, a "developmental crisis"[100]. Women with postpartum depression or psychosis face severe additional difficulties, and their motherhood becomes a very complex experience. Unlike many other medical conditions, these are "*very silent*"[81] disorders, that are typically hidden or overlooked. Therefore, women's narratives collected in this paper are essential to help other affected mothers recognize themselves and make sense of their experience.

Women who courageously shared their stories of postpartum depression or psychosis in this study are the true storytellers who give voice to many other women: "*This illness needs a voice, and I am happy to talk about my postpartum psychosis journey to raise awareness*"[21]. To our best knowledge, this is the first review of the lived experience of postpartum depression and psychosis that has been co-written by experts by experience and academics.

We found that the experience of the onset of postpartum depression may be described with the metaphor of "being hit by a ton of bricks", alerting us to the sudden and acute onset of symptoms. Soon after the onset, women with this condition feel enveloped in unbearable loneliness and sadness, that are extremely difficult to communicate and are generally suffered in silence. Affected mothers describe the alienating experience of feeling like mechanical robots stripped of all positive feelings. They perceive themselves as no longer the person they were before, and, at the same time, feel unable to prospectively reorientate their lives towards the future[101].

The content of thoughts and emotions in women with postpartum depression is typically polarized on a suffocating burden of guilt for being bad mothers, feeling unable to adhere to social norms and expectations, and feeling incapable of taking care of their newborn. These ruminations may trigger cognitive difficulties, mental fog, and lack of concentration or control over thoughts and emotions. Women may summarize these experiences with the "tightrope walker" metaphor or report feeling besieged with insecurity or needing to be mothered themselves. The most disruptive experience of postpartum depression is living in a nightmare and contemplating death as a glimmer of hope to escape it, highlighting the profound depth of despair these women may confront.

Women with postpartum psychosis share most of these experiences but, at the same time, the occurrence of psychotic symptoms further disrupts their mental and cognitive functions. In a few cases, women feel like they are "sinking in the depths of hell", because their psychotic symptoms may relate to thoughts of harming themselves or their baby. Compared to postpartum depression, postpartum psychosis is characterized by a more pervasive disruption of the sense of self and more pervasive feelings of unsafety and losing trust in others, and the stripping down of social relationships. Consequently, the journey to recovery from postpartum psychosis is experienced as a perilous effort to reassemble a sense of self that psychotic symptoms have fragmented, and to become a new person.

We hope that these first-person accounts of postpartum depression and psychosis will allow other women to view their experiences through the eyes of the individuals quoted in this study, and encourage them to seek early treatment.

We found that the lived experience of postpartum depression

and psychosis is closely intertwined with social and family dimensions. Therefore, these conditions should not be only framed as health problems, but also as core social and relational problems[36]. Much of the isolation, guilt and disorientation experienced in these conditions relates to a gulf between how women feel and a web of societal norms and expectations surrounding motherhood. This results in a crisis in one's idea of family and the social roles that one would like to embody, disrupting the continuity of the traditions inherited from the family of origin[33].

Our first-person accounts clearly indicate that women's social situation has a profound effect on how depression is experienced, as well as its trajectory over time. Mental suffering during the postpartum period can involve something approximating what has been termed "disenfranchised grief"[102] (i.e., experiences of loss that are either not acknowledged or actively stigmatized due to predominant social norms, practices and narratives). When grief is disenfranchised, its experience and interpretation are compromised by the extent to which resources for regulation and coping are available in the social environment. Interestingly, "disenfranchised grief" is also a common theme in the first-person accounts of involuntarily childless women, who sometimes remark that society does not recognize their grief over what never was or how their identity has been affected by it[103].

Many women, although not all of them, described experiences of uncaring relationships with their families, lack of social support, loneliness, and isolation associated with deep shame. Direct and explicit stigma from others (i.e., enacted stigma or discrimination), particularly amongst socially disadvantaged groups such as ethnic minorities, was frequently reported[39]. In most cases, stigma was related to lack of knowledge of postpartum depression or psychosis.

Most families recognize that they lack the knowledge, resources and skills to serve as supporters for these problems[92]. On the other hand, trying to help with childcare tasks can sometimes unintentionally send the message that the mother is not competent or flawed. This vicious circle self-amplifies stigma, leading mothers and their families towards a "subconscious agreement whereby neither the mother nor family and friends publicly acknowledge the depression"[36], and everyone suffers in silence. The lived experiences described in this study may be accessed by family members and represent an essential tool to improve awareness of these disorders, and their ability to hear, tolerate and understand the mothers' emotional pain.

The gulf between women's feelings and societal norms, and the associated stigma, also hinders access to resources for understanding and support. Stigma emerges as a common barrier to undergoing screening, seeking professional help, accessing health care services, and receiving available care such as pharmacological or psychological therapies.

We found that stigma may equally be related to a lack of knowledge among health care providers. For example, in some countries, most providers report only some basic knowledge of postpartum depression and psychosis[104]. This is especially marked for postpartum psychosis, which is not only rare but also an "orphan" disease not recognized in the DSM[66]. Consequently, this condition is frequently unrecognized or misdiagnosed as postpartum depression or blues[9], particularly in low- and middle-income countries[83]. Many women affected with postpartum psychosis who die from suicide or who commit infanticide were not diagnosed or misdiagnosed and did not receive adequate treatment[4]. Mother-baby psychiatric units, which provide the safest and most effective support and care for these disorders[105], are available only in very few countries.

Furthermore, knowledge about postpartum depression and psychosis is often not shared by the legal and judicial system, leading to many mothers being compulsorily admitted to mental institutions without adequate care, or receiving excessively harsh sentences when prosecuted[106].

This study should inform clinical practice. Our experts by experience highlighted the need for training of health care workers to support outreach and preventive care[107]. The lived experiences described here will be accessible to many health professionals and therefore inform future training programs, support mental health literacy, help to maintain a compassionate and non-judgmental stance, refine the psychopathological and diagnostic knowledge, and ultimately facilitate culturally sensitive recognition and treatment of these disorders[4,5]. The study can also facilitate the rolling out of screening programs by informing the content of training and supervision for non-specialists and improving public awareness of postpartum depression and psychosis[75].

The first-person accounts collected in this paper illustrate the extent to which the experiences of postpartum depression and psychosis can be not just "situated within", but "inextricable from" social and cultural environments. Accordingly, this study points to distinctive interventions that may help facilitating self-interpretation and promoting shared understanding[108]. It is also tempting to propose that the management of these conditions might include challenging predominant cultural narratives of motherhood that leave many women feeling alienated and adrift.

Qualitative meta-synthesis allows for and demands interpretation by researchers. We have mitigated sociocultural biases by establishing a global writing team of experts by experience and academics. As in previous studies of this series[17-19], we acknowledge that the experiences reported are not exhaustive and systematically transportable to all individuals, but more often presenting with phenomenological heterogeneity. Moreover, this study does not distinguish between specific diagnostic subtypes, because this approach would have rendered the analytic task unfeasible. Future studies could focus on the different experiences of the prepartum vs. postpartum period. While we primarily focused on individuals' experiences of postpartum depression and psychosis, future research could further address these experiences in the context of interpersonal relationships (e.g., the couple, family).

In conclusion, this study highlights the vast complexity and range of experiences associated with disorders that are too often misunderstood and stigmatized. The narratives collected in this paper provide a new voice for women's experiences of postpartum depression and psychosis, plus rich insight for their families, health care workers, and other stakeholders. Disseminating the stories gleaned from these lived experiences can be a powerful means to

improve literacy and awareness about these disorders, and overcome misunderstanding and stigma.

We hope that this work can help expand options regarding how motherhood is constructed, bringing voice to the unspoken and unheard, and building and maintaining relational connections to create a context in which negative and positive experiences of mothering may be expressed within networks of support. This is vital to providing the most supportive care to women experiencing such pervasive psychiatric disorders at a critical, fragile time in their lives.

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DOI:10.1002/wps.21264

The hypothesis of biologically based subtypes of schizophrenia: a 10-year update

A decade ago we proposed that there are two biological subtypes of schizophrenia: type A, characterized by mesostriatal hyperdopaminergia, and type B, without hyperdopaminergia[1]. One clinical implication was that type A would be associated with good treatment response to antipsychotics, which all act on the dopamine system by blocking dopamine D_2 receptors, whereas type B would be associated with poor antipsychotic treatment response[1]. We also proposed that glutamatergic dysfunction would underlie type B, and suggested additional biologically-based subtypes (C, D, etc.), linked to poor treatment response, yet to be discovered. The hypothesis predicted that biological differences would be present from illness onset. It would be falsified if, for example, there was no response to antipsychotic treatment in schizophrenia despite mesostriatal hyperdopaminergia. Ten years on, we provide here an update on evidence addressing the hypothesis and evaluate the impact it has had.

Much of the evidence for dopaminergic differences between treatment-responsive and treatment-resistant groups available ten years ago was potentially confounded by group differences in severity of ongoing symptoms. This has been addressed since then. Positron emission tomography (PET) imaging was used to measure dopamine synthesis capacity (DSC), through radiolabelled ^{18}F-DOPA, comparing people with treatment-responsive schizophrenia taking first-line antipsychotic treatment to people with treatment-resistant schizophrenia whose illness had responded to clozapine (a second-line antipsychotic licensed for treatment resistance)[2]. When matched for current symptom severity, lower DSC was still observed in the treatment-resistant group, consistent with the hypothesis[2].

Given that most individuals with treatment-resistant schizophrenia are treatment-resistant from illness onset, a key test of the hypothesis is whether dopaminergic differences are already present from the first episode[3]. Consistent with the hypothesis, an ^{18}F-DOPA PET study in first-episode psychosis found higher striatal DSC at baseline in patients who went on to show good antipsychotic treatment response, relative to those with poor response. By including people not taking antipsychotic treatment, possible confounding effects of antipsychotic medication on baseline dopamine function were also addressed[4]. A related methodological approach involves magnetic resonance imaging (MRI) to measure neuromelanin (a by-product of dopamine metabolism) in the midbrain. Using this paradigm in first-episode patients, significantly lower neuromelanin signal was found within the substantia nigra of those who went on to show poor response to treatment relative to those who responded[5].

Studies have also supported the original proposal that non-response is associated with glutamatergic dysfunction. For example, a study using ^{1}H-magnetic resonance spectroscopy (^{1}H-MRS) found increased glutamate levels in the anterior cingulate cortex in people with treatment-resistant, relative to treatment-responsive, schizophrenia[6]. Genetic studies in the past ten years have also provided evidence that treatment resistance is associated with enrichment in risk variants affecting glutamatergic signalling pathways, further supporting this aspect of the hypothesis[3].

It is important to note that not all studies comparing dopaminergic or glutamatergic measures between patients who have responded and those who have not responded to antipsychotic drugs have found differences[7]. However, as adherence was not established using objective measures (such as antipsychotic plasma levels), it remains unclear if the patients had received adequate treatment. As adequate treatment is a prerequisite to test the hypothesis, poor adherence is a potential confound in a number of studies.

One reading of the hypothesis is that the proposed types represent discrete categories. In this case, relevant biological measures should show a bimodal distribution in unselected populations of individuals with schizophrenia. However, evidence to date in unselected populations is more consistent with a unimodal normal distribution, albeit analyses may lack power to detect differences. Notwithstanding the need to test the distribution of data in larger unselected samples, this suggests that the proposed types might potentially be better understood as poles of a continuum.

Epidemiological evidence has shown that, in a subset of schizophrenia patients, illness initially shows a good response to treatment, but resistance develops over time[3]. This is not consistent with a simple A/B dichotomy. The original hypothesis posited that there may be more than one biological subtype associated with treatment resistance, but this finding indicates that some subtypes may develop during the course of illness. This could either be due to iatrogenic effects of treatment, such as D_2 receptor upregulation, or changes in the dopaminergic system during the illness that cause breakthrough symptoms[3].

Other biologically-based categorizations of schizophrenia have been developed, for example using structural imaging measures, and there are examples of subtypes that are unrelated to antipsychotic response[8]. It is not surprising that a classification based on a biomarker unrelated to the dopaminergic system does not predict treatment response, but these findings highlight that there are aspects of the neurobiology of schizophrenia not covered by our classification.

A decade ago, we proposed that biological tests for A and B schizophrenia subtypes could guide treatment decisions and lead to earlier use of clozapine. Since then, ^{18}F-DOPA PET assessment of patients with schizophrenia has shown good predictive power to differentiate responders from non-responders[9]. Furthermore, it was estimated that, after accounting for the cost of PET imaging, fast-tracking treatment-resistant patients to clozapine in this way would provide a significant reduction in health care expenditure[9]. More recently, neuromelanin-sensitive MRI was used to identify non-responders and was able to separate them from responders

with areas under the curve (AUC) of 0.62-0.85[5]. Alternatively, measuring glutamate in the anterior cingulate cortex through ^{1}H-MRS was able to distinguish antipsychotic non-responders from responders with an AUC of 0.59[7]. These studies show that tests based on biological subtyping are being developed, albeit their translational benefits have yet to be evaluated in routine clinical practice.

We also proposed that research into type B schizophrenia could provide insights into its neuropathophysiological underpinnings. In addition to neuroimaging and genetic findings related to glutamate signalling, other biological systems have been investigated. For example, measures of oxidative stress, such as lipid peroxidation, were found to be higher in people with treatment-resistant, as compared to treatment-responsive, schizophrenia[3]. Thus, a number of biological differences between the subtypes are emerging, which could lead to new therapeutic alternatives for people with type B schizophrenia, up to 60% of whom show limited response even to clozapine[3].

Whilst evidence accrued in support of the hypothesis during the past decade, some uncertainty remains. This is partly because not all the studies have been positive, although none have disproven the hypothesis and confounds may explain discrepancies, as discussed above. The hypothesis may also need revision to explain the biological basis of treatment resistance that develops during the illness. Notwithstanding these points, there is encouraging evidence of potential clinical utility and cost-effectiveness of tests based on the subtyping. An important avenue for work over the next decade will be to determine their value in clinical practice.

Another valuable focus for the future is the further characterization of the neurobiology of type B schizophrenia, which could improve diagnostic approaches further. Critically, this could also identify novel therapeutic targets, and determine if there are further biological subtypes linked to therapeutic outcomes. There is dissatisfaction with psychiatric classificatory systems, such as the DSM, based purely on clinical features. The approach suggested here offers an alternative that links biology to clinical outcomes. We look forward to further testing of the hypothesis and evaluating its translation to clinical practice.

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This study was funded by the UK Medical Research Council (grants nos. MC_U120097115, MR/W005557/1 and MR/V013734/1), and the Wellcome Trust (grants nos. 094849/Z/10/Z and 227867/Z/23/Z). R.A. McCutcheon is funded by a Wellcome Trust Clinical Research Career Development grant (no. 224625/Z/21/Z). The views expressed here are those of the authors and not necessarily those of the funding bodies.

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DOI:10.1002/wps.21265

Past, present and future of research on brain energy metabolism in bipolar disorder

Nearly a hundred years ago, Looney and Childs reported that the level of lactate in the blood of patients with schizophrenia was 38.8% higher than in healthy individuals[1], making bioenergetic dysfunction one of the oldest biomarkers proposed in psychiatry. Blood lactate concentration is classically understood to be an indicator of inefficient metabolism, and this finding is buttressed by related neglected putative biomarkers in major psychotic disorders, including reduced pH and abnormal carbohydrate metabolism. These historic findings suggest a shift away from efficient aerobic energy generation towards the less efficient glycolytic pathway, which has been confirmed by contemporary methodologies. Indeed, the brain is the most energy dependent tissue, and the phenomenology of many psychiatric conditions features energy dysregulation.

Bipolar disorder is likely to be a disorder of brain energy metabolism. It can be conceptualized as the outcome of a state dependent biphasic dysregulation of energy generation, with depression characterized by inability to meet metabolic demands and mania by excessive energy generation[2]. Neuroimaging evidence supporting this hypothesis has been available for almost half a century, with Baxter et al[3] showing that people in bipolar depressed or mixed states had significantly lower supratentorial whole brain glucose metabolic rates than those in unipolar depression or bipolar mania and healthy controls. In contrast, resting energy expenditure is increased in mania, as is oxygen consumption (VO_2).

Mitochondria are at the heart of energy generation. They are the source of adenosine triphosphate (ATP), hence energy through oxidative phosphorylation in the electron transport chain. In addition, mitochondria have other critical roles such as calcium homeostasis, reactive oxygen species production, and modulation of growth factors such as brain-derived neurotrophic factor. These aggregate roles regulate synaptic plasticity and the activation of neurotransmitters, which are ultimately related to higher-order

functions such as learning and memory. Critically, dysregulation of all these elements are documented in bipolar disorder[4]. Mitochondrial dysfunction can instigate a vicious cycle of progressive cellular damage that aggravates the disease, drives neuroprogression and premature aging, and compromises clinical and functional outcomes.

Progress in mitochondria research has been largely driven by post-mortem human brain analyses and animal studies. For example, Andreazza et al[5], using post-mortem methodology, explored the components of the mitochondrial electron transport chain in the prefrontal cortex. Bipolar disorder patients had significantly reduced complex I activity compared to people with major depressive disorder or schizophrenia, adjusted for antipsychotic or antidepressant medication, age, sex, post-mortem interval, and brain pH. However, phase-specific effects are poorly captured by post-mortem methodology[4].

Many known medications for bipolar disorder have extensive effects on mitochondrial function[6]. Lithium regulates the expression of numerous mitochondrial enzymes. In human brain tissue, it activates several respiratory chain enzyme complexes, including complexes I + III, II + III and specific complex I subunits such as NDUFB9, NDUFAB1 and NDUFS7, as well as succinate dehydrogenase. It also inhibits GSK-3B, which in its turn inhibits the conversion of pyruvate into acetyl-coenzyme A (acetyl-CoA). Both lithium and valproate have antioxidant effects; they can attenuate cell death induced by peroxide or rotenone, and they both stabilize intracellular calcium dynamics and thereby inhibit glutamate-induced increases in intracellular calcium levels, protein oxidation, lipid peroxidation, DNA fragmentation, and cell death. Human magnetic resonance spectroscopy data show that lithium increases levels of N-acetylaspartate (NAA), a putative neuroprotective marker. Lithium also increases NAA/creatine ratio, also regarded as a marker of neuronal health.

Importantly, a rodent model of bipolar disorder with face, predictive and construct validity was developed by Kasahara et al[7]. They generated transgenic mice with a neuronally specific mutation of the mitochondrial DNA polymerase (*POLG)* gene. These mice had abnormal monoamine function and mitochondrial DNA mutations in the forebrain. They showed distorted day-night wheel-running activity, and switched to mania-like high activity with antidepressant administration and to standard "normal" activity with lithium treatment, which supports the model's predictive and face validity. The mitochondrial DNA abnormalities were consistent with post-mortem studies in bipolar disorder patients.

We do not have robust biomarkers reliably indexing mitochondrial function in stored samples. While metabolomic markers such as lactate and the lactate-to-pyruvate ratio are used, levels are affected by many medical and lifestyle variables, and can change after venipuncture through ongoing metabolism. Several exercise physiology measures can provide insights into mitochondrial function, including maximal oxygen consumption, VO_2max (the maximum amount of oxygen used during intense exercise) and respiratory exchange ratio, RER (the ratio of carbon dioxide produced to oxygen consumed during metabolism). Neuroimaging technologies – such as ^{18}F-fluorodeoxyglucose positron emission tomography, blood oxygen level-dependent functional magnetic resonance imaging, near-infrared spectroscopy, and magnetic resonance spectroscopy – can index brain energy metabolism, but carry cost as well as feasibility and hence translational barriers.

Presently, the flux biogenesis assay (Seahorse) is the most advanced methodology to assess mitochondrial function. It can measure oxygen flux, oxygen consumption rate, proton flux, as well as the extracellular acidification rate, a marker of glycolysis. However, it carries methodological complexities, usually requiring live cells such as lymphocytes that do not necessarily reflect central nervous system activity.

So, what does the future hold? If there is indeed a regulatory failure in brain energy metabolism underpinning the state dependent oscillations between mania and depression, then detecting the responsible regulatory target is a top order candidate to unpick the cause of the disorder and identify mechanistic targets for intervention. Several master regulators of mitochondrial function have been explored, including peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and calcium/calmodulin-dependent protein kinase 2[8].

Several plausible therapeutic options targeting mitochondrial biogenesis and function are already available. There is active interest in the ketogenic diet as a potential therapeutic strategy. Ketones are an alternative energy source by feeding acetyl-CoA into the Krebs cycle, by-passing the traditional pathway through glycolysis. Exercise, which is well established to have benefits in mood and related disorders, impacts mitochondrial biogenesis amongst other pathways.

Mitochondria are also a potentially druggable target. Several strategies have been explored in recent trials, including N-acetylcysteine, coenzyme Q10, alpha lipoic acid, acetyl-L-carnitine, and choline. Very preliminary findings suggest that augmenting pharmacological mitochondrial strategies with lifestyle strategies such as exercise might provide synergistic benefits.

Trimetazidine is a selective inhibitor of 3-ketoacyl-CoA thiolase, a key enzyme in fatty acid oxidation. By selectively inhibiting beta-oxidation of free fatty acids, this drug promotes glucose oxidation and increases ATP production per molecule of oxygen in the brain, as measured by Seahorse assay[9]. It has been in use for 50 years as an anti-angina agent to increase metabolic efficiency in the heart when metabolic processes are compromised, and may have potential in bipolar disorder.

In summary, research on the mitochondrial foundation of bipolar disorder is rapidly progressing, and has the potential to unlock a variety of new therapeutic prospects.

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M. Berk is supported by a Senior Principal Research Fellowship and Leadership 3 Investigator grant (1156072 and 2017131) from the Australian National Health and Medical Research Council. J.H. Kim is supported by the Australian Research Council Future Fellowship (FT220100351).

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DOI:10.1002/wps.21266

Duration of untreated psychosis: a global perspective

Over the past thirty years, a substantial body of research has shown that many people experience long delays before receiving treatment after initial onset of a psychotic disorder. These delays are associated with poorer outcomes across multiple domains, over the short, medium and long term[1,2]. This underpins initiatives to reduce the average duration of untreated psychosis (DUP) and to intervene early to reduce suffering and improve outcomes.

In a recent meta-analysis[2], marked variations in length of DUP were found by continent. The pooled mean DUP was 70 weeks in Africa; 49 weeks in Asia; 49 weeks in North America; 39 weeks in Europe; 35 weeks in South America; and 28 weeks in Australasia. Large variations also exist between and within countries. For example, a longer average DUP has been reported in North India (34 weeks) compared with South India (16 weeks)[3]. In the AESOP study conducted in UK, the average DUP was longer in London compared with Nottingham[4].

A complex set of factors and processes, at multiple levels, influence DUP in diverse settings and underlie these variations. Three levels for which there is substantive evidence are the societal (including health care systems), community, and individual ones.

The structure and content of local health care systems are important in shaping DUP. The sources of support available, how accessible they are (e.g., distance, costs), and the extent to which they are consistent with popular beliefs about mental illness, all influence willingness to seek help and, therefore, DUP. In many low- and middle-income countries, local health care systems are characterized by a relatively small public (mental) health sector and a larger folk sector comprising a plethora of religious, spiritual and traditional healers. Relative to mental health services, healers are often more accessible, and their models of causation and treatment are more congruent with popular beliefs about the nature and origins of mental illness. It is, therefore, not surprising that, in many of these settings, healers are often the first source to which individuals and families turn when psychosis occurs. This can contribute to a longer DUP. For example, in a study in KwaZulu Natal, South Africa, earlier contact with a traditional healer was associated with longer DUP[5]. Conversely, in settings where mental health services are free and relatively well-resourced, DUP is generally shorter. In INTREPID[6] – a programme of research in India, Nigeria and Trinidad – we found that DUP was shortest in Trinidad (median: 11 weeks), which has a free at point of contact public health system.

How individuals and families make sense of and respond to psychosis is further influenced by the communities within which they live and by the social and material resources they have access to. There are multiple facets to this. First, attitudes toward, beliefs about, and knowledge of mental illness within communities and social networks can shape help-seeking and DUP. For example, community, family and internalized stigma can affect willingness to seek help from and engage with mental health services, prolonging DUP[7]. Second, there is evidence that the extent, nature and quality of community and family ties and relationships are associated with DUP: in particular, loose community ties, fractious and unsupportive family relationships, and social isolation can contribute to extended periods of untreated psychosis[7]. Third, there is evidence that household and individual material resources (e.g., income) are, in some settings, associated with DUP[7].

These factors clearly interlink with local health care systems, e.g., material resources may be less relevant where services are relatively cheap or free. We should, therefore, expect variation by setting in the extent to which indicators of social connectedness and resources are associated with DUP. Illustrating this, a study of samples in Mauritius and China[8] found an association between low income and DUP in the Mauritius but not the China sample. Furthermore, high levels of community stigma may mean that individuals and families seek help outside of their communities, often travelling considerable distances. In other terms, the powerful effects of stigma may override the material costs and inconvenience of travelling to seek help. This is what we found at the Kancheepuram, India site of our INTREPID study[6].

Psychoses are clinically heterogeneous, and many studies have reported variations in DUP by mode of onset and presenting symptoms[1]. There is, for example, consistent evidence that an insidious mode of onset, i.e., the gradual emergence of symptoms over months, is associated with a longer DUP[7]. A gradual onset, by definition, constitutes a less sharp break with previous experience and behavior and is consequently less immediately visible. In settings where popular ideas about psychoses centre on outwardly visible disturbance and disruptive behavior, this process may be more pronounced, contributing to an even more prolonged DUP. Related to this, several studies have found associations between negative symptoms and a long DUP[1]. Conversely, an acute or sudden onset is associated with a shorter DUP. In Indonesia, for example, in a series of in-depth studies[8], a rapid onset of psychosis was associated with a short DUP. Interestingly, in this context, initially seeking help from religious healers did not substantially lengthen DUP. Rather, if the help received was perceived not to be working, families quickly sought help from alternative sources, including mental health services.

A further consideration is that, in many settings, a substantial – largely unknown – fraction of people with psychosis never come into contact with mental health services, or indeed any services. In the INTREPID study, we sought to identify individuals with psychosis in communities, i.e., not solely via mental health services.

We found that, at point of identification, around 21% of patients at the Kancheepuram site had never sought help from any source[6]. However, most studies that report on DUP comprise samples identified via mental health services, including those in low- and middle-income countries. These, by definition, systematically exclude those who are untreated, and consequently underestimate the full extent of untreated psychosis in specific settings.

There are several implications that follow from the above findings. First, it is possible to discern several interconnected factors that influence DUP at societal, community, interpersonal and individual levels. The precise ways in which these factors combine and interact in specific settings to influence DUP vary substantially by place, group and time. Second, the concept of DUP, particularly applied to settings with diverse and more plural health care systems, may be too linear and narrow to provide a meaningful primary target for intervention. In many settings, contact with mental health services is not necessarily an end point that signifies the beginning of sustained treatment. It is often one point on a winding, disjointed, sometimes circular trail, as individuals and families seek support and care from multiple sources.

From this perspective, other priorities come to the fore. For example, the potential value of closer collaboration and integration between mental health services and other components of local health care systems, including spiritual and traditional healers[9]; the importance of identifying and engaging those who are never treated; and the need to improve the quality of mental health services and ensure sustained follow-up to retain in care those who do make contact, including the use of telepsychiatry to reach remote populations. In the end, reducing DUP is no use if the end point is poor quality services and care, with limited follow-up and rapid disengagement.

All this also points to the need for more sustained programmes of in-depth research that can generate locally meaningful knowledge. This is essential to inform, in diverse settings globally, the development and implementation of more accessible, affordable and effective services and interventions for people with a psychotic disorder.

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DOI:10.1002/wps.21267

Learning health systems for community-based mental health

Mental disorders are the top causes of morbidity and mortality globally[1]. However, over half of individuals with these disorders lack adequate access to mental health services. Even with adequate access, quality of care often remains suboptimal, as over a third of individuals do not receive an adequate follow-up treatment, which increases the risk of suicide and other adverse events[2]. Despite the availability of effective treatments for mental disorders, only a fraction of individuals are offered these interventions and, if so, fewer complete recommended regimens[3]. Frontline mental health providers (notably nurses, counselors and clinical social workers), who provide much of the care to these individuals, lack the time, tools or training to implement evidence-based mental health treatments.

While innovations in health information technologies may enhance individual access to mental health interventions, the quality of care from these modalities can vary widely, and there are potential safety risks when treatments are provided without direct practitioner supervision[4]. The rapid growth of artificial intelligence also brings forth opportunities as well as challenges with data privacy and accuracy of therapeutic delivery, and most providers to date are unprepared to implement these new technologies to ensure full benefit for their patients.

Learning health systems are promising approaches for improving quality and outcomes of care for persons with mental disorders in community practices, because they can provide the infrastructure and tools to help frontline providers deliver evidence-based treatments more effectively[5]. First defined by the US Institute of Medicine (now National Academy of Medicine), a learning health system involves a process by which scientific discovery, available data (e.g., from electronic health records), health care policies, and organizational culture are aligned to support progressive research innovation and direct quality improvement simultaneously, so that evidence-based treatments and practices are automatically embedded into routine health care practice.

There are three core features to learning health systems: a learning community; an underlying infrastructure to curate, summarize and manage data; and a repeatable cycle of research and quality improvement initiatives.

Learning communities typically include patient (as well as family and caregiver), provider, researcher, and health system leader representatives who identify a common health priority goal and pathway for new research and quality improvement initiatives. In particular, health system leader representatives should have direct line to authority and responsibility over care decision-making, data access, information technology governance, and other administrative requirements in the health system to maximize opportuni-

ties for practice change.

The underlying infrastructure of learning health systems involves ascertainment of data from electronic health records, symptom and diagnostic assessments, and other sources. This infrastructure also includes governance (e.g., standardized processes) to allow use of data for research and quality improvement purposes, and appropriate privacy ad ethics reviews. Data can include utilization, procedural, laboratory, medication, and diagnostic information; care processes such as completion of guideline-recommended care; patient-centered outcomes; co-occurring conditions; social determinants of health such as environmental factors, and, increasingly, genomic information. A common data infrastructure enables providers to more immediately identify gaps in quality or outcomes of care in their patient population, understand how new treatments can reduce gaps in quality or outcomes, and evaluate implementation or quality improvement strategies to scale up and spread effective treatments over time.

Finally, the repeatable cycle supports research and quality improvement initiatives that aim to enhance patient health outcomes for a given priority identified by the learning community. Using the underlying data infrastructure, the cycle supports continuous generation and analysis of data, and uses that knowledge to determine which treatment innovations are most effective (e.g., in a pragmatic clinical trial) and how to increase their scale-up and spread over time via quality improvement initiatives. For example, researchers may start with analyses of genomic, physiological or social determinants data embedded in the electronic health record to identify risk factors for a given condition. Then they use data curated from evidence syntheses, longitudinal studies, and clinical trials to identify optimal treatments. Finally, they use the electronic health record at the point of patient care to offer treatments and evaluate their implementation by frontline providers over time in real-world practice.

Community mental health systems are well-suited to implement learning health systems, in part because the above core features are primarily derived from measurement-based care[2] and the collaborative care model (CCM)[6]. Developed to better adapt the health system to address chronic illness management, including mental health care, the CCM involves alignment of leadership support, informatics, and quality improvement processes to help providers care for the ongoing needs of their patients using clinical guidelines, self-management support, ongoing care management, and linkage to community resources.

CCMs have been shown to improve quality and outcomes of care in community mental health settings for both physical and mental health conditions[6]. The initial "evolutionary leap" from CCMs to learning health systems occurred when it became possible to automate core features of the CCM, namely the systematic curation and analysis of data to identify at-risk populations and measure their clinical status (e.g., from electronic health records), and use these data to embed quality improvement processes such as audit and feedback or treatment reminders. To this end, providers are able to promote a culture of continuous learning through data, demonstration and evaluation of new discoveries and quality improvement methods.

In the ongoing evolution of learning health systems as a process for improving quality of care in mental health, emerging examples can be found across different community-based settings worldwide, such as the Mental health INTegration programme in South Africa (MhINT)[7], the OnTrack New York (OnTrackNY)'s coordinated specialty care learning health system[8], and the US Disparities Elimination through Coordinated Interventions to Prevent and Control Heart and Lung Disease (DECIPHeR) Center at Johns Hopkins University and University of Michigan[9].

Specifically, MhINT focuses on the role of data to empower frontline providers to task-share collaborative care management for mental disorders in the primary care setting. OnTrackNY leverages common data infrastructure to improve detection and treatment of early psychosis in a population-based cohort. The DECIPHeR Center is leveraging policy changes at the US state level that enable increased reimbursement for integrated physical and mental health care in community-based practices to improve the quality of cardiovascular disease care for persons with serious mental illness. Collectively, these initiatives seek to leverage common data that can empower frontline clinicians and the patients they care for to better manage mental disorders, especially when faced with organizational or financial constraints, and sustain best practices using quality improvement methods.

Overall, learning health systems hold promise for improving quality of care for mental health disorders. The next evolutionary leap of these systems holds great promise for improving the lives of people with mental disorders in three ways. First, there is ongoing interest in the further development, validation and implementation of informatics and artificial intelligence tools to better automate data ascertainment, synthesis and analysis to inform patient care in a secure way that minimizes risk of bias. Second, advances in pragmatic clinical trial methods have potential to enable more rigorous, cost-efficient and generalizable studies to evaluate novel treatments on changes in patient-centered Quintuple Aim goals, namely improved outcomes, experience, value, equity and access. Finally, learning health systems can be leveraged to better scale up and spread effective treatments using quality improvement methods, especially through automation of clinical decision-making, ultimately empowering frontline providers to adopt evidence-based treatments and practices more readily.

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DOI:10.1002/wps.21268

Post-traumatic stress disorder: evolving conceptualization and evidence, and future research directions

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The understanding of responses to traumatic events has been greatly influenced by the introduction of the diagnosis of post-traumatic stress disorder (PTSD). In this paper we review the initial versions of the diagnostic criteria for this condition and the associated epidemiological findings, including sociocultural differences. We consider evidence for post-traumatic reactions occurring in multiple contexts not previously defined as traumatic, and the implications that these observations have for the diagnosis. More recent developments such as the DSM-5 dissociative subtype and the ICD-11 diagnosis of complex PTSD are reviewed, adding to evidence that there are several distinct PTSD phenotypes. We describe the psychological foundations of PTSD, involving disturbances to memory as well as to identity. A broader focus on identity may be able to accommodate group and communal influences on the experience of trauma and PTSD, as well as the impact of resource loss. We then summarize current evidence concerning the biological foundations of PTSD, with a particular focus on genetic and neuroimaging studies. Whereas progress in prevention has been disappointing, there is now an extensive evidence supporting the efficacy of a variety of psychological treatments for established PTSD, including trauma-focused interventions – such as trauma-focused cognitive behavior therapy (TF-CBT) and eye movement desensitization and reprocessing (EMDR) – and non-trauma-focused therapies, which also include some emerging identity-based approaches such as present-centered and compassion-focused therapies. Additionally, there are promising interventions that are neither psychological nor pharmacological, or that combine a pharmacological and a psychological approach, such as 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy. We review advances in the priority areas of adapting interventions in resource-limited settings and across cultural contexts, and of community-based approaches. We conclude by identifying future directions for work on trauma and mental health.

Key words: Post-traumatic stress disorder, trauma, complex PTSD, memory, identity, genetics, neuroimaging, prevention, psychological interventions, pharmacotherapy, community-based interventions

(World Psychiatry 2025;24:52–80)

The world is currently experiencing the highest number of state-based conflicts (i.e., conflicts in which one of the actors is a government or state) since the Second World War, as well as a very high number of non-state-based conflicts (i.e., conflicts between formally or informally organized groups)[1]. Approximately 468 million children are currently living within a conflict zone, often in areas where armed groups or forces recruit and use them in those conflicts[2]. A variety of individual, relationship, community and societal factors are being associated with increased levels of gender-based violence[3]. Childhood and domestic abuse as well as exposure to traumatic events at work are on the rise[4,5], and recent health-related events have had a huge traumatic impact at various levels of population worldwide[6]. In the coming years, climate change is likely to further exacerbate the frequency of traumatic events, and their direct and indirect impact on adults and children[7].

Since 1980, the management of psychological trauma has become inextricably bound up with the diagnosis of post-traumatic stress disorder (PTSD). Although there were initially numerous skeptics, this diagnosis has since established itself and has become an extremely effective vehicle for publicizing the effects of all kinds of traumatic events. Not only has knowledge of trauma and its effects grown enormously as a result, but in many countries there is now an infrastructure to support these developments, and a high visibility of trauma-related conditions in the planning of governments and non-governmental organizations (NGOs).

With increasing knowledge has come a greater appreciation of the complexities of understanding people's response to traumatic events. First, what is a traumatic event? Initially this was conceptualized as an event that would have an overwhelming effect on anyone, while now it is understood as an event that has a potential overwhelming effect on some people. This effect can take forms other than PTSD – for example, depression or prolonged grief. Thus, the definition of a traumatic event cannot be considered solely in the context of PTSD.

Views were initially shaped by the lists of traumatic events contained in standard survey instruments, but greater recognition of the symptoms has led to trauma reactions being acknowledged in many other contexts, such as after a very difficult childbirth or a psychotic breakdown. Moreover, there is increasing appreciation that events may impact whole families and communities, and that the relation of persons to their community may affect their individual response.

The effective management of psychological trauma requires that new knowledge is constantly reviewed, evaluated and reflected upon. In this paper, we start by discussing the current understanding of what constitutes a traumatic event in different contexts. We continue by summarizing how PTSD has been diagnosed for most of the time since its introduction in 1980, and what has been discovered about its epidemiology using the relevant diagnostic criteria. Subsequent sections address changes and controversies in the definition of a traumatic event, and more recent developments in diagnosis, including the introduction of complex PTSD in ICD-11. We then review some of the most important psychological and biological processes involved in PTSD. Later sections

summarize how this condition can most effectively be prevented and treated, and identify trends and avenues for research and practice that are likely to be important in the future.

WHAT IS A TRAUMATIC EVENT AND WHAT MAY BE ITS EFFECTS?

A traumatic event is one with a potential to severely challenge the ability of an individual or a community to adapt, requiring major changes to ways of living or thinking.

Exposure to this category of events is a universal aspect of the human experience. In the health literature, we tend to focus on the adverse effects that traumatic events can have on the lives of individuals and communities[8]. However, it is worth noting at the outset that the effects of exposure to traumatic events are complex and varied, and that they may elicit strong reactions without leading to maladaptive responses[9].

Normal reactions to traumatic events are often linked to the specific circumstances of the occurrence. For example, ongoing threat is associated with anxiety; loss is associated with grief and depression; negligence by others, injustice and betrayal are associated with anger; and abandonment is associated with despair[10,11]. If the traumatic exposure is time-limited, these reactions are typically brief, and may be adaptive and occasionally lead to personal growth[12]. However, traumatic events can have a significant and sometimes widespread and devastating negative impact.

Many factors help explain the substantial variation in the impact of trauma. Some of them depend on the characteristics of the traumatic event itself[13,14]. For example, the course of untreated PTSD arising from events that are considered intentional (e.g., domestic violence) has more frequently a worsening trajectory and shows a greater tendency to chronicity than that of untreated PTSD after unintentional events (e.g., natural disasters)[15].

Moreover, individuals' psychological, genetic and neurobiological characteristics can predispose them to maladaptive reactions to trauma[16-18], and act in combination with their sociocultural and societal-structural context. For example, exposure to traumatic events, urbanicity, ethnoracial discrimination, socioeconomic deprivation, and limited opportunities as a migrant all act in concert with genetic and other forms of vulnerability to enhance the risk of psychotic symptoms and disorders[19,20].

These interactions affect all aspects of traumatic exposure and its consequences, including the probability of exposure to psychosocial trauma[21]; the range of emotional reactions to traumatic exposure[22]; variations in risk, symptoms and course of resulting trauma-related conditions[22,23]; the availability and type of supports that people can engage[24]; the availability and effectiveness of mental health interventions[23]; and the process of recovery[25].

The sociocultural and societal-structural context exerts its influence by shaping people's life circumstances and risks, their interpretation of events, the coping and healing options that they have access to and use, and community reactions that influence their experience.

The impact of trauma can also be transmitted across generations, as in the case of children of survivors of the Second World War Holocaust[26] and the Cambodian genocide[27]. These community-level traumas have been argued to influence recurring cycles of mass violence. "Historical trauma", a term coined by Native American researchers to describe the impact of European and Anglo-American colonization, is thought to be a significant factor contributing to elevated rates of alcohol dependence and abuse, PTSD, suicide, violence and depression in Native communities[28,29].

In more sociocentric or collectivistic societies, communal elements may exert a larger influence on trauma reactions than they do in more individualistic societies. In many parts of Africa, for example, the predominant *Ubuntu* worldview ("I am because we are") holds that an individual's fate and well-being are closely tied to those of others in his/her social network[30,31]. A person can then experience PTSD symptoms due to an event happening to another member of the community.

Data from the World Mental Health Surveys have shown that, in societies that tend to be collectivistic (such as in South Africa and Japan), traumatic events occurring to others within a person's social network are associated with a high conditional prevalence of PTSD[32]. Among North Korean defectors, PTSD severity was more strongly associated with witnessing trauma events involving family members than with exposure to physical abuse or political-ideological trauma (e.g., being a political detainee)[33].

How do communal risk factors exert this influence on a person's reactions to traumatic events? Several mechanisms are currently being examined. One involves the impact of contextual factors on individual experience. Even when traumatic events affect entire communities, sociocultural/structural factors apportion risk differently, including by neighborhood characteristics and resources available to the person's support systems[34]. For example, among residents affected by Hurricane Andrew in Florida, Latinxs were significantly more likely to experience PTSD symptoms than non-Latinx Whites, a vulnerability partly mediated by Latinxs' acculturative stress as immigrants[35]. Specific living circumstances can also pattern trauma-related reactions. For instance, living among unpunished perpetrators in settings of mass violence can result in long-standing anger and frustration, complicating trauma-related psychopathology[36,37].

Another mechanism of communal effects involves meaning traditions that become part of personal identity, and shape collective reality. For example, among Tibetan refugees fleeing Chinese government rule, religious persecution – e.g., witnessing the destruction of monasteries or being forced to publicly renounce the Dalai Lama – was more strongly associated with PTSD symptoms than torture or imprisonment[38]. Forced interruption of these meaning traditions can foster the onset and/or persistence of traumatic grief states, such as during the Rwandan genocide, when the grief of survivors was magnified by traditional beliefs about the precarious spiritual status of deceased relatives who had not been properly buried[39].

Individual transgressions of collective moral codes can also have a greater pathogenic effect than other severe traumatic exposures. Among US veterans in the National Vietnam Veterans Readjustment Study, harming civilians and prisoners was associ-

ated with higher odds of PTSD onset than either combat exposure or vulnerability factors preceding military service (e.g., childhood physical abuse)[40].

A further mechanism of communal effects involves the patterning of trauma reactions by cultural syndromes and other idioms of distress[41,42]. These are culturally specific forms of expressing emotional distress that arise in local contexts in response to specific culturally-based attributions[43]. Examples relevant to trauma reactions include *ataques de nervios* (attacks of nerves) in Latinx populations, *khyâl* attacks among Cambodians, *ihahamuka* (literally, lungs without breath) among Rwandan genocide survivors, and "thinking too much" in many cultural settings[41,44,45]. These patterned behavioral responses may be evoked as an embodied reaction by traumatic events, if they are linked to a traumatic etiology by the cultural group[46].

Despite this variability in the contexts where potentially traumatic events occur and in the range of their effects, the literature has focused overwhelmingly on one specific type of psychopathology, i.e. PTSD. However, issues raised in this section about the nature of traumatic events continue to be central in the remainder of the paper, whether it be how PTSD should be diagnosed, what are its psychological foundations, or how it can be treated.

DIAGNOSIS OF PTSD

DSM-III to DSM-IV-TR

Although many argue that post-traumatic stress syndromes have been described at least as far back as Homer's Iliad[47], PTSD was not codified as an official mental disorder diagnosis until publication of the DSM-III[48]. Earlier versions of the DSM had included combat-stress reaction as a syndrome, reflecting a long history of research documenting the psychological effects of war on soldiers, including large-scale empirical studies of First World War veterans conducted in the UK and elsewhere[49].

The inclusion of PTSD in the DSM-III has been credited to the convergence of several social movements in the US in the 1960s and 1970s. These included veterans' advocates recognizing the impact of the Vietnam war on those who served; feminists raising awareness of the prevalence and consequences of violence against women; and psychiatrists treating Holocaust survivors[50].

From its introduction, PTSD has been unique in the DSM in requiring a specific environmental stressor for its diagnosis. This component of PTSD has been one of the most debated aspects of its diagnostic criteria. Actually, it plays a gatekeeper role in focusing the disorder on reactions to events involving very high levels of physical threat. The intention has been to prevent a diagnosis of PTSD being applied following events that are regarded as more everyday stressors, such as financial problems.

Up to and including the publication of the DSM-IV-TR in 2000, four sets of symptoms have been consistently part of the PTSD diagnosis: re-experiencing of the traumatic event, avoidance of reminders of the event, numbing in the form of restricted affect or detachment from others, and symptoms of hyperarousal such as sleep disturbance and exaggerated startle response[51]. These have been distributed among three symptom groups, with the allocation of symptoms to groups changing somewhat with successive editions of the DSM. Survival guilt featured in the DSM-III only. Memory impairment for significant aspects of the event has remained in all editions, although it is the symptom most weakly associated with the others[52]. The total number of PTSD symptoms increased from 12 in the DSM-III to 17 in the DSM-III-R.

Since the DSM-III-R, symptoms have been required to be present for a minimum of one month prior to diagnosis, and since the DSM-IV there has been an additional requirement for them to be accompanied by clinically significant distress or impairment in functioning. These changes have reflected the prevailing view that the symptoms do not indicate pathology in themselves. Pathology is indicated by the failure of the symptoms to remit of their own accord, and by their impact on everyday life.

ICD-10

PTSD was first recognized by the World Health Organization (WHO) as a diagnosis in the ICD-10[53], over a decade after the DSM-III publication. A key difference between the ICD-10 and the DSM-III/IV was that the former used a descriptive text and "diagnostic guidelines" rather than requiring the presence of specific diagnostic criteria. Although potentially helpful in terms of facilitating clinician judgment and applicability in very diverse clinical and cultural settings, the ICD-10 approach has not been easily translated into specific research instruments. This has likely contributed to the use of structured measures of the DSM construct of PTSD, rather than the ICD guidelines, in most research before 2013.

The ICD-10 stressor description was "a stressful event or situation (either short- or long-lasting) of an exceptionally threatening or catastrophic nature, which is likely to cause pervasive distress in almost anyone". Symptom descriptions included the following phrases: "Commonly there is fear and avoidance of cues that remind sufferers of the original trauma" and "There is usually a state of autonomic hyperarousal with hypervigilance, an enhanced startle reaction, and insomnia". The diagnostic guidelines stated: "In addition to evidence of trauma, there must be a repetitive, intrusive recollection or re-enactment of the event in memories, daytime imagery, or dreams. Conspicuous emotional detachment, numbing of feeling, and avoidance of stimuli that might arouse recollection of the trauma are often present but are not essential for the diagnosis. The autonomic disturbances, mood disorder, and behavioural abnormalities all contribute to the diagnosis but are not of prime importance".

These extracts highlight the many similarities between the two diagnostic systems, but also some differences. In the ICD-10, there was also no requirement for symptoms to last a minimum length of time or to be accompanied by distress or functional impairment. In one large-scale study, agreement between the ICD-10 and the DSM-IV was found to be moderate, with higher rates for the ICD-10 being mainly attributable to the requirement for significant distress or functional impairment in the DSM-IV[54].

DSM-5 and DSM-5-TR

In the DSM-5[55], PTSD was moved from Anxiety Disorders to a new diagnostic section named "Trauma- and Stressor-Related Disorders", and the definition of trauma was narrowed to events requiring "actual or threatened death, serious injury or sexual violence".

Significant restructuring of the symptom criteria also occurred. The symptom clusters were expanded from three to four, and the number of symptoms was increased from 17 to 20. To meet diagnostic criteria in the DSM-5, the individual must have one re-experiencing symptom, one avoidance symptom, two symptoms reflecting negative alterations in cognition or mood, and two symptoms reflecting alterations in arousal or reactivity. These changes resulted in a lower PTSD prevalence using the DSM-5 criteria, as compared to the DSM-IV ones. For example, Kilpatrick et al[56] found a lifetime prevalence of 9.8% using the DSM-IV and 8.3% with the DSM-5, when assessing PTSD symptoms in relation to the same event.

The DSM-5 criteria as described above apply to children over 6 years of age, with some qualifications to the re-experiencing symptoms to ensure that they are developmentally appropriate. For example, children may re-enact aspects of the trauma in play rather than explicitly describe recurrent intrusive memories of the trauma.

Following research that found under-diagnosis in pre-school children and tested the validity of alternative criteria[57-59], diagnostic criteria were added in the DSM-5 for children aged 6 and under. These include specifying that the child could develop PTSD if he/she witnessed or heard about a traumatic event happening to a parent or caregiver. There are only three symptom clusters: re-experiencing (one symptom required), avoidance and negative alterations in cognition or mood (one symptom required), and alterations in arousal or reactivity (two symptoms required). Moreover, the descriptions of specific symptoms have been changed to be developmentally appropriate. For example, the adult symptom of irritability or aggression includes "extreme temper tantrums" in children.

The criteria for PTSD remained unchanged in the DSM-5-TR[60]. The description of the disorder in the text was expanded in many areas, including more detailed discussion of what constitutes a traumatic event, the prevalence of PTSD from the World Mental Health Surveys and in conflict-affected populations, and the role of cultural factors and sex- and gender-related issues in the development and clinical expression of the disorder.

Delayed-onset PTSD

There has been an explicit recognition within successive editions of the DSM that PTSD does not always begin directly, or even soon, after the traumatic event. The "delayed-onset" form of PTSD ("with delayed expression" in the DSM-5) is defined as occurring at least 6 months after the traumatic event.

This claim has been controversial in some quarters, because it appears to contradict the commonsense notion that traumatic events overwhelm physical, emotional and psychological defenses. This assumption would imply that PTSD will almost always have an immediate onset. The ICD-10 in fact suggested that onset almost always occurred within 6 months of the traumatic event. As we will see below, however, there is robust epidemiological evidence for a distinct type of PTSD with delayed presentation.

Critiques of the PTSD diagnosis

One initial critique argued that PTSD was a Western construct of limited utility to other cultures and belief systems. However, subsequent research has determined the cross-cultural relevance of the diagnosis, while identifying culturally specific forms of trauma-related distress[41].

Other initial critiques suggested that PTSD did not offer anything additional to, and was not distinguishable from, existing diagnoses of anxiety and depressive disorders. However, PTSD did include symptoms that were not part of other disorders. Although some of these symptoms, such as intrusive memories and the avoidance of such memories, turned out to be present in other disorders[61], other symptoms did discriminate. Following a traumatic event, flashbacks and dissociative amnesia were found to be present in cases of PTSD but not in cases of non-PTSD psychiatric disorders[62].

Longitudinal studies have successfully discriminated individuals who developed PTSD following trauma from those who developed different psychiatric disorders, identifying separate risk factors for each trajectory[63-65]. However, prospective work which followed people who had no history of depression before trauma exposure showed that depression only developed in those with PTSD[66]. High levels of comorbid depression remain a feature of PTSD, with some twin and molecular genetic studies reporting a high genetic correlation between PTSD and major depression. How best to understand this comorbidity remains a matter of debate, given the limitations in all research designs. One possibility is that individuals with both disorders constitute a distinct phenotype from those with PTSD alone[67].

A persistent critique focuses on the heterogeneity of PTSD, with more than 600,000 combinations of DSM-5 symptoms theoretically able to lead to the diagnosis[68]. The analysis of a large military cohort confirmed that, in practice, over half of the participants who met criteria for PTSD had a unique pattern of symptoms, emphasizing that a DSM-5 PTSD diagnosis does not reflect a uniform phenotype[69]. Some responses to this problem are described in a following section of this paper.

EPIDEMIOLOGY OF PTSD

Prevalence

Due to the ubiquity of trauma exposures globally, PTSD is among the most prevalent mental disorders in the community. Strong evidence for the global burden of PTSD comes from the World Mental Health Surveys, a series of studies conducted using

the same measures across multiple countries, allowing for cross-country comparison. A study conducted in 24 countries, with 71,083 respondents, found that the overall lifetime PTSD prevalence in the general population was 3.9%, and varied across high-income (5.0%), upper-middle-income (2.3%), and low- to lower-middle-income (2.1%) countries[70].

Several country-specific population-based studies, and systematic reviews of these studies, confirm the cross-national – and even intra-national – heterogeneity in the prevalence of PTSD. Studies based on World Mental Health Surveys report lifetime prevalences ranging from as low as 1.3% in Japan[71], through 2.2% in Spain[72], and 2.3% in South Africa[73], to the relatively high prevalence of 8.8% in Northern Ireland[74]. The first nationwide mental health survey in China reported a lifetime prevalence of 0.4%[75]. In the US general population, most studies find a lifetime prevalence around 5% in men and 10% in women, with an overall prevalence of about 8%[76].

Studies of current or one-year prevalence of PTSD highlight the worldwide variation. An analysis of the Adult Psychiatric Morbidity Survey in England reported a prevalence rate for current PTSD of 2.9%[77], similar to the 2.4% reported for Canada[78] and Italy[79]. The Australian National Survey of Mental Health and Well-Being found a 12-month prevalence of PTSD of 1.3%[80]. In contrast, a systematic review and meta-analysis of sub-Saharan African countries reported an overall prevalence during periods from the past week to the past year of 22%. There was substantial heterogeneity in the sample, with the pooled prevalence being 8% in conflict-unexposed and 30% in conflict-exposed regions[81].

The prevalence of PTSD thus appears to vary widely. This is partly due to the population studied, but also to variation in reporting of and exposure to traumatic events. For example, if specific trauma events that are associated with a high risk of PTSD, such as sexual assault, are not reported due to stigma, this will lead to underestimates of PTSD prevalence at the population level.

Another source of variation is methodological. The World Mental Health Surveys tend to report lower lifetime prevalence rates than other studies due to a key difference in assessing for PTSD. Most other studies have employed the "worst trauma" method, in which participants describe PTSD symptoms attributable to the worst traumatic event that they have ever experienced. This tends to overestimate the community prevalence of PTSD because "worst traumas" are not the most prevalent in any community, and less severe traumas may have a different conditional risk for developing PTSD[82]. The World Mental Health Surveys, in contrast, use the "random event" method, in which a random event is selected from the list endorsed by a participant, and PTSD symptoms are assessed in relation to it. Random events might more accurately reflect occurrence of traumatic events in the community, so the PTSD prevalence based on these events might be more representative of the actual burden in the community[32]. Surveys can also vary in numerous other ways, including their sampling frames, the use of interviews or self-administered questionnaires, and the choice of the survey instrument with its associated skip-outs, thresholds, or cut-off scores.

However, methodological standardization does not guarantee that diagnostic instruments are identifying equivalent conceptualizations and experiences of mental disorder. People endorse symptom queries within particular contexts of professional diagnostic practice; there are various levels of public awareness of nosologically defined forms of psychopathology across societies; and local variation affects response sets to survey instruments (e.g., different experiential thresholds at which a symptom is endorsed). All these factors may affect diagnosable rates of disorder[41].

Conditional risk

Whereas the overall prevalence of PTSD reflects the number of cases of the disorder in a population – with a number of factors likely contributing to different cross-national estimates – *conditional risk* refers to the prevalence of PTSD among those exposed to specific traumatic events, focusing on the variation by event type[73]. Overall prevalence is comparable to prevalence estimates for other psychiatric disorders, whereas conditional risk (which may be referred to as "prevalence" in some papers) is not. Conditional risks for trauma-exposed populations are higher than overall prevalences documented in population-wide surveys[32].

Most studies have shown that the conditional risk of PTSD varies depending upon the type of traumatic event, although the ordering of risk across specific events tends to be different across studies. For example, a representative sample of US adults under the age of 45 found the highest conditional risk of PTSD after assaultive violence (20.9%)[83]. In a European study, the highest conditional risks for PTSD were found after having a child with serious illness, being raped, being beaten by partner, being stalked, and being beaten by caregiver[84]. A study of a Brazilian urban population found the highest conditional risks after war-related trauma, childhood sexual abuse, adult sexual violence, and interpersonal violence[85].

In a range of studies, cumulative traumatic events have been found to be associated with greater subsequent risk of PTSD and greater severity of PTSD symptoms[86].

Demographic differences

Women are reported to have a 2-3 times higher risk of developing PTSD than men[87]. While men are more likely to experience traumatic events, women are about twice as likely to have PTSD after most of them. However, the conditional risk of PTSD is reported to be similar for men and women after childhood sexual abuse and sexual assault[88]. Importantly, traumatic events experienced by men and women tend to differ, with women experiencing more sexual assault and childhood sexual abuse, two of the traumatic events with the highest conditional risk for PTSD.

Evidence also suggests that gender non-binary and transgender persons have a prevalence of PTSD three to ten times higher than that reported in general population studies[89]. Although further research is needed, this higher prevalence is likely to reflect the higher burden of violence faced by lesbian, gay, bisexual, transgender, queer or questioning (LGBTQ+) populations as well

as the additional impact of discrimination[90].

Age differences in PTSD are unclear. Findings from a German community-based study did not show substantial differences in PTSD reports by age[91], consistent with a review of available studies[92]. In Northern Ireland, being younger than 65 was associated with increased PTSD risk[74]. Some smaller studies have noted differences by age, including, for example, a longitudinal study of survivors of motor vehicle accidents, which found higher PTSD reports among middle-aged vs. younger or older-aged women[93].

Several individual-level markers of social and economic status have been documented to be linked to PTSD[94]. These include low education[79], lower household income[70], and being retired or unemployed[70,74].

Sociocultural differences

The risk of PTSD differs by ethnoracial background, likely due to societal-structural factors, cultural interpretations, and/or trauma-exposure-related characteristics that covary with race/ethnicity in unequal societies[41,95].

For example, a higher prevalence of PTSD has been reported among Latinx vs. non-Latinx White individuals in several circumstances, including as combat veterans of the Vietnam War (after adjusting for degree of exposure and other demographic characteristics); as residents of lower Manhattan after the September 11, 2001 attacks; as police officers exposed to line-of-duty trauma; and as survivors of a devastating hurricane (adjusting for trauma exposure)[95].

The risk of PTSD also varies according to cultural interpretations and social contexts that influence the perceived severity of a stressor[41]. Among these are the relative severity of traumatic events affecting family members vs. the individual[33], the impact of religious persecution over other stressors[38], or the effect of being unable to conduct burial rituals beyond the impact of the death itself[39].

Among the covariates that likely influence the relation between traumatic event exposure and risk of PTSD according to ethnoracial background are the availability of social support and other social resources that tend to facilitate recovery from traumatic events[96], as well as the exposure to discrimination and persistent inequality (e.g., in wealth and other assets)[97,98].

There are probably important cross-cultural differences in PTSD symptomatology, although they are incompletely documented. For instance, numbing-avoidance reactions vary cross-culturally, as noted in studies with Vietnamese refugees and Kalahari bushmen, while somatic complaints are prototypical features of PTSD in some cultural groups while less common in others[46,99]. Some PTSD symptoms tend to be especially salient in certain groups, such as nightmares among Cambodians[100] and American Indians/Alaskan Natives[101]. These variations in PTSD symptoms are often influenced by the idioms of distress that are considered culturally normative responses to traumatic exposures. Nevertheless, despite these local variations, there is considerable cross-cultural validity of PTSD as a construct[41].

Some of the previously mentioned demographic differences vary across cultural and ethnoracial groups. For example, in a large US community-based epidemiological study, gender differences were found for non-Latinx White, African American and Afro-Caribbean women, but not for Latinx or Asian-origin women[102]. Also, little association between PTSD and gender has been found in South Africa[73]. These differences have been attributed, among other factors, to variation in types of trauma exposure (e.g., similar exposure across genders to state-sponsored violence during the apartheid regime in South Africa), to shared societal-structural factors such as discrimination among US Latinx, and to cultural variations in gender-based expectations of what constitutes abuse[73,102].

Mass traumatic events

There is a substantial literature suggesting that the population burden of PTSD can be high after mass traumatic events. For example, a systematic review and meta-analysis of the global burden of PTSD in war-affected countries found an overall population prevalence of 26.5%[103]. However, variability in the mass traumatic events studied, the exposure among persons in samples, the methods of measurement, and the assessment tools used – in studies that are often conducted quickly after unexpected events – make generalization about the consequences of these mass traumatic events difficult.

It is probably not useful to provide single estimates of PTSD prevalence in the aftermath of mass traumatic events, given the diverse populations that likely experience the event differently from one another. For instance, a review that synthesized the available literature estimated the prevalence of PTSD after mass traumatic events at 30-40% among direct victims, 10-20% among rescue workers, and 5-10% in the general population[104]. The prevalence of PTSD has been documented to be particularly high among children directly exposed to mass traumatic events[105].

In recent years, several studies have documented the burden of PTSD in the context of global traumas such as the COVID-19 pandemic. A meta-analysis of 63 COVID-related studies found an overall PTSD prevalence of 17.5% at the population level[106].

Trajectories after trauma and course of PTSD

After a traumatic event, four main trajectories have been usually reported: resilient (or resistant), in which persons have stable long-term healthy functioning and no (or few) PTSD symptoms; chronic, indicating long-lasting PTSD symptoms; recovered, with early onset of PTSD symptoms and subsequent remission; and delayed-onset, in which PTSD develops sometime after trauma exposure[107-109]. There is little consistency across studies about the relative prevalence of these trajectories. Among 54 studies reviewed, however, the resilience trajectory was the modal response (average of 65.7% across populations), followed by recovery (20.8%), chronicity (10.6%), and delayed onset (8.9%)[108].

The majority of research has been concerned with the course of established PTSD. A systematic review found that, after a mean observation period of 40 months, an average of 44.0% of individuals with PTSD at baseline no longer met disorder criteria. There was wide inter-study variation in remission rates from 8 to 89%, with rates being higher the sooner PTSD was measured after the traumatic event[110]. Among patients assessed in clinical settings, 18-50% experienced recovery within 3-7 years, while the remainder had a recurrent or more chronic course[111].

Most of the evidence suggests a dose-response effect of traumatic load on the probability of long-term spontaneous remission of PTSD: a higher cumulative exposure to traumatic events is associated with a lower probability of remission[112]. The type of the experienced traumatic event(s) also contributes to the course of PTSD. One systematic review of untreated PTSD suggested that the perceived intentionality of traumatic events – such as domestic abuse (intentional) vs. natural disasters (unintentional) – was associated with worsening as opposed to improving trajectories, respectively. In five studies of exposure to intentional trauma, about one-third of persons with PTSD remitted after 3 months, while another third had chronic PTSD lasting more than 6 months[15].

PTSD course may also be affected by social disadvantage, via the link between resources and access to treatment. The World Mental Health Surveys highlight substantial differences in treatment seeking[70], with the proportion of people with PTSD accessing treatment in the previous 12 months being 53.5% in high-income countries, 28.7% in upper-middle-income countries, and 22.8% in low- and lower-middle-income countries. A subsequent analysis of data from 17 surveys across 15 countries[113] found that 43% of people with PTSD received any mental health services, including 50.6% in high-income countries vs. 19.8% in low- and middle-income countries.

Of special interest has been delayed-onset PTSD. Meta-analyses of prospective studies report that around a quarter of PTSD cases have their onset at least 6 months after the traumatic event[114,115]. Factors associated with delayed-onset PTSD are found to be encountering trauma in a professional capacity (e.g., military personnel, firefighters, rescue workers, police) and "Western" cultural background (defined by country of origin).

A systematic review found that delayed-onset PTSD in the absence of any prior symptoms was rare[116,117]. Delayed onsets that represented exacerbations or reactivations of prior symptoms accounted for 38.2% of military and 15.3% of civilian cases[116].

ROLE OF THE TRAUMATIC EVENT

With the introduction of PTSD in the DSM-III[48], traumatic events were conceptualized as being so extreme as to produce "significant symptoms of distress in almost anyone". This claim helped to justify the need for PTSD as a disorder that, most unusually for a psychiatric diagnosis, was primarily caused by environmental factors. The DSM-III-R[118] further specified such events as being "outside the realm of normal experience" and added a list of characteristics, including serious threat or actual injury, destruction of one's home or community, and witnessing mutilation or violent death. There was also a recognition that the events included serious threat or harm to one's children, spouse, or other close relatives and friends.

The DSM-IV[119] expanded the range of qualifying stressors affecting family and close friends to include learning about their sudden and unexpected death from any cause, and learning about traumatic events that they experienced. Furthermore, it included the person him/herself being sexually abused in childhood or diagnosed with a life-threatening illness. It recognized that traumatic events were not outside normal human experience but were relatively common.

The DSM-IV also acknowledged a subjective component in how individuals responded, with events not having to be "markedly distressing to almost anyone" but instead requiring that the "person's response involved intense fear, helplessness, or horror". Whether this response had to be present at the time of the trauma itself or could arise later, for example with the development of delayed-onset PTSD, was not specified. Compared to the DSM-III-R, most of the additional PTSD cases brought about by expanding the list of qualifying events were attributable to learning about the sudden unexpected death of a close relative or friend[120], emphasizing the importance of social attachments in PTSD.

The subjective requirement introduced in the DSM-IV was argued to add little diagnostic specificity. In fact, in surveys, events that did not involve intense fear, helplessness or horror were unlikely to meet the remaining criteria for the diagnosis. This finding was partly responsible for the requirement being dropped in the DSM-5, with a consequent reduction in the role of subjectivity[55]. The DSM-5 clarified that the diagnosis required exposure to actual or threatened death, serious injury, or sexual violence, either through direct experience, or witnessing in person the event happening to someone else, or learning that it occurred to close relatives or friends.

In cases of the actual or threatened death of a family member or friend, the event was required to be violent or accidental. This eliminated many events considered traumatic under the DSM-IV, such as non-immediate, non-catastrophic, but nevertheless life-threatening medical events with natural causes. An extensive body of research documents that after such events, for example receiving a cancer diagnosis or having a heart attack, people may present symptoms of traumatic stress and meet other criteria for PTSD[121-123].

A fourth type of exposure new in the DSM-5 involved repeated or extreme encounters with aversive details of a traumatic event, e.g., first responders collecting human remains. Such exposure was excluded if it occurred solely via electronic media, unless this was work-related, for example police officers examining Internet sites for evidence of child abuse.

This persistent expansion of qualifying traumatic events led to concerns about "criterion creep", whereby PTSD would become trivialized and associated with stressors such as divorce, financial problems, and verbal bullying[124,125]. This tendency has been evident in the proliferation of the term "trauma" in colloquial language and social media. However, concerns about criterion

creep were mainly raised in the context of litigation and claims for damages, rather than arising in the clinic. We are unaware of any substantiated claims of PTSD being formally diagnosed after such stressors in the absence of a history of more serious trauma.

An opposite concern lies in the growing recognition that the voices of various relevant groups have been marginalized in the discussions and decisions made on what qualifies as a traumatic event. The diagnostic formulation has reflected the views of influential clinicians and researchers, but has not considered the input of people with lived experience of trauma in different contexts.

The approach taken by the DSM in specifying the objective nature of traumatic events is designed to prevent the inappropriate use of the diagnosis and its application to non-traumatic stressors. There is an assumption that traumatic events involving life threat or risk to the integrity of one's person are qualitatively different from other stressful life events, so that the PTSD trauma definition should be limited to events meeting this high bar of exposure severity[126]. Survey evidence, however, suggests that relaxing the criteria so that a broad range of events can potentially qualify as traumatic makes little difference to prevalence rates of PTSD as defined by the DSM-IV[127,128].

Since even catastrophic events are generally followed by PTSD in some individuals but not others, there are likely to be complex interactions between individual risk factors and the harmfulness of a given stressful event[129]. The implication is that, in the presence of relevant risk factors, events not included in the DSM definition might be followed by a syndrome with the characteristics of PTSD. Consistent with this, there are least three categories of events not considered by the DSM that are empirically associated with high levels of PTSD symptoms. These include: a) repeated, cumulative aversive experiences such as stalking, bullying, emotional abuse, neglect and harassment, sometimes exacerbated by systemic discrimination[130-132]; b) terrifying hallucinations experienced by patients with psychosis or undergoing sedation in intensive care[133,134]; and c) stressors encountered by non-neurotypical groups such as people with autism[135]. Such cases have not been prominent in general population surveys, but may account for significant degrees of morbidity in more specific groups.

In the DSM-5, the majority of these presentations would currently have to be diagnosed as adjustment disorders, a situation that has been acknowledged as possibly incongruous if the same symptoms lead to two different diagnoses[129]. However, reports of PTSD diagnoses in response to events not considered in the DSM might instead be indicative of psychometric deficiencies in the measures used, particularly if these rely upon self-report. In the case of an individual experiencing terrifying hallucinations of events that did not occur in reality, the hallucination would not be considered a traumatic event by the DSM-5, but would be accounted for by the primary psychotic diagnosis and the associated impairment in reality testing.

We will see later on that the ICD-11 allows a diagnosis of PTSD in a wide variety of traumatic situations, as it only requires exposure to an event or series of events judged by the clinician to be extremely threatening or horrific. An alternative proposal[136,137] is to acknowledge the poor validity of attempts to define traumatic events by dispensing with this altogether, relying instead on the pattern of symptoms and resulting disability to diagnose PTSD.

A related view is that PTSD is often an outcome of specific peritraumatic and post-traumatic responses. These responses are usually associated with the objective circumstances identified in the DSM-5, but may also occur in other situations. The responses may reflect a specific phenotype associated with a failure to recover from the normal effects of trauma[18], or be related to prior exposure to childhood adversity, or to different patterns of environmental exposure such as overwhelming or cumulative trauma, or to specific types of appraisal, or to the use of certain coping strategies.

Peri-traumatic responses that increase the risk of PTSD can reflect both previous history and psychological or biological susceptibility. They typically involve the subjective experience of fear, helplessness or horror, but may have additional components that mark them out from everyday stress responses. To date, psychological variables appear to be stronger markers of these responses than biological ones. They are characterized by cognitive overload (being unable to reflect or plan normally), mental defeat or resignation, and dissociative symptoms such as changes to visual and body perception[138-140].

A frequent pattern of PTSD development takes place when these peri-traumatic responses are followed by negative appraisals and maladaptive post-traumatic behaviors such as thought suppression and rumination[141], or by negative social reactions such as criticism and rejection[142-144]. The occurrence of subsequent stressors, not necessarily of a traumatic kind, is also an important contributor to onset[94].

The adoption of fixed and objective versus more flexible criteria for what constitutes a traumatic event primarily reflects strategic priorities. The former approach helps to exclude invalid cases of PTSD, whereas the latter is designed to include all valid cases of the disorder. In moving forward, what is needed are more data on how PTSD presents following more "objectively" and more "subjectively" traumatic events. It is important to establish, for example, whether PTSD following repeated low-impact or hallucinated events, or occurring in non-neurotypical groups, is different in any respect from more conventionally recognized cases of PTSD, either in the way it develops, its symptom pattern, or its chronicity. Studies may lead to the identification of additional conditions within a "family" of post-traumatic stress disorders.

A separate, but equally important, issue is whether the different situations in which PTSD manifests require similar, or dissimilar, treatment approaches. The expansion of potentially traumatic stressors may offer an important opportunity to better understand the nature of the condition, and to more appropriately tailor its management.

DEVELOPMENTS IN DIAGNOSIS

The DSM-5 dissociative subtype

The DSM-5 introduced a dissociative subtype of PTSD characterized by meeting full criteria for the disorder and exhibiting on-

going symptoms of depersonalization and/or derealization. This addition was based, in part, on the results of latent class and profile analyses which showed that a small subset of individuals with PTSD (from 10 to 30%) exhibited prominent symptoms of depersonalization or derealization, and that PTSD severity alone did not predict who would manifest these symptoms[145].

Close to 20 studies have used latent class or profile analysis across a range of cohorts differing in age, geographic location, civilian status, and primary trauma exposure type, and provided support for this unique presentation of PTSD[146-149]. A recent study compared the fit of class models (which directly support the unique group of individuals with the dissociative subtype) to confirmatory factor models (which would account for the dissociative symptoms dimensionally by virtue of their correlation with PTSD symptom severity) and factor mixture models (a mix of factors and classes) among trauma-exposed veterans. The results indicated that, of these three types of models, the subtype structure provided the best fit to the data[150].

Consistent with this, there is preliminary evidence that the dissociative subtype may be associated with unique biological correlates relative to the core symptoms of PTSD. These include genotypes that are predictive of the dissociative symptoms after covarying for PTSD severity[150], and alterations in brain morphology and function[150-154]. However, the implicated brain regions and the nature of these alterations have varied greatly across studies[150,152,155,156]. It is also important to note that these studies have generally focused on trait dissociation (as opposed to a state of active dissociation), so that these alterations may reflect a vulnerability or proclivity to dissociative experiences rather than the neurobiology of an active dissociative experience. In addition to potential biological differences, there is also evidence that individuals with the dissociative subtype may respond less well to psychotherapy for PTSD[157] and to pharmacological treatment[158].

Collectively, these differences in symptom presentation, biology and treatment response highlight the importance of delineating the dissociative subtype for both research and clinical purposes.

ICD-11 PTSD and complex PTSD

The ICD-11 set out to achieve several goals in its definition of stress-related disorders. These included maximizing clinical utility, by making the diagnoses simpler and more focused on core features to distinguish them from other disorders; raising the threshold for PTSD relative to the ICD-10 by including consideration of functional impairment; integrating PTSD more successfully with the ICD-10 "enduring personality change after catastrophic experience" diagnosis; and addressing the perceived need for a diagnosis of complex PTSD. The Working Group who developed the proposals included trauma experts from many parts of the globe[159].

Attempts to establish the core features of PTSD have most commonly identified nightmares, flashbacks, exaggerated startle response, and hypervigilance[62,136,160-162]. Avoidance has been suggested as another essential component of PTSD (even though one shared with other anxiety disorders and depression)[136]. In line with these observations, PTSD is defined in the ICD-11 by three sets of symptoms, with one indicator of each being required: a) re-experiencing of the event in the here-and-now (presence of flashbacks or nightmares); b) avoidance of traumatic reminders (avoidance of thoughts and memories or external situations and reminders); and c) a sense of current threat (presence of either hypervigilance or exaggerated startle response). Symptoms must follow an extremely threatening or horrific event or series of events, last for several weeks, and be accompanied by functional impairment[159].

Although those symptoms also appear in the DSM-5, the ICD-11 formulation is narrower and more specific. This is particularly true for the re-experiencing cluster. Intrusive thoughts and memories are found in many disorders. What characterizes PTSD is that the intrusive memories have strong sensory elements and are experienced as happening again in the present[61]. Like the DSM-5, the ICD-11 describes flashbacks as existing on a continuum, from intrusive memories with a fleeting sense of "nowness" to complete absorption in the traumatic memory and loss of awareness of the current environment.

The ICD-11 also includes a separate diagnosis of complex PTSD, a more severe condition. This differs in several respects from previous formulations of complex PTSD[163] and from the ICD-10 "enduring personality change after catastrophic experience"[164]. Unlike them, it requires the presence of ICD-11 PTSD symptoms. Another difference is that exposure to chronic or repeated trauma is conceptualized as a risk factor, likely to be present but not required for the diagnosis.

In addition to the three PTSD symptom clusters, the ICD-11 diagnosis of complex PTSD is defined by three further sets of symptoms that emerge or intensify following the traumatic event, i.e. affective dysregulation, negative self-concept, and disturbances in relationships. These symptoms are collectively labelled "disturbances in self-organization". Symptoms were selected because they were frequently reported by participants in the DSM-IV field trials of a complex form of PTSD[165], and were identified by expert clinicians as the most common and impairing in clinical practice[166].

In the ICD-11, individuals may be diagnosed with PTSD or complex PTSD, but not both. A PTSD diagnosis implies that the requirements for complex PTSD are not met. The requirements for ICD-11 PTSD or complex PTSD are markedly harder to be met than those for ICD-10 PTSD, and somewhat harder to be fulfilled than the DSM-IV or DSM-5 criteria for PTSD[167]. Comorbid depression, while still frequent, appears to be less common in PTSD diagnosed according to ICD-11 than DSM-IV or DSM-5[167]. Individuals who qualify for the diagnosis of PTSD according to ICD-10 or DSM-5, but not for the ICD-11 diagnosis of PTSD or complex PTSD, may meet requirements for alternative diagnoses such as major depressive disorder.

The distinction between ICD-11 PTSD and complex PTSD has been extensively tested by research[167-170]. Confirmatory factor analysis carried out in many different cultures has found that complex PTSD includes six correlated first-order factors in line with the six symptom clusters, and two correlated second-order

factors in line with the dimensions of PTSD and disturbances in self-organization. Distinct groups with symptom profiles corresponding to PTSD and complex PTSD have been repeatedly identified in mixture-modeling studies with disparate groups such as children and adolescents, military veterans, refugees, and asylum seekers. Those in the complex PTSD class typically report more functional impairment than those in the PTSD class.

It is sometimes suggested that complex PTSD is simply a more severe form of PTSD[171]. This possibility is addressed by factor-mixture modeling, a technique that combines dimensional and categorical analysis. An early study[172] reported factor-mixture models in two cohorts and found that, after controlling for a gradient of symptom severity, the PTSD and complex PTSD classes differed quantitatively but not qualitatively. In contrast, a study of refugees found evidence for qualitatively distinct PTSD and complex PTSD classes[173]. However, both these studies were performed before tailored instruments for the assessment of ICD-11 complex PTSD symptoms were available.

Two recent studies utilized the International Trauma Questionnaire[174], specifically developed for ICD-11 PTSD and complex PTSD, to assess symptom structure in a sample of young people and one of adults from the general population. Both studies found that ICD-11 PTSD and complex PTSD formed distinct latent classes and did not simply differ on a severity dimension[175,176]. Additional research employing factor-mixture modeling in large and diverse cohorts is needed to further address this question.

The evidence base for ICD-11 PTSD and complex PTSD now includes research, predominantly psychometric, carried out in five continents. It is not yet known whether these diagnoses will fulfil the WHO's intention of improving the recognition of trauma-related disorders. Studies are required that evaluate the relevance and practical utility of these diagnoses in different cultural settings, as exemplified by research among young people in violent neighborhoods in Brazil[177].

Another important issue is to understand why some people receive a PTSD diagnosis with the DSM-5 but not with the ICD-11. This could shed valuable light both on the nature of PTSD and on the strengths and weaknesses of both systems.

Comparing ICD-11 and DSM-5

The ICD-11 and DSM-5 approaches to representing post-traumatic psychopathology diverge in important ways. While the ICD-11 reduced the number of PTSD symptoms (relative to the ICD-10) to three core features of the disorder, and encompassed other enduring post-traumatic responses in the diagnosis of complex PTSD, the DSM-5 increased the number of symptom clusters (to 4) and symptoms (to 20) under the PTSD criteria.

Both approaches have advantages and disadvantages. The DSM-5 attempts to represent a greater breadth of symptoms under one diagnosis, and includes more items per symptom cluster, which allows for greater reliability[178]. However, the inclusion of more non-specific diagnostic criteria that are characteristic of generalized distress (e.g., chronic mood disturbance, distorted negative cognitions, sleep and concentration difficulties) may artificially inflate diagnostic comorbidity and introduce redundancy into the diagnostic taxonomy across a variety of mood and anxiety disorders.

In contrast, the ICD-11 approach is streamlined in its focus on the core and perhaps defining features of PTSD, but may fail to identify some individuals who experience alternative manifestations of post-traumatic psychopathology. For example, there may be some intrusive traumatic memories that do not meet the definition of flashbacks or nightmares. Given the transdiagnostic nature of intrusive memories, and the need for accurate assessment to differentiate them from rumination about the causes or consequences of a traumatic experience, additional research is needed to determine whether such manifestations are best considered as indicative of PTSD or as part of other disorders such as major depression.

In contrast to the DSM-5, the ICD-11 does not include a dissociative subtype of PTSD or complex PTSD. However, one of the two ways by which an individual can meet the ICD-11 re-experiencing criterion is by having flashbacks, which are generally regarded as dissociative experiences. Further, affective dysregulation can be manifested as emotional numbing, which can be an expression of dissociation wherein an individual is separated from his/her own emotional experience. Thus, dissociation is actually represented in the current ICD-11 criteria. There is also evidence that individuals with complex PTSD may be particularly prone to dissociation[179,180], perhaps in relation to childhood trauma exposure[181].

Additional research is needed to determine if dissociative experiences are a core component of PTSD or complex PTSD, or are evident only in a unique subgroup of individuals with these conditions. The definition of dissociation employed will impact the results of research addressing this question, as some forms of dissociation (such as reduction in awareness of experience) are common and appear to covary linearly with PTSD symptom severity, while other forms (such as derealization and depersonalization) are far less common and are not strongly correlated with PTSD severity[145].

PSYCHOLOGICAL FOUNDATIONS OF PTSD

PTSD involves many different psychological processes, including attention, causal and other beliefs, affective reactions, coping strategies, and social interactions[182]. However, psychological theories of PTSD have mostly focused on disturbances to memory for the traumatic event and on the impact of the event on the survivors' identity, in particular the way in which they conceptualize and experience the self.

Trauma memory disturbance

Many different aspects of memory are affected in PTSD. When it comes to non-trauma-related material, people with this disorder have difficulty learning and remembering new items, particularly verbal items; their working memory functions less well; when giv-

en the task of recalling specific personal experiences to cue words, they tend to retrieve examples that are overgeneral in that they are repeated or last more than one day; they are also more prone to associative memory illusions[183]. However, more pertinent is the way in which memory for the person's traumatic experiences functions – this is central to psychological theories of PTSD and to the aims of psychological therapy.

Enhanced re-experiencing

The most distressing and disruptive form of re-experiencing of the traumatic event in PTSD consists of flashbacks. These are usually brief and involve a few specific scenes, although they may involve a series of scenes that are experienced as like a videotape[184,185]. They contain very prominent sensory elements, as well as emotions and bodily sensations – such as heat, cold or pain – that were part of the traumatic event[186], and cannot be retrieved deliberately as ordinary autobiographical memories can. Another way in which they differ from ordinary memories is that there is a distortion in the sense of time, whereby they are to a greater or lesser degree re-experienced in the present or here-and-now[187-189] rather than as belonging to the past.

Re-experiencing trauma memories in this way is predictive of the course of the disorder over and above the overall symptom severity[190,191]. With treatment, intrusive memories of the traumatic event become less vivid, less distressing, and have less of a sense of being relived in the present[192,193].

Less commonly, there may be intrusive images that are partly based on the traumatic event but contain fantasy elements such as "what could have happened", as well as images that are entirely based on imagination[194,195]. There may also be involuntary autobiographical memories of aspects of the traumatic event that are experienced as belonging wholly to the past. Compared to flashbacks, much less is known about the significance of these intrusions and how best to treat them.

Impaired voluntary recall

Trauma clinicians are familiar with PTSD patients reporting puzzling gaps in their memories for the index event(s) or, more frequently, difficulty in constructing a coherent and ordered narrative. It is not uncommon for significant details to be recalled, apparently for the first time, during the course of psychological therapy[196]. Moreover, impairments in voluntary trauma memory have been found consistently to be related to self-reported dissociation, either during or after the traumatic event, and to predict the course of PTSD[197].

Studies of coherence and disorganization in trauma memories have mostly used three types of measurement. First, respondents rate the overall amount of fragmentation or disorganization in their own memories, or write trauma narratives that are rated by themselves or independent judges. Second, similar overall measures assess narrative coherence, on the assumption that this is the opposite of fragmentation and disorganization. Third, trauma narratives are divided into individual utterance units, and raters assess linguistic markers of disorganization and fragmentation such as repetition and non-consecutive chunks.

There has been disagreement over whether these studies do[197] or do not[198] provide evidence for greater fragmentation or disorganization in the trauma narratives of PTSD patients compared to healthy controls. A recent meta-analysis[199] found that there is a significant association of moderate size between PTSD and fragmented trauma narratives. However, this is qualified by the methods used. Measures that assess disorganization and fragmentation directly, whether by self-ratings or judge ratings, show a strong association, but measures that define them as an absence of coherence show little if any association. This indicates that a narrative may be clearly disorganized in parts, perhaps during the most terrifying moments, without necessarily affecting elements of coherence such as having an overall story with a logical structure that makes sense.

Theoretical perspectives

Encoding of context

Some cognitive accounts of PTSD see the condition as reflecting the operation of normal episodic, or more specifically autobiographical, memory[200,201]. These accounts propose that – after traumatic events – factors such as the memory's emotional intensity, its tendency to come repeatedly to mind, and its salience all strengthen the accessibility of a memory, the links with its associated context, and its ease of retrieval. Although these theories can account for many aspects of PTSD, the evidence for memory fragmentation and disorganization is counter to their predictions.

In contrast, clinical theories of PTSD have often incorporated the idea that contextual information is less strongly, not more strongly, associated with the traumatic stimuli. In conditioning theories, a process of stimulus generalization is thought to affect elements of the traumatic situation, such that similar stimuli encountered in dissimilar contexts act as reminders and lead to the return of the fear memory[202]. According to another model, the traumatic event alters the way in which contextual information is represented. For example, following an unexpected attack, many situations previously regarded as safe now become unsafe, so that a wide range of environmental cues can potentially trigger a fear memory[203].

Other clinical theories emphasize that, in PTSD, frightening or horrific moments are poorly elaborated, not fully situated in time and place, and inadequately integrated into the person's general autobiographical knowledge[61,204]. These clinical theories have much in common with biological models that also associate PTSD with impairments in the learning of context[205,206].

Single versus multiple representational formats

Several authors have attributed the symptoms of PTSD to an exceptionally strongly encoded trauma memory in a single repre-

sentational format. An influential perspective[203,207] holds that the trauma memory representations take the form of highly associated networks containing stimulus, response and meaning elements. The activation of any element, for example by encountering a trauma reminder, then activates all the elements in the network, leading to a re-experiencing of the event.

Although these theories explain many aspects of PTSD, they cannot readily account for the subjective distinction that people with PTSD make between involuntary phenomena, such as flashbacks, and ordinary memories that are easily retrieved, reflected upon, and communicated to others[208]. In contrast, dual representation theory[61] explicitly posits that traumatic events are encoded separately in a lower-level, image-based memory system governed by associative principles, and in a fully contextualized episodic memory system. Under normal conditions these systems are well integrated, but extreme fear, helplessness or horror causes the balance to shift, so that sensation-near images are strongly encoded while contextualized representations are weakened, failing to provide a context for re-experiencing. This model accounts for the fact that people with PTSD can appraise and provide linguistic accounts of many aspects of their trauma, while being unable to control the re-experiencing of specific moments.

Similarly, the cognitive model of PTSD[204] refers to the existence of parallel data-driven and conceptual processing during traumatic events. Data-driven processing is a lower-level form of processing and is associated with automatic, cue-driven retrieval of trauma memories and enhanced perceptual priming, defined as a reduced perceptual threshold for trauma-related sensory stimuli. Conceptual processing is language-based and is associated with the conscious appraisal of traumatic events and their sequelae.

Although differing in their emphasis on representations versus processes, both the cognitive model and the dual representation theory posit lower-level associative memories and higher-order, language-based memories of traumatic events[141].

Identity disturbance

Identity is a construct that spans past and future, summarizing previous experience but also projecting into the years that remain to be lived. Objective identity, or the Me-self, consists of a person's perception of his/her own traits and characteristics. Subjective identity, or the I-self, consists of the person's experience, including the emotional and bodily states that accompany feelings such as pride, shame or guilt.

The way in which people have been treated, and are being treated, by family, friends, teachers, colleagues, employers, and the wider community shapes their perceptions of who they are and what they can expect from social relationships. Not surprisingly, the quality of social relationships post-trauma is one of the strongest predictors of PTSD, with criticism or verbal attack being particularly detrimental[94,142,209].

Identity is multi-faceted, deriving from each person's physical and mental attributes, from the many different experiences in the multiple roles that the person plays (e.g., child, sibling, student, employee) and the situations that he/she encounters (work, family, school, interactions within own community, interactions with different communities), and from his/her goals and aspirations. Individuals differ in the degree to which these different facets are perceived to be integrated into a whole, with early childhood trauma making this process harder[210]. Some of these facets will correspond to identities that attract social stigma, whether or not this is observable to others[211]. Internalized stigma is the process by which people apply negative stereotypes to themselves, and expect to be rejected by others[212]. It is normal to try to manage one's identity by strengthening the positive, desired aspects and avoiding the negative or feared aspects coming to mind[213].

The impact of the traumatic event on the Me-self of the individual with PTSD has been regarded as a major feature of the condition from the very beginning. The event is frequently seen as bringing about drastic negative changes in the person's perception of him/herself, other people, and his/her future, that are often viewed as permanent[214,215], and can become a central turning point in the person's autobiographical narrative[216].

The event can cause disruptions in beliefs about core social expectations of safety, trust, power, esteem and intimacy[217]. It can be seen as challenging long-held assumptions that the self is basically worthy and that other people have benevolent intentions[218]. Alternatively, it may strongly reinforce existing concerns about the self and others, created by processes such as self-stigmatization and previous exposure to adversity[207].

It has been argued that survivors respond to these challenges in a number of different ways[219]. The situation may be reinterpreted in a distorted way, so that it can be assimilated into existing beliefs. For example, someone with a prior belief that bad things only happen to bad people may conclude that he/she must have done something wrong for the traumatic event to have occurred. Over-accommodation takes place when the event is followed by a complete abandonment of the pre-existing belief and the adoption of a new, extreme variant. For example, after an unexpected assault, someone may adopt the belief that nowhere is safe for him/her and no one is to be trusted.

Identity-related perceptions in PTSD, such as self-blame and holding others to be untrustworthy, have been suggested to derive from deep-seated beliefs of the form "I am totally incompetent" or "The world is completely dangerous"[207]. People already holding such rigid negative views may have them confirmed by negative appraisals of the traumatic event, of symptoms that developed afterwards, of interference with successful functioning, and of others' responses.

A focus on negative beliefs and cognitions plays a central role in the cognitive theory of PTSD[204]. Individuals may blame themselves for the event happening, for their reactions or behaviors during or after the event, or for the symptoms that they develop subsequently. They may perceive that the event has led to a permanent change for the worse[220]. These appraisals predict the course of the disorder, often over and above initial symptoms[190,221,222], as well as driving symptom change in PTSD therapy[223,224]. Identity-protective responses such as thought suppression, rumination, and safety behaviors (i.e., actions aimed to prevent the occurrence

of a feared outcome or reduce associated distress) appear to maintain the disorder[141].

In PTSD, changes to the I-self are also routinely observed. It is common for people to experience their body differently, for example with areas of medically unexplained pain[179,225,226]; to feel that their character or body is worthless or shameful[227-229]; to experience themselves as defeated, empty or even dead[204,230]; and to feel alienated from others[231].

Veterans with PTSD frequently report the experience of shame [232], as well as feelings of disconnection from the civilian world [233]. One factor that is sometimes involved is moral injury, an experience of powerful negative emotions arising from the person's sense of having violated his/her own moral standards, or of having been betrayed by others[234]. Moral injury is common to a wide range of professions, including emergency services and health care workers[235], and is an important predictor of PTSD symptoms in former military samples[236].

The Memory and Identity theory[168] proposes that alterations in both the Me-self and the I-self are central to complex PTSD. Traumatic events confirm and prompt the reactivation of prior negative identities emerging due to childhood adversity, leading to a more pervasive and negative sense of self. The re-enactment of situations in which the self was experienced as worthless or inferior is linked to pervasive negative self-concept symptoms. Re-enactment of the self being abandoned, betrayed and/or alienated from others is linked to the disturbed relationship symptoms. Re-enactment of all these selves, and of experiencing being fragmented or non-existent, may foster the development of emotion regulation problems.

The theory further posits that chronic or repeated traumatic events may also create new negative identities, even in the absence of childhood adversity. For example, exposure to extreme situations such as torture can result not only in pain and suffering, but in dehumanization, degradation, and emotional isolation[237]. The repeated humiliation, criticism, and body shaming that are frequently part of intimate partner violence have been argued to be attempts to destroy positive identities and replace them with a sense of worthlessness[238,239]. War and genocide may also involve the conscious attempt to destroy the cultural identity of an entire population[240].

Identity is also an important element of Conservation of Resources theory, a general theory holding that stress emerges in response to actual, or threatened, loss of resources[241,242]. Among the many types of resources, some of the most important are the physical (e.g., housing), the social (e.g., family and community support), and the structural (e.g., employment) ones. Numerous studies have found an increased occurrence of PTSD to be associated with traumatic events producing greater resource loss[243,244], and recovery to be predicted by resource gains[245]. This theory makes the important point that resource loss is critical to survival, social attachments, and social status. It thus generally threatens core aspects of the individual's Me-self and I-self, and often the identity of the family and wider group in which the individual is embedded.

Delayed-onset PTSD

The mnemonic model of PTSD suggests that the disorder arises not from the traumatic event itself but from the memory of that event[52]. Delayed-onset PTSD illustrates that in some cases the traumatic memory does indeed appear to change over time, for example becoming more distressing and intrusive.

There has been little investigation of the foundations of this form of PTSD. One study that compared immediate and delayed onsets in military veterans[232] found that the number of respondents reporting depression and alcohol abuse before the main trauma in service was significantly greater in the delayed-onset group. The two groups described similar amounts of military trauma exposure, but those in the delayed-onset group reported significantly less peri-traumatic dissociation, anger and shame. The delayed-onset group also reported a gradual accumulation of symptoms that continued throughout their military career, with an excess of other stressors unrelated to their traumatic event occurring in the year preceding their onset.

If replicated, these findings suggest that many delayed onsets involve a more general stress sensitivity and a progressive failure to adapt to continued stress exposure, rather than an experience of being overwhelmed by reactions to a specific event. It may be useful to consider biological processes that could explain the gradual build-up of cumulative stress effects, such as kindling or sensitization.

A small group of delayed onsets appears to occur in the absence of previous symptoms. These may reflect new circumstances that prevent reminders of a traumatic event being avoided, changes in the meaning of individual traumatic events over time, or the development of a neurological or cognitive impairment that prevents unwanted memories being inhibited.

Implications

Of the two most central disturbances in PTSD, one involves excessive intrusion and fragmentation in traumatic memories, so that the person experiences a marked lack of control over when they come to mind, and over the emotional and physiological consequences of this occurring. The other involves sometimes profound experiences of the self as being defeated, morally reprehensible, divorced from others, and sometimes as barely existing. Both disturbances often involve experiences, such as psychic and somatic dissociation, that are not integrated with the sense of self. These disturbances, and the compensatory behaviors adopted to mitigate them, are the main focus of psychological therapies, but are as yet poorly understood.

There is an urgent need for more phenomenological research to describe these core experiences in more detail. For example, little if anything is known about the extent to which intrusive memories during an episode of PTSD include images of prior traumas as well as the index event, or how repeated events are represented. Biological research, especially neuroimaging, also has an important

role to play, and has produced preliminary findings supporting the theoretical position that traumatic memories are fundamentally different from ordinary episodic memories[246,247]. Disturbances in the sense of self, such as feeling the self to be fragmented or non-existent, have been linked to altered functioning in the default mode network[248].

BIOLOGICAL FOUNDATIONS OF PTSD

Biological research on PTSD has expanded significantly in the past decade[249]. Several reviews on specific aspects of PTSD biology have been published in the last five years, including on inflammation[250], the immune system[251], neural circuits[252], biomarkers[253], and the microbiome[254]. In this section, we touch on a few areas that have been recently the subject of meta-analysis, and then summarize more deeply key findings in the fields of genomics and neuroimaging, which have advanced exponentially over the past decade through large multi-site studies producing robust and replicable findings. Preliminary findings in the areas of epigenomics and other "omics" are also considered.

Motivated by clinical observations of some of the core features of PTSD, such as exaggerated startle response and reactivity to trauma-related reminders, many of the early rigorous empirical studies on PTSD biology were focused on the autonomic nervous system. These included key findings of increased heart rate and skin conductance, as well as facial electromyography reactivity, during traumatic script-driven imagery and during exposure to trauma-related stimuli in persons with PTSD[249]. A recent meta-analysis[255] reinforced these findings, concluding that PTSD is associated with autonomic nervous system dysregulation. Persons with PTSD were found to have significantly higher heart rate and lower heart rate variability (i.e., variation in time between heartbeats), both at rest and during stress paradigms.

The role of hypothalamic-pituitary-adrenal (HPA) axis alterations in PTSD has also been an active area of research for many decades. Early findings suggested a differentiation in findings between PTSD and depression, with the former characterized by over-sensitization, and the latter by dysregulation of the axis[256]. However, findings from individual studies have been inconsistent. A recent meta-analysis reported that morning and 24-hour cortisol levels were lower, while evening dehydroepiandrosterone (DHEA) levels were higher, in PTSD subjects than controls, but concluded that there was not a consistent pattern of HPA axis alteration in PTSD[257].

The robust association of PTSD with chronic diseases – including cardiovascular diseases, diabetes, and autoimmune conditions – has motivated studies of the role of inflammation and oxidative stress in PTSD biology. A recent systematic review and meta-analysis[258] found that C-reactive protein, interleukin 6, and tumor necrosis factor-alpha were elevated in persons with PTSD versus controls. In contrast, oxidative stress markers were not associated with the disorder. The association between PTSD and inflammation appears to be bi-directional. Thus, it may be a mechanism through which PTSD increases risk of chronic diseases, while at the same time inflammation may increase risk of PTSD[258,259].

The findings concerning inflammation raise a key question relevant to many areas of PTSD biological research: most studies are cross-sectional, and it is not clear whether the observed findings – be they related to inflammation, cortisol secretion, or autonomic nervous system dysfunction – reflect a vulnerability for PTSD, are acquired because of developing PTSD, or perhaps both.

Genomics

Genetic factors are appealing for biological research on PTSD due to temporality. That is, an individual's DNA sequence is established at conception and therefore must precede the development of PTSD. Unlike many other biomarkers, a DNA sequence cannot be a consequence of developing the disorder. Genetic factors may increase the risk for PTSD through at least two pathways: increasing the likelihood of experiencing a traumatic event and increasing the risk of developing PTSD following trauma. Twin studies have shown that both the experience of trauma and PTSD are heritable, meaning that both are influenced by genetic factors[260,261].

Genetic risk for experiencing trauma and/or developing PTSD is not limited to a handful of genetic variants but is highly polygenic, with thousands of single nucleotide polymorphisms (SNPs) contributing to risk[262]. Here we focus on major findings related to PTSD risk. The role of genetic factors in trauma exposure[263] and how trauma influences genetic risk for PTSD[264] are discussed elsewhere.

Identifying causal SNPs requires the use of genome-wide association studies (GWAS) while accounting for genetic influences on trauma exposure[265]. Very large sample sizes are necessary to conduct GWAS in complex disorders such as PTSD, which led to the creation of the Psychiatric Genomics Consortium - PTSD Working Group (PGC-PTSD). This combined studies of PTSD with genetic data from around the world[266]. Understanding of the genetics of PTSD has also advanced through the Million Veterans Program (MVP)[267]. Together, the PGC-PTSD and the MVP have produced four robust genetic findings for PTSD.

First, the most recent GWAS, which combined data from the PGC-PTSD and MVP, included over 1.2 million participants and 150,000 PTSD cases. They identified 95 loci associated with PTSD, in genes related to neurotransmitter and ion channel synaptic plasticity modulators; developmental, axon guidance and transcription factors; synaptic structure and function; and endocrine and immune regulators[268].

Second, SNP-based heritability of PTSD from PGC-PTSD and MVP ranges from 0.053 to 0.092[267,268]. No significant differences in the SNP-based heritability of PTSD were found between male and female subsets.

Third, PGC-PTSD and MVP analyses produced a robust polygenic risk score for PTSD. This score is created by summing the number of risk alleles for a participant weighted by the alleles' effect estimates. Participants in the highest quintile of polygenic risk scores for PTSD were found to have 2.4 times the relative risk

for PTSD compared to individuals in the lowest quintile[268]. Overall, the polygenic risk score explained 6.6% of the variance in PTSD[268].

Fourth, PTSD was found to be genetically correlated with attention-deficit/hyperactivity disorder, alcohol dependence, anorexia nervosa, autism, bipolar disorder, major depressive disorder, obsessive-compulsive disorder, schizophrenia, and Tourette's syndrome[268]. As found in previous studies[269,270], PTSD and major depressive disorder were highly correlated. However, their genetic correlation varied with the population and method of assessment of PTSD. Genetic correlations between PTSD and major depression from a military cohort were around one-third lower than from an electronic health records-based cohort[268].

There are several limitations to our current genetic knowledge of PTSD. Addressing these limitations is necessary to translate genetic associations to causal biology, which remains an ongoing effort[252,271,272].

First, the latest PGC-PTSD results were not conditional on lifetime trauma exposure, which previous analyses have found to alter SNP-PTSD associations, as the genetic loci may increase risk for trauma exposure rather than PTSD[270]. This makes it difficult to disentangle risk for experiencing trauma and risk for PTSD.

Second, current GWAS combine cohorts that assess lifetime and current PTSD, thus losing the ability to determine if the identified genes are relevant to onset or course. Moreover, the latest and largest GWAS of PTSD used a simple case-control definition of PTSD based on ICD codes from electronic health records for around two-thirds of participants, rather than a validated scale measuring each PTSD symptom[267,268,273]. Including participants with less-validated diagnoses is necessary for GWAS, as large numbers of participants are needed[274]. However, this also further increases the heterogeneity of PTSD case status. Lack of precision in PTSD diagnosis also likely inflates genetic correlation with other mental disorders such as major depression.

Third, GWAS of PTSD have focused primarily on participants of European ancestry. Recent work on polygenic risk scores in PTSD[275-277] shows limited cross-population transferability and, by extension, poorer performance in populations from other parts of the world. Until this inequity is corrected, there is also a significant risk that the recent advances in PTSD genetics will result in a widening of the massive research and treatment disparities. This inequity is particularly troubling given the disproportionately high burden of trauma and PTSD faced by under-represented populations. For example, African Americans face a higher burden of PTSD driven by higher levels of exposure to violence at younger ages[278].

Epigenomics

While a person's DNA sequence is established at conception, how genes work can be influenced by many epigenetic factors. The most commonly studied measure of epigenetics in PTSD research has been DNA methylation, which modifies gene expression by binding a methyl group to DNA, usually at cytosine-guanine dinucleotides[279-285]. Epigenome-wide association studies of blood have found changes in DNA methylation in the genes *NRG1, AHRR, MAD1L1*, and *TBXAS1* to be associated with PTSD[279-281,286].

PTSD has also been associated with two epigenetic markers of accelerated biological age: shorter telomere length and older DNA methylation estimated age.

Telomeres are repeating patterns of DNA at the end of chromosomes that protect DNA during cell division and whose shortening leads to apoptosis of cells[287,288]. Shorter telomere length is considered a marker of biological age[289], as it has been associated with mortality[290]. Recent meta-analyses have found PTSD to be associated with shorter telomere length[291,292].

DNA methylation has also been used to estimate biological age. Older estimated biological age is associated with mortality and chronic diseases[293-296]. PTSD has been associated with accelerated DNA methylation age[297], although these studies have primarily been conducted in cross-sectional military samples[298-305].

Finally, building on efforts in depression[306], the PGC-PTSD Working Group is creating methylation risk scores to predict risk for PTSD by combining DNA methylation associations from across the genome, as is done with polygenic risk scores[307].

Other "omics"

Other "omic" methods focus on the downstream products of genetic and epigenetic factors to identify biological pathways that differentiate PTSD cases from controls. In the largest meta-analysis to date, differential gene expression has been observed for interleukin-1 beta (a pro-inflammatory cytokine previously associated with PTSD) and integrin-linked kinase (which is expressed in the brain and associated with dysregulation of the hippocampus)[308]. Another study had also found differential expression in another hippocampus-related gene (*DSCAM*)[309]. Beyond elucidating biological pathways, differential gene expression profiles (i.e., combinations of differentially expressed genes) have been used to predict PTSD, and have been reported to be a potential screening tool for the disorder[310].

Proteomic studies, which focus on identifying and quantifying proteins that are critical for every aspect of cellular life, have detected biological pathways associated with PTSD including immune response and cardiovascular and metabolic disorders. They have been used to create composite risk scores predictive of PTSD[311,312]. Finally, an emerging area for PTSD biological research is metabolomics, although to date studies have focused on a small number of candidate metabolites, with inconsistent patterns of association[313].

Neuroimaging

Many studies have examined structural and functional neural alterations associated with PTSD, primarily using magnetic resonance imaging (MRI). Given the sample sizes required to observe small neuroimaging effects, and the need to adjust for multiple testing across brain voxels and regions, the most convincing work in this area is derived from a more limited number of large-scale consortia studies, such as the Enhancing NeuroImaging Genet-

ics through Meta Analysis (ENIGMA) collaboration[314], which includes a PTSD Workgroup with relevant data from thousands of individuals.

This work has suggested PTSD-related differences in subcortical structural brain parameters, including smaller hippocampal volume[315] and reduced microstructural integrity of the tapetum area of the corpus callosum (which connects right and left hippocampus)[316]. Cortical brain structures have also been implicated in PTSD by consortium data (i.e., reduced volume of lateral orbitofrontal gyri bilaterally[317]).

Smaller studies and meta-analyses involving hundreds of individuals have suggested that PTSD is associated with thinner cortical tissue in the right fusiform gyrus[318], and reduced gray matter in prefrontal (anterior cingulate and ventromedial) and temporal cortical regions[319].

Meta-analytic studies of resting state functional connectivity parameters have revealed increased connectivity in the ventral anterior cingulate and parahippocampus/amygdala regions, and decreased connectivity in the posterior insula, cerebellar pyramis, and middle frontal gyrus. This is thought to reflect PTSD-associated decreased default mode network activity (associated with internally focused mentalization and self-reflection) and increased salience network connectivity (associated with attention to external stimuli)[320,321].

Like many other biological investigations of PTSD, most neuroimaging studies are unable to determine if the structural or functional alterations that are observed represent risk factors for PTSD or consequences of the disorder, or if they could be relevant to understanding the chronicity of symptoms and the likelihood of positive treatment response. Research has only just begun to address these questions. For example, there is some evidence from longitudinal studies that the smaller hippocampal volume identified in individuals with PTSD represents a stable vulnerability factor for the disorder[322].

This conceptualization is further supported by studies of individuals who undergo MRI shortly after trauma exposure. The following neural parameters are predictive of future PTSD (over 3-14 months) when measured shortly after trauma exposure, suggesting that they represent premorbid vulnerability factors: a) less functional connectivity between the left dorsolateral prefrontal cortex and the arousal network (primarily defined by limbic structures); b) greater connectivity between the right inferior temporal gyrus and the default mode network; c) reduced right hypothalamic volume; d) greater activation of the inferior frontal gyrus while performing an emotion modulation task; and e) hyperactivation of the insula and dorsal anterior cingulate cortex during threat-related tasks[323-326].

However, in some of these studies of adult trauma exposure, individuals had also experienced childhood trauma, raising the possibility that the predictive results may have been confounded by trauma-related psychiatric symptoms that pre-dated the adult trauma exposure[326]. Further, failure to replicate associations between post-trauma task-based brain activation and future symptoms raises doubt about the utility of neural parameters for predicting chronicity of symptoms[327].

Other studies have reported evidence for the reverse direction of association. A study of 254 veterans found that PTSD symptoms at baseline were associated with greater cortical degeneration over the course of two years. This effect was augmented among older veterans, suggesting that older individuals may be more neurologically vulnerable to the deleterious effects of traumatic stress[328].

Implications

There are at least four future directions or next steps for biological research on PTSD. First, except for genetic studies focused on DNA sequence variation, the majority of biological investigations are not designed to test whether biological factors increase risk of PTSD or are a consequence of developing the disorder. Second, most studies use a case-control design and, as a result, provide limited information on how biological factors may predict course or trajectories of PTSD. Third, because of the large numbers of subjects needed for robust findings, consortium analyses tend to pool heterogeneous PTSD diagnoses and populations, which leaves questions about whether different PTSD presentations are related to biological variation. Finally, some populations, especially those from low- and middle-income countries, have been neglected in PTSD biological research. This has been noted in genetic studies of PTSD, but is also the case in other areas. The result is limited knowledge of how biological factors related to PTSD may be shaped by context.

PREVENTION

The requirement of exposure to a traumatic event with specific characteristics appears to lend itself to the development of effective preventive strategies for PTSD. Unfortunately, despite considerable efforts, we are a long way from being able to prevent people from developing the disorder.

A systematic review[329] identified six randomized controlled trials (RCTs) considering pre-incident prevention, within the context of exposure to combat trauma (five trials) or to fire and emergency-services trauma (one trial). Various interventions were investigated, including attention bias modification training[330] and stress inoculation training[331]. The only statistically significant finding was in favor of attention bias modification training over a no-intervention control for the prevention of the development of PTSD after combat trauma[330], although replication is clearly required.

The same review identified 75 RCTs of post-incident preventive interventions[329]. These were separated into those that were conducted over a single session and those delivered over multiple sessions.

Two interventions in the single-session group were found to be superior to no-intervention: single-session eye movement desensitization and reprocessing (EMDR) and the Group 512 Psychological Intervention Model, an intervention for military personnel based on debriefing but supplemented with cohesion training[332]. Despite significant concerns around the quality of these studies

and the risk of bias, the positive signals from them should not be ignored, and both interventions appear to be good candidates for further evaluation.

Among multiple-session interventions, only brief dyadic therapy[333] and self-guided Internet-based cognitive-behavior therapy (CBT)[334] were superior to no-intervention/care as usual, again with significant concerns about study quality and risk of bias.

As to multiple-session interventions for people with emerging symptoms but without a diagnosis of PTSD (indicated prevention), stepped/collaborative care, brief CBT with a trauma focus (TF-CBT), EMDR, and Internet-based guided self-help were superior to no-intervention/care as usual, with the strongest evidence for stepped/collaborative care and brief TF-CBT[329].

The International Society for Traumatic Stress Studies (ISTSS) guidelines[335] used the above results to identify Group 512 Psychological Intervention Model and EMDR as single-session interventions, and brief dyadic therapy and self-guided Internet-based CBT as multiple-session interventions with emerging evidence for the prevention of PTSD. TF-CBT, cognitive therapy, and EMDR were recommended as multiple-session early treatment options, although the level of recommendation for them as preventive interventions was "standard", as opposed to the "strong" recommendation given to them for the treatment of established PTSD. Stepped/collaborative care was identified as an "intervention with low effect", while Internet-based guided self-help and structured writing interventions were rated as having emerging evidence.

The guidelines also considered RCTs of pharmacological interventions to prevent PTSD, and found hydrocortisone to be the only drug that was superior to a placebo control condition, which resulted in its rating as an intervention with emerging evidence.

For the prevention of PTSD in children and adolescents, the guidelines found emerging evidence for self-directed online psychoeducation for caregivers and children and for children alone, and emerging evidence *not* to recommend individual psychological debriefing for children and adolescents.

The latest US Department of Veterans Affairs and Department of Defense (VA/DoD) guidelines[336] state that "for the prevention of PTSD among individuals who have been exposed to trauma, there is insufficient evidence to recommend for or against psychotherapy or pharmacotherapy in the immediate post-trauma period".

The disappointing results of research to date mean that our focus should be on developing more effective preventive interventions, and on subjecting those with emerging evidence to more rigorous evaluation. There are also some interesting novel developments with respect to early intervention, including the emergence of interventions with a purported mechanism of consolidation/reconsolidation of traumatic memories[337].

The current evidence strongly suggests that, pending the emergence of more effective universal and selective preventive interventions, a focus on practical pragmatic support delivered in an empathic manner may be the best way forward, coupled with the raising of societal awareness of PTSD to facilitate the early identification of people who would benefit from evidence-based treatment[338].

TREATMENT

In the last two decades, there has been a significant increase in the number of RCTs completed and in the types of treatment evaluated for PTSD. The systematic reviews that led to the ISTSS guidelines identified 361 RCTs[339].

The main treatments developed and evaluated to date can be classified as either psychological or pharmacological, but there are an increasing number of interventions, such as transcranial magnetic stimulation and yoga, that cannot be readily classified as either. There is also considerable interest in the development of pharmacologically assisted psychotherapy.

Another developing paradigm concerns alternative methods of delivering established approaches to treatment. Examples are guided Internet-based programs of TF-CBT[340], digital therapies such as capnometry-guided respiratory intervention[341], and support tools such as PTSD Coach (https://www.ptsd.va.gov/appvid/mobile).

The wide range of treatment approaches advocated for PTSD is to be welcomed, but brings with it challenges, not least in terms of evaluating the evidence available for different treatments and accurately determining their true effectiveness. Moreover, very little research has been done on matching individual persons with PTSD to the most effective treatments for them. This is further complicated by powerful lobbies for different approaches, potential conflicts of interests, the challenge of grouping related treatments in a meaningful way, and generalizing results from one population to another. These challenges are, of course, not unique to PTSD, but are important to remember.

The current evidence base for the treatment of PTSD is much stronger than ever before, but it is vital to acknowledge that there remain major gaps in our knowledge. Although several treatments have been shown to be effective for people with PTSD, exactly how effective they are, who is likely to benefit from them, and who can deliver them are all up for debate. It is also clear that the treatments with the strongest evidence do not work for everyone, are relatively costly to deliver in terms of time and other resources, and have been challenging to disseminate, so that we need to identify more effective treatments in the future.

Psychological treatments

Psychological treatments for PTSD are commonly described as either trauma-focused or non-trauma-focused approaches. The former are by far the most researched. Within this group, TF-CBTs have been studied more than any other form of treatment. These include TF-CBT for children and adolescents[342], prolonged exposure therapy[343], cognitive processing therapy[344], cognitive therapy for PTSD[345], and more recently written exposure therapy[346]. Although clearly drawing on a wider range of therapeutic approaches, a number of other interventions have also been grouped as TF-CBTs (e.g., brief eclectic psychotherapy[347], narrative exposure therapy[348,349], and skills training in affective and interpersonal regulation with narrative exposure[350]).

Although the relative emphases and exact methods vary, TF-CBTs tend to include two elements. First, there is graded or controlled exposure to feared memories, particularly the content of flashbacks, or to feared situations, with the aim of making them less distressing and aversive. There are several candidate mechanisms that could account for the value of exposure. Habituation, a form of non-associative learning, refers to the decrement in response that occurs when a stimulus is repeated. Extinction refers to the loss of a learned association between a frightening event and previously neutral cues, which occurs when the cues are repeatedly presented in non-frightening situations. The current view is that extinction procedures create new memories of alternative contexts in which the cues are associated with safety rather than danger, and memories of these experiences inhibit retrieval of the memory of the original frightening event[351].

The other element is the use of cognitive techniques to help people with PTSD challenge distorted patterns of thinking. These include believing oneself to be inadequate, weak, or as having no future; seeing others as untrustworthy; and blaming oneself for the traumatic event occurring, for one's actions during it, and for subsequent symptoms. Negative appraisals of the self, of other people, and of the future predict the course of the disorder, often over and above initial symptoms[141,352].

The second most researched group of trauma-focused interventions is EMDR[353]. This involves focusing on a traumatic memory alongside the associated negative cognitions, affects and body sensations whilst being subjected to bilateral stimulation (e.g., through eye movements or taps). Distancing and free association are also part of EMDR. The mechanism underpinning this treatment remains unknown, despite several hypotheses. Some experts argue that EMDR is a TF-CBT, but most guideline committees have considered EMDR and TF-CBT separately.

A new group of trauma-focused interventions that has gathered momentum over recent years are those purported to work through the mechanism of mobilizing and reconsolidating traumatic memories, so that they are less threatening[337]. Reconsolidation theory proposes that retrieval returns memories to a labile state in which they can be altered and then reconsolidated in a new form. These interventions use several different procedures, but all involve rapidly rewinding an imaginary film of the traumatic event with great precision. They are so brief that, despite exposure, habituation seems unlikely to be the underpinning mechanism.

Reconsolidation therapies have many similarities with another trauma-focused intervention with good evidence for effectiveness in PTSD, including cases related to childhood abuse. This is imagery rescripting[354-356]. This therapy also involves deliberately manipulating traumatic imagery in one's mind, in this case introducing new imaginary elements that increase feelings of mastery, control and self-acceptance. It has been suggested that the mechanism involves creating alternative, less threatening competitor memories that are then more likely to be retrieved when the person encounters trauma reminders in the future[357].

Non-trauma-focused approaches include a range of techniques, such as stress inoculation training (which aims to teach coping skills, so that the person can find new ways to deal with PTSD symptoms and to manage other stressful events in his/her life), relaxation techniques, supportive counseling, and interpersonal therapy[358].

Other emerging interventions are present-centered therapy and compassion-focused therapy. The former addresses negative identity changes (for example, helping with interpersonal disconnection through developing a positive therapeutic relationship and exploring interpersonal difficulties, or overcoming helplessness by problem-solving)[359]. The latter draws on the fact that people with PTSD can often express compassion to others but not to themselves, and addresses the experience of a shameful, inadequate or blameworthy self by techniques such as vividly imagining being the recipient of compassionate responses from actual or fantasized others[360].

Different forms of individual TF-CBT are recommended by all the main guidelines as a first-line treatment for PTSD. However, there are important differences, and some TF-CBTs are given more priority than others by different guidelines. For example, the ISTSS guidelines strongly recommend TF-CBT (undifferentiated), cognitive processing therapy, cognitive therapy, and prolonged exposure. Despite having similar evidence available, the latest VA/DoD guidelines only recommend cognitive processing therapy and prolonged exposure as first-line TF-CBTs; cognitive therapy is given a weaker recommendation[336]. Guidelines appear to consistently agree that group TF-CBTs have less supporting evidence than individual ones.

EMDR is also strongly recommended by most guidelines, although the latest UK National Institute for Health and Care Excellence (NICE) guidelines specifically state that it is not recommended for use in individuals with PTSD following combat exposure[361].

Guided Internet-based TF-CBT is given a lower-strength recommendation by ISTSS and NICE, although more recently published RCTs[362] have resulted in two specific forms of this intervention being recommended by NICE[363]. Narrative exposure therapy is given a lower-strength recommendation by most guidelines, but a strong one by NICE, while VA/DoD found insufficient evidence to recommend for or against it.

There is considerable heterogeneity between guidelines in terms of recommendations for non-trauma-focused psychological interventions. The VA/DoD guidelines include stress inoculation training, present-centered therapy, and interpersonal therapy among recommended interventions. The ISTSS guidelines include present-centered therapy among recommended interventions, while interpersonal therapy, relaxation training, and supportive counseling are listed among therapies with "insufficient evidence to recommend".

Pharmacological treatments

There is agreement across guidelines that various pharmacological treatments can reduce the symptoms of PTSD, though most guidelines recommend them less strongly than psychological interventions. The reasons for this are worthy of some consideration. In meta-analyses, effect sizes for pharmacological treat-

ments are much lower than those for psychological interventions and, consequently, a weaker recommendation appears to be justified. Notably, however, the standard comparator condition for pharmacological treatments is placebo, in contrast to either usual care or waitlist for psychological interventions. There are also major differences in terms of "effective blinding" of participants and clinicians between pharmacological and psychological treatment trials.

Some guideline committees – e.g., that for ISTSS guidelines – have tried to address the control-group issue with *a priori* agreements regarding the adjustment of evidence thresholds for different levels of recommendation according to the control condition used. This is a step in the right direction, but such agreements reflect the consensus of a committee and should be considered informed rather than necessarily correct.

Some treatment guidelines (e.g., NICE) group drugs together when making recommendations, whereas others do not. A clear example is given by recommendations for selective serotonin reuptake inhibitors (SSRIs): NICE guidelines just recommend SSRIs; ISTSS guidelines recommend the SSRIs fluoxetine, paroxetine and sertraline, but not others (based on the availability of RCTs in PTSD for those three specific drugs); and VA/DoD guidelines only recommend paroxetine and sertraline. Venlafaxine is recommended by name by most guidelines. Quetiapine is rated as an intervention with emerging evidence by ISTSS guidelines.

Most guidelines do not consider augmentation, although systematic reviews and meta-analyses provide some evidence to support augmentation of either SSRIs or venlafaxine with the alpha1-adrenoceptor antagonist prazosin[364]. The VA/DoD guidelines, however, take a different stance and consider the evidence strong enough to recommend *against* prazosin for the treatment of PTSD.

Overall, it is clear that further research evidence is needed to guide the use of medications, especially SSRIs, in the treatment of PTSD. In particular, the features of the clinical picture of PTSD that can support their use, and their utility when combined with psychological interventions, should be the focus of specific research.

Emerging treatments

Increasing numbers of novel treatments for PTSD are being developed and tested. In the latest ISTSS treatment guidelines, 26 treatments were recommended as interventions with emerging evidence. Psychological treatment examples for adults include couple TF-CBT[365] and virtual reality exposure therapy[366]. Group TF-CBT and group psychoeducation[367] were considered interventions with emerging evidence for children and adolescents.

All these interventions have their proponents, and all appear worthy of further research. Interestingly, a meta-analysis of TF-CBTs for veterans[368] found that the strongest effect sizes were for RCTs of reconsolidation of traumatic memories. Arguably, this treatment was wrongly classified as a TF-CBT, as it probably relies on a different mechanism.

Several emerging interventions use neither a psychological nor a pharmacological approach. To give two diverse examples, five RCTs of yoga and three RCTs of transcranial magnetic stimulation were considered by the ISTSS committee. This evidence, and subsequent systematic reviews and meta-analyses[369,370], suggest that both these interventions are likely to have a role in the treatment of PTSD in the future.

An example of an emerging intervention that combines a pharmacological and a psychological approach is 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy. MDMA is a psychostimulant and hallucinogen. Although not yet recommended by any guideline, the evidence for this approach appears to be strengthening. Its exact mechanism of action is not known, but it has been proposed that the properties of MDMA allow exposure to traumatic memories without overwhelming distress that can hamper processing[371].

Other non-invasive treatment approaches appear to show some promise for the future, for example controlled breathwork[372], although they clearly require more rigorous evaluation before being recommended. It is important to acknowledge that alternative approaches to the treatment of PTSD may be more acceptable to some people than the current recommended first-line treatments. As argued in a seminal paper over a quarter of century ago, effective evidence-based practice is not dictated by RCTs and guidelines alone, but is "about integrating individual clinical expertise and the best external evidence"[373].

Treatment evidence for children and adolescents

Sadly, the level of evidence available to determine the most efficacious treatments for children and adolescents with PTSD is lagging far behind that for adults. However, there is enough evidence for most guidelines to make several treatment recommendations.

The main recommended psychological treatments for children and adolescents are TF-CBT delivered to caregiver and child, TF-CBT delivered to child alone, and EMDR, although the latter is less strongly recommended by NICE than by ISTSS. There is insufficient evidence to recommend any pharmacological treatments for children and adolescents with PTSD.

Adapting interventions in resource-limited settings and across cultural contexts

The translation of RCT evidence into practice represents a challenge particularly in low-resource settings and across cultural contexts. The relatively few RCTs for PTSD that have been conducted in resource-limited settings show promising results, for example in the case of group-based TF-CBT for bereaved children in Kenya and Tanzania[374], and group-based CBT for survivors of sexual violence in the Democratic Republic of Congo[375].

Other promising approaches include Islamic healing therapy, based on the principles of TF-CBT, adapted using a community-based participatory research process to be more accessible in the Islamic context[376]; treatments developed in Indigenous communities for PTSD and other mental health consequences of historical

trauma[377]; and interventions aimed at helping persons address PTSD related to racial trauma[132].

More research is required to determine how best to implement the most efficacious treatments in a sustainable manner in low-resource settings. There is clearly a need for more accessible and cost-efficient forms of treatment that can be delivered/facilitated by therapists without highly specialist training. Guided Internet-based TF-CBT appears to be a good candidate for this, along with currently less developed non-invasive interventions such as imagery rescripting, reconsolidation therapies, and various non-trauma-focused approaches.

A helpful briefing paper recently published by the ISTSS[378] notes multiple barriers to implementing evidence-based interventions to support people affected by PTSD and other conditions in low- and middle-income countries. These include stigma and the lack of mental health professionals. The paper makes recommendations for public health and policy, for researchers, and for practitioners/service providers. These include increasing mental health literacy and reducing stigma, training community health workers to deliver effective interventions, and developing culturally specific adaptations of evidence-based treatments.

Community-based interventions

It has sometimes been argued that the evidence supporting the effectiveness of trauma-informed psychological interventions at the community level is inconsistent, suggesting the need for alternative approaches[379]. Among the considerations are that measures of symptom severity alone provide an incomplete picture of the individuals' experience, making it necessary to evaluate other factors such as increased understanding of the mental health condition, skills building, coping, and well-being[380].

Since there is often a communal or societal component in the trauma experience, it is important to consider how this might be addressed. Community-based interventions would not only potentially benefit collectivistic societies, but could find more general application in situations of mass trauma exposures and among minoritized or under-served populations in high-income countries.

The Adaptation and Development after Persecution and Trauma (ADAPT) model[381] focuses on the core psychosocial pillars in a community that are likely to be disrupted and to need repair following mass trauma. These include the general sense of safety and security, the social bonds and networks that link community members, the availability of justice, the reinstatement of lost roles and identities, and a shared existential meaning.

Similarly, other recommendations emphasize the importance of interventions that address the broader social context of trauma, and the need for community-level support and healing, facilitating recovery by rebuilding and strengthening social support mechanisms[382].

Community capacity-building to foster resilience (conceptualized as dissemination of trauma-informed education and training, community outreach and engagement, and linkage of community members to resources) showed benefits with regards to emotional and instrumental support as well as in increasing the sense of community connectedness[383].

However, the evidence for the efficacy of community-based interventions in improving trauma-related symptoms is currently less than optimal, partly because less work has been done in this area compared to clinical-setting interventions, and the quality of research is also variable[384]. The small number of studies examining these interventions makes it difficult to evaluate their acceptability, feasibility and effectiveness[380].

Implications

Despite the progress made, there are many evidence gaps in the treatment of PTSD. Even the best-evidenced treatments require more research, and there is an urgent need for more effective treatments. Most RCTs to date have excluded people with more complex presentations of PTSD and, given their prevalence and the morbidity associated with such presentations, a research focus on them is required. It is to be hoped that the ICD-11 diagnosis of complex PTSD will help in this regard. There are clearly major opportunities to build on basic science to develop new interventions and to enhance the effects of existing treatments.

Evidence is currently lacking to determine whether recommended treatments work as well for people with certain characteristics as for others. Important relevant characteristics include age, gender, ethnicity, socioeconomic status, culture, nature and number of traumatic events exposed to. For some populations, significant adjustments are likely required to existing treatments to maximize their effectiveness. Such work is in progress. Examples include a RCT of EMDR for people with learning disability[385], and the development of approaches for older people with PTSD[386]. Asylum seekers and refugees clearly represent another group of people with a high prevalence of trauma-related problems and an urgent need for tailored approaches[387,388].

TRAUMA AND MENTAL HEALTH: FUTURE DIRECTIONS

Following the successful introduction of the PTSD diagnosis, it is now possible to discern a second phase in research on trauma and mental health that is a product of that success. One manifestation of this is the recognition that the construction of the PTSD diagnosis in terms of a response to a specific traumatic event does not reflect the reality of exposure to trauma[389]. A history of childhood and adult trauma, repeated episodes of trauma, or multiple types of traumatic event, are the rule rather than the exception. Subsequent stressors, not necessarily PTSD-qualifying traumatic events, contribute to the prediction of PTSD, particularly the delayed-onset type. In some individuals, particularly members of the military and emergency services, PTSD develops after lengthy periods of resilience to high levels of stressors and traumatic events. Yet, this knowledge is often not reflected in assessment instruments and research designs, or reported in scientific papers. Little

is known about how these different histories impact on core symptoms such as re-experiencing, a current sense of threat, or disturbance in the sense of self.

Another manifestation of this new phase of research is the active questioning over the advantages and disadvantages of attempting to define trauma in objective terms. There is increasing recognition that the experience of socially marginalized, neurodiverse and other relevant groups has not been sufficiently valued as yet. Increased focus on different populations, including people undergoing intensive care or those with psychosis, can be highly informative about the relative contribution to symptoms of the subjective and objective impact of stressful events, and about the value of standard trauma-focused interventions in these different circumstances.

Relatedly, it is becoming evident that there are several different PTSD phenotypes, including those with delayed onset, the dissociative subtype of DSM-5 PTSD, and ICD-11 complex PTSD. These developments suggest that, in the future, it will be necessary to talk about post-traumatic stress disorders in the plural. Some explanatory mechanisms are likely to be shared, but others may not. This has major implications for biological research, which is generally best served by focusing on a small number of clearly defined phenotypes.

An approach similar to the exploration of subjective experiences in schizophrenia[390], based on a greater involvement of experts by experience, could be useful in research on PTSD, focusing on intrusive memories and flashbacks, but also on shifts in the experience of the self in response to trauma reminders. Initial research in this area is promising, and provides both some theory and some methodological tools for isolating specific post-traumatic phenomena[246-248].

The reinstatement of threat to identity as one of the psychological foundations of PTSD has several advantages. As a broader concept, it is not tied to the specific negative cognitions that have been found to be pathogenic in Western samples, but acknowledges the role of other cognitions, social practices, and value systems that are important in different cultural contexts. It brings into play a wide variety of long-standing observations about the subjective experience of being traumatized, for example that individuals sometimes feel deeply alienated from others or as though they have been mentally destroyed. It also helps to explain the efficacy of interventions that are not primarily focused on the traumatic memory, but address more general physical, social and mental resources such as the quality of close relationships, self-acceptance, and problem-solving.

One question for the future is when interventions should focus primarily on disturbances to memory and when on disturbances to identity. In mass-trauma situations, there appears to be widespread acceptance that the initial focus should be on the depletion of identity-relevant resources such as housing, employment, social norms, and community structures[381,391,392]. Response is likely to require local or national governmental involvement.

In individual trauma, clinical services are usually ill-equipped to restore specific resource losses and are set up to deliver physical or psychological interventions. We know that memory-focused interventions have the potential to bring about positive changes to identity in the form of improved relationships, greater optimism, and more positive beliefs about the self. There are promising developments in imagery-based interventions that may offer accelerated improvements. However, there is much to learn about whether and how identity-focused interventions, such as present-centered and compassion-focused therapies, reduce intrusive trauma memories and flashbacks. The optimal match between different interventions and various PTSD phenotypes is likely to be crucial.

One important issue on which evidence is lacking is how low- and middle-income countries can design trauma-related interventions that are tailored to be culturally and structurally valid, and how they can obtain the maximum return for their investment. There is already a focus on brief transdiagnostic interventions delivered by para-professionals or peers, such as Problem Management Plus [393]. These interventions can be made more available using Internet and mobile technology resources, which have the potential to reduce barriers created by geographical isolation, stigma and cost[394,395]. Lacking to an even greater degree is evidence concerning the effectiveness of interventions for specific cultural idioms or concepts of distress[44].

To conclude, the explosion of knowledge about PTSD has revealed its central importance, but also its limitations in capturing the variety of psychopathological reactions that are made more likely by traumatic events. The next ten years will probably see consolidation in the form of establishment of an accepted set of different phenotypes, which will enable a more focused investigation of mechanisms and treatment response. Studies of different populations exposed to different types of stressors in different contexts will deepen our understanding of what is universal and what is specific about the response to trauma.

ACKNOWLEDGEMENTS

The authors are grateful to E. Wolf for her contribution to a previous version of this paper.

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DOI:10.1002/wps.21269

What exactly is post-traumatic stress disorder?

When post-traumatic stress disorder (PTSD) was introduced in the DSM-III, it was conceptualized as a uniform syndrome based on extreme fear responses that emerged from over-consolidation of trauma memories. In the subsequent 40 years, much has been learnt about the nature of this disorder and its implications for treatment. As noted by Brewin et al[1] in their thoughtful review, one issue that is repeatedly raised is the complex nature of the condition. Indeed, the diagnostic definitions of PTSD have evolved over time by adding more symptoms, including additional clusters, and recognizing various subtypes.

Although the study of PTSD has advanced since its early conceptualizations, it is likely that we are still a long way from accurately understanding the multitude of phenotypes of post-traumatic stress. Whereas different subtypes have been identified, these categorizations are quite broad, and lump many patients into groupings that may disguise important differences. The observation that most people with PTSD have a unique symptom presentation[2] indicates that there are more than simply two or three typologies of post-traumatic stress.

Emerging evidence demonstrates that PTSD involves a range of phenotypic presentations, which can include fear, dysphoria, numbing, anger, and several others[3]. This pattern is reflected, in part, in the high rates of comorbidity of PTSD with mood and anxiety disorders, which can be attributed to patients experiencing an array of symptoms that belie the presumption of a unitary syndrome. Initiatives such as the Research Domain Criteria have attempted to move the field towards a more phenotypic-based conceptualization of clinical presentations, but we still appear wedded to diagnostic systems in our conceptualizations and assessments of post-traumatic stress.

One of the limitations of current diagnostic definitions of PTSD is that they assume a somewhat simplistic summation of requisite symptoms. For example, the DSM-5 requires that a minimum number of symptoms in each of four clusters be present in order for the person to meet the diagnostic criteria. It is presumed that each symptom has equal weight, so that simply summing the symptoms provides an accurate way to determine if PTSD is present. This approach ignores the possibility that some symptoms may be more important than others in contributing to distress or functional impairment, and therefore require greater weighting than other symptoms.

Network analyses provide insights into symptoms that may have more influence on psychological well-being than others, because they allow each symptom to be mapped in terms of its influence and potential downstream impact on other PTSD and related problems. For example, one study has shown that re-experiencing and dysphoric processes may be particularly influential in PTSD[4]. This hierarchy, however, may be different from one patient to another, requiring an individualized network analysis.

The problem of identifying the major clinical presentations of people with PTSD is compounded by the observation that these presentations are not static. Longitudinal studies indicate that PTSD fluctuates markedly over time[5], and ecological momentary assessments suggest that these dynamic shifts occur rapidly[6]. This pattern highlights that it is problematic to pigeonhole PTSD patients into a single category (or subtypes of a category) based on a single assessment at one point in time, because the major presenting symptoms that a person has, and how they are interacting, can change on a daily basis.

Of course we cannot conduct clinical interviews of our patients on a daily basis, but recent developments in real-time assessments via smartphone apps have opened up the opportunity for more accurate and temporally relevant assessments of a patient's symptoms at any one time[7]. As machine learning and artificial intelligence tools become more sophisticated and are thoroughly tested in clinical settings, phenotypic responses to trauma may be measured in a real-time manner that provides clinicians with more reliable information on the patient's most pressing needs.

In recent years, adaptive assessment procedures have yielded promising ways to assess a range of psychiatric conditions. These approaches have utilized a multidimensional response item theory framework to capture the broad range of potential symptoms that a person may experience, using a hierarchical system of domains, subdomains and factors that recognize the heterogeneity of a person's presentation[8]. Although these approaches have been shown to be successful across a range of disorders, they have yet to be fully applied to people with post-traumatic stress.

The search for the capacity to measure more nuanced phenotypes of post-traumatic stress is not simply an academic exercise. As Brewin et al note, we have much evidence that several varieties of trauma-focused psychotherapy can alleviate PTSD symptoms effectively. However, one of the major challenges facing the field is that up to half of patients do not respond to our frontline treatments. Moreover, the success rates of treatments for PTSD have not improved over decades, suggesting that we have hit a ceiling in the ability of these interventions to assist most patients.

One of the problems with current interventions is that we adopt a one-size-fits-all approach in which packages of treatment (e.g., prolonged exposure, eye movement desensitization and reprocessing, cognitive processing therapy) are applied to patients if they meet criteria for PTSD. This practice assumes that all patients have the same constellation of symptoms and the same primary presenting problems, and that the symptoms are static throughout treatment. Each of these assumptions have been shown to be false, but treatment approaches tend to ignore this clinical reality.

It is for this reason that there have been increasing calls for a more flexible process therapy framework. In this approach, patients are not given a standard treatment according to a diagnostic classification, but rather the assessment focuses on the presenting problems that they experience[9]. For example, a patient with PTSD may present with intrusive memories and avoidance, but also experience marked anger, substance use problems, and relationship issues. In this case, rather than simply administering trauma-focused psychotherapy, a therapist may apply evidence-based

strategies to address each of these problems. Some of these therapeutic interventions would involve elements of trauma-focused psychotherapy, such as exposure therapy to address the intrusive memories, but other interventions would also be prioritized to mitigate other clinical problems.

In summary, Brewin et al highlight many of the complexities of the definition, assessment and treatment of PTSD. It is difficult for the field to advance without a more nuanced assessment of the many varieties of post-traumatic stress, accounting for the oscillating nature of the clinical presentations that require treatment. By extending our approach in the above-mentioned multiple ways, there may be an opportunity for more tailored and relevant interventions that can hopefully achieve better outcomes.

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DOI:10.1002/wps.21270

The promise of ICD-11-defined PTSD and complex PTSD to improve care for trauma-exposed populations

Brewin et al[1] provide an engaging and thorough review of the empirical literature on the nature, prevalence, assessment, potential prevention, and treatment of post-traumatic stress disorder (PTSD). An important contribution is the summary of the evidence on the validity of the new ICD-11 diagnoses of PTSD and complex PTSD. Here we focus on the potential benefits of these diagnoses in improving outcomes and increasing engagement into care, two important concerns in PTSD treatment.

To date, the most evidenced treatments for PTSD as defined by the DSM-5 are trauma-focused cognitive behavioral therapies (TF-CBTs) and eye movement desensitization and reprocessing (EMDR), which have clinically significant and equivalent effects. Nevertheless, only 40-50% of recipients of these interventions no longer meet criteria for PTSD at treatment end, and many experience significant residual symptoms. In addition, engagement and completion rates are modest: medical records reviewed by the US Veterans Health Administration from 2001 to 2015 indicated that, of veterans with PTSD offered an evidence-based psychotherapy, only 23% initiated and 9% completed treatment[2].

The DSM-5 increased the number of symptoms in the PTSD diagnostic criteria in order to recognize the more extensive and diverse problems found among those who experience chronic and repeated trauma. This decision has led to criticism that the possible unique PTSD symptom profiles generated from the DSM-5 algorithm are so numerous that the construct does not warrant a unified approach to treatment. At the very least, applying a single treatment to individuals with very different symptom profiles may constrain potential treatment benefits.

The ICD-11 has taken a different approach. It organizes trauma sequelae into two diagnoses, each with a limited number of empirically supported symptom clusters. As indicated by Brewin et al, the validity of the ICD-11 PTSD/complex PTSD distinction has been documented in various trauma-exposed populations, including children, college students, first responders, combat veterans, refugees, and adults with histories of childhood trauma and domestic violence. Rates of ICD-11 PTSD have been shown to be higher than those of complex PTSD in populations that have recently experienced trauma exposure[3], and there is some evidence that ICD-11 PTSD may convert to complex PTSD over time in a subset of patients[4]. These observations suggest that the ICD-11 PTSD/complex PTSD distinction may have clinical utility for treatment planning, as well as scientific value in terms of allowing a better understanding of risk factors and change in symptoms over time, and of what drives symptom development.

Most treatments conceptualize PTSD as resulting from fear-generated disruptions in memory organization of the trauma and alterations in belief systems and perceptions. Accordingly, current evidence-based therapies typically include two key elements: exposure to traumatic memories to reduce fear responses, and exploration and reappraisal of the memory to facilitate an adaptive evaluation of the experience. The application of these techniques is relevant to and appropriate for PTSD as defined by the ICD-11.

The symptom profile of complex PTSD typically reflects the impact of severe, chronic and usually interpersonal trauma, and may be conceptualized within a social-attachment framework[5]. Interpersonal trauma activates the fear system, in which threat to sense of safety is mediated by a disruption or violation of attachment processes. Moreover, interpersonal trauma – particularly betrayal trauma by important people or communities – has a strong negative impact on self-identity, leading to fundamental shifts in sense of value and worth. Lastly, emotion regulation capacities are substantially influenced by social context, not only during the developmental years, in the form of internalization of the observed behaviors and attitudes, but also across the lifespan, via the presence or absence of social support. This formulation provides a theoretical foundation for developing interventions or ex-

tending established protocols so that they are relevant to patient populations with complex PTSD.

Given the status of ICD-11 PTSD and complex PTSD as newly recognized diagnoses, there are no established guidelines for their treatment. Two recent meta-analyses may orient clinical practice while evidence about effective treatment develops. Coventry et al[6] evaluated clinical trials that included PTSD populations with complex trauma (e.g., combat veterans, individuals with histories of childhood abuse) as representative of those who might qualify for complex PTSD, and found that phase-based or multimodal therapies were more effective than unimodal therapies. Another meta-analysis[7] included all PTSD randomized controlled trials (RCTs) through 2018 and found that TF-CBTs provided clinically meaningful improvements in symptom clusters represented in complex PTSD (i.e., re-experiencing, avoidance, hypervigilance, emotion dysregulation, negative self-concept, relationship difficulties), but that childhood trauma was a moderator of outcome associated with lesser benefits across all six symptom clusters.

Therapies in which symptom-specific modules (e.g., PTSD, emotion regulation, negative self-concept, relationship difficulties) are delivered in a flexible sequence, depending on the needs and preferences of the patient, may be an effective and efficient approach to treating complex PTSD[8]. Previous work in matching patients to modules has found this approach to be more effective and result in shorter treatment duration relative to full protocols for a single disorder. This approach is also associated with higher clinician satisfaction and better uptake in treatment systems[8].

One recent RCT[9] evaluated a sequential four-module treatment compared to treatment as usual (TAU) among veterans with complex PTSD seeking treatment at a national UK charity. Results indicate the superiority of the modular treatment, with 80% compared to 11% of the TAU participants no longer meeting diagnostic criteria for either ICD-11-defined complex PTSD or PTSD at treatment end, and with gains maintained at 3-month follow-up. In addition, dropout rates were low and equivalent (18% vs. 14%).

This latter trial did not include a flexible delivery component. The addition of a collaborative process between patient and therapist to order the treatment modules according to their preference, beginning with a set of interventions that are relevant and of interest to the patient, would bring true meaning to the therapeutic goal of "meeting patients where they are at" and may increase treatment engagement and completion. The number of sessions or modules completed during the treatment may vary depending on the observed course of improvement, and duration can be tailored to patient success rather than to a protocol with a designated endpoint, creating a mental health service approach that optimally distributes resources adapted to the specific patient.

There have been a few RCTs comparing versions of modular treatments to established TF-CBTs treatment, with no significant differences in outcomes. However, these studies included individuals with PTSD defined according to the DSM-5, or fulfilling both DSM-5 and ICD-11 criteria, and tested treatments developed for the DSM-5 symptom profile. Future studies will need to evaluate innovative treatments in patients with ICD-11-defined PTSD and complex PTSD regardless of their DSM-5 status.

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DOI:10.1002/wps.21271

Navigating the landscape of trauma treatments: the need for personalized care

Post-traumatic stress disorder (PTSD) significantly impairs an individual's daily functioning and quality of life. Although both pharmacological and psychological treatments are effective for this disorder, the latter are commonly used as a first line of support. Fortunately, various psychological treatments have been developed over the years and have been proven effective in managing and alleviating the symptoms of PTSD. Following the excellent overview by Brewin et al[1], we comment here on the primary psychological treatments for PTSD, some challenges in their implementation, and important future research directions in this area.

Traditional trauma treatments have laid the foundations for contemporary therapeutic interventions. Among the most widely recognized is trauma-focused cognitive-behavioral therapy (TF-CBT), which combines cognitive restructuring techniques with exposure therapy to address maladaptive thought patterns and desensitize individuals to traumatic memories. Its structured format, typically delivered over a series of sessions, has garnered empirical support for its efficacy in treating PTSD. Eye movement desensitization and reprocessing (EMDR) is another established treatment modality for trauma treatment, which integrates bilateral stimulation, such as eye movements or taps, with guided imagery to facilitate the processing and resolution of traumatic memories. Despite ongoing debate regarding its underlying mechanisms, numerous studies have demonstrated its effectiveness in reducing trauma-

related symptoms and improving overall well-being.

While such exposure treatments for PTSD are effective for many patients, they are not universally so. This is the case especially for certain groups, such as those with history of childhood trauma[2], who tend to suffer from more complex forms of traumatization[3], highlighting the need for ongoing research and innovation. Emerging psychological therapies, such as virtual reality exposure therapy (VRET), and pharmacological adjuncts offer promising avenues. VRET leverages immersive technology to create controlled, realistic simulations of traumatic environments. This can enhance the exposure experience providing a safe yet vivid context for trauma processing. Initial research indicates that VRET may be as effective as traditional exposure therapy[4]. Pharmacological adjuncts to psychological therapies are also under investigation. For example, the use of 3,4-methylenedioxymethamphetamine (MDMA) has shown promise in enhancing the therapeutic process, potentially by reducing fear responses and facilitating emotional engagement with traumatic memories[5].

The introduction of complex PTSD as a new condition in the ICD-11 has provided an opportunity to identify effective interventions for those who have developed complex presentations as a result of traumatic stressors. Complex PTSD has a greater number of symptoms than PTSD, typically resulting from multiple, interpersonal, chronic and/or childhood stressors[6]. Therefore, a personalized approach to care and treatment might be especially appropriate.

It can be argued that complex PTSD requires a greater number of different kinds of interventions or a longer course of treatment compared to PTSD. Modular therapies with a cognitive behavioral orientation[2] that target the symptom clusters of the condition individually and sequentially in a person-centred manner, using skills development and memory processing – such as enhanced skills in affective and interpersonal regulation (ESTAIR) – have been proposed as an alternative to TF-CBT or EMDR approaches for the treatment of complex PTSD[7]. Preliminary findings suggest that modular interventions can be effective[8]. However, it is possible that the same treatments used for PTSD are also effective for complex PTSD, with equally good outcomes. Considering that most randomized controlled trials to date have excluded people with more complex trauma presentations, further research on this matter is required.

Despite the breadth of trauma treatments available, several challenges persist within the field. Access to specialized care remains a significant barrier for many individuals, particularly those from marginalized communities or remote areas. Additionally, cultural considerations and systemic inequalities may influence the suitability and acceptability of certain treatment modalities, underscoring the need for culturally competent care and equitable access to resources[9]. Furthermore, considering the scarce resources for treatment delivery in many parts of the world, there is a need to adapt existing interventions into more cost-efficient forms that can be delivered/facilitated by therapists without highly specialist training.

Overall, current evidence does not match clinical needs. As discussed by Brewin et al[1], "although several treatments have been shown to be effective for people with PTSD, exactly how effective they are, who is likely to benefit from them, and who can deliver them are all up for debate". The heterogeneity of trauma presentations necessitates a nuanced understanding of each individual's unique needs and preferences. Treatment planning should prioritize collaborative and client-centred approaches, empowering survivors to actively participate in their treatment journey. Additionally, further research is essential to elucidate the mechanisms of action underlying the various interventions and optimize treatment for different groups of patients.

Continued innovation and personalized approaches are essential to address these challenges, ensuring that all individuals with PTSD and complex PTSD have the opportunity to heal and reclaim their lives. It is essential to identify which treatments work for whom. Currently, in clinical practice, we offer the same interventions to all clients, while we should aim to match every trauma survivor with the right treatment for his/her needs. A personalized approach to trauma care and treatment will result in improved treatment efficacy, higher patient as well as clinician satisfaction, and reduced dropout rates and treatment disengagement. Clients and therapists should discuss right from the beginning of the therapeutic process the different treatment approaches, and collaboratively agree on which one or ones to use. Although the modular treatment paradigm is in line with this personalized treatment agenda, further research using innovative designs in identifying what works for whom is essential.

Specific research is also required on the effectiveness of treatments for complex PTSD. For example, a key question identified by Brewin et al[1] is whether interventions for this condition should focus primarily on disturbances of memory, as per PTSD theories, or on disturbances of identity, as per complex PTSD theories. Moreover, although there is substantial evidence for the treatment of PTSD in adults, this is less the case for children and young people. In addition, considering that traumatic life events that are considered intentional (e.g., domestic violence) are more toxic and are associated with poorer outcomes, it is worthwhile to explore whether different treatments work differently in groups who have been exposed to different traumatic events.

As research progresses, integrating new modalities and refining existing ones will be crucial in the ongoing effort to provide comprehensive, effective and personalized care for those affected by trauma. The ethos of offering personalized trauma care and treatment should be a substantial component of the training of future clinicians.

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DOI:10.1002/wps.21272

Trauma, coloniality and survivance among Indigenous peoples in the US

Psychological trauma has featured in the lives of Indigenous Americans (i.e., American Indians and Alaska Natives or, simply, Natives) in pronounced fashion since the arrival of Europeans to these lands. My own Indigenous people, the *Aaniiih*-Gros Ventres of the Northern Plains, for example, experienced cataclysmic adversity during the late 1860s. First, measles and smallpox – originally brought to North America by Europeans – swept through our homelands, decimating our people. Additionally, a massacre by Indigenous rivals, competitors for violent control of the Euro-American fur trade, combined to reduce our population by half within this same five-year period.

Although we had become intimately acquainted with such setbacks during the preceding century, the late 1800s were especially devastating. By 1895, only 596 of us had survived on our Montana reservation. Our travails were not over. Diseases of poverty and malnutrition – tuberculosis, trachoma, scrofula – induced further suffering. Corrupt Indian agents ruled our lives in dictatorial fashion. Much of our territory, supposedly guaranteed by treaty with the US, was coercively ceded by government officials.

A reservation industrial school was established to "civilize" us. One elderly woman blinded her grandson with her sewing awl rather than allowing him to be carried away to this loveless and abusive institution. The namesake of the Gone family endured ten years as a child in this boarding school. When he emerged, his mother and other relatives were dead, and nobody had told him. The brutality that he encountered there marred him, and later as a husband and father he wounded his own family. Since those desolate days, our homelands have remained hemmed in by racism and mired in poverty, with the accompanying ills of addiction, accident, violence and suicide being tragically common among our loved ones[1].

These realities are not unique to my people, but impact lives in hundreds of other Native American communities, for which the long legacy of colonial subjugation has sedimented for individuals and families as a cascade of trauma. In their review of post-traumatic stress disorder (PTSD) and its symptoms among Native Americans, Bassett et al[2] identified 37 studies published between 1993 and 2012. Although prevalence rates for the entire national Indigenous American population have not been reported, high-quality epidemiological findings exist for some samples and communities. High rates of PTSD in Native respondents were evident from population studies. Among Vietnam-era military veterans, lifetime PTSD in Indigenous veterans was the highest of any ethnoracial group. Native Americans were more likely than other Americans to report traumatic events, including physical attacks and threats to the well-being of loved ones. Indigenous men and women both reported high levels of vulnerability to trauma, but of different types: exposure to accidents for men and to violence for women. Native women were twice as likely as Native men to present lifetime PTSD as a result.

Adverse childhood experiences such as physical and sexual abuse contributed independently above other risk factors to PTSD, though experiences of abuse, addiction, illness and violence in adulthood contributed to mood and anxiety disorders more generally. It has been argued that disproportionately high rates of PTSD among Indigenous Americans are primarily due to disproportionately high rates of exposure to trauma. Minimal research on potential benefits of PTSD treatment for our populations has been conducted.

PTSD pertains to maladaptive responses to personal trauma. The construct has limitations, however, in accounting for the cascade of trauma described as the colonial legacy for Native Americans. Beginning in the 1990s, Indigenous health scholars heralded new ways of conceiving of Indigenous suffering from histories of colonization as complex trauma and intergenerational PTSD[3]. Described as a "soul wound" or "historical trauma", this concept recognizes the condition of coloniality, arising from both past and ongoing subjugation, as causal for health inequities – and especially mental health inequities – within Native communities.

During the past three decades, Indigenous historical trauma (IHT) has circulated widely in Native settings as an explanation for suffering, impairment and distress. IHT is described as differing from PTSD in several important ways (referred to as the "four Cs" of IHT[4]): it is *colonial* in origin, *collective* in impact, *cumulative* across waves of adversity, and *cross-generational* in its reach from ancestors to descendants.

In essence, this concept historicizes and socializes trauma beyond the medicalized and individualized dysfunction of PTSD (which privileges the psychological and biological foundations associated with psychiatric illness), emphasizing community disorder. Thus, whereas only a minority of Indigenous people might warrant a formal diagnosis of PTSD, nearly all Native people are understood to be impacted by IHT. Indeed, IHT offers an explanatory model for Indigenous social suffering, ensuring that prevalent mental health problems – addiction, PTSD, conduct disorder, and suicide[5] – are related to their constituting social conditions, rooted in coloniality.

Of course, it is nearly impossible to establish cause-effect relationships using the methodological tools of the health sciences to link specific instances of ancestral trauma among prior generations to the suffering of current descendants within Native communities. Many Indigenous proponents of IHT harbor high hopes for the burgeoning science of epigenetics to one day afford such links spanning multiple generations of Native people.

Yet, Walters et al[6] have called attention to conceptual confusion surrounding IHT with respect to future scientific investigation. Specifically, they noted that, over time, IHT has been characterized in the scholarly literature in four distinct ways: as etiology, mechanism, stressor, or syndrome. Similarly, Hartmann et al[7] observed three modes of scholarly engagement with IHT across the scientific literature: as clinical condition, life stressor, or criti-

cal discourse. Gone et al[8] described formidable limitations in the current measures of IHT that have been developed and deployed within the health sciences, concluding that, as a result, "this literature has yet to cohere into a body of knowledge with clear implications for health policy or professional practice".

Interestingly, few investigators have shown interest in establishing distinctive profiles of ancestral trauma for particular Native respondents (e.g., number of great-grandparents to survive a historical military massacre) or in designing studies that aspire to disentangle evidence for intergenerational causal impacts. All of this suggests that the real contributions of the concept of IHT are more critical and discursive rather than empirical and scientific[1].

Indeed, several non-scientific, discursive functions may be served by IHT[1]: explain Indigenous health inequities, re-socialize Native community health problems, destigmatize these conditions with reference to shared suffering, legitimate Native healing traditions, harness trauma discourse for claims-making, tap into more plentifully resourced health care services, and represent an Indigenous scholarly contribution to health research.

Beyond these, IHT also anchors an "alter-Native psy-ence"[5], an Indigenous mental health framework that contests and recasts conventional psychiatric knowledge across several domains: with respect to *distress*, IHT is preferred over mental disorders; with respect to *well-being*, Indigenous forms of relational selfhood are preferred over neoliberal individualism; with respect to *intervention*, Native healing traditions are preferred over empirically supported mental health treatments; and with respect to *evaluation*, Indigenous "ways of knowing" are preferred over scientific outcome studies.

Perhaps most importantly, Native promotion of the concept of historical trauma expresses *survivance* in the health domain[9]. A portmanteau of "survival" and "resistance" introduced by Anishinaabe intellectual G. Vizenor, survivance attests to the improbable persistence of Indigenous peoples beyond the long colonial encounter. It rejects "victimry" and insists that Native self-determination is the way forward from trauma, PTSD, and colonial subjugation. It refuses narratives that reductively restrict attention away from Indigenous agency, kinship, love, struggle, tradition, humor and homeland. It insists that *we shall remain*.

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DOI:10.1002/wps.21273

The PTSD Gestalt switch

Approaching the 45th anniversary of the introduction of post-traumatic stress disorder (PTSD) in the psychiatric nomenclature, Brewin et al[1] have written a masterful review of the history and current status of research on this condition. This allows us to reflect on the level of our knowledge and think about the opportunities and challenges that lie ahead.

The field of traumatic stress research is in an odd place. The two main psychiatric diagnostic manuals, the DSM-5-TR[2] and the ICD-11[3], provide distinct descriptions of trauma-related psychopathology. What people believe about the nature of this psychopathology probably depends in large part on which system they more closely adhere to. This is not a completely healthy situation[4].

Reading Brewin et al's paper was a peculiar experience. Through the various sections of the review, I was continually stuck by how much knowledge has been acquired, but yet how unable we are to provide answers to so many basic questions, such as: what is a traumatic event; how many post-traumatic stress disorders are there; what are the defining features of PTSD; what is the optimal way to assess PTSD; what proportion of the population has PTSD; whether PTSD is the same across cultures; what causes PTSD; who in the population is most likely to develop PTSD; what is the best way to treat PTSD; how effective are treatments for PTSD; why do treatments work, when they work; and who benefits most from treatment.

Reading this review was like a Gestalt switch optical illusion. Look at the literature one way, and we seem to have a deep and profound understanding of so many fundamental issues. Look at it another way, and we seem to understand almost nothing about these same issues.

Consider just a few of these issues. We basically know what constitutes a traumatic event. Any event that provokes feelings of extreme threat or horror, whether occurring suddenly or gradually, at the moment it occurs or sometime later when meaning is assigned, can be traumatic. Furthermore, we know what the core post-traumatic stress response is, and what distinguishes it from other forms of psychopathology: it is the occurrence of intrusive experiences, usually images but also thoughts, sounds, smells or bodily sensations, in which the person feels like he/she is reliving the traumatic event again in the present moment. Additionally, we basically understand why this occurs: the cause lies fundamentally in the operation of memory. Extreme fear or horror inhibits hippocampal binding while promoting amygdala binding, resulting in the memory of the traumatic event containing little contextual information about time and place, and lots of sensory informa-

tion about emotions and somatic experiences. The disjunction between contextual and sensory information in memory means that, when it is cued, the individual feels like he/she is reliving the traumatic event in the present moment. Moreover, we basically know how to treat this problem, i.e. by reprocessing the traumatic memory in a way that it becomes integrated within autobiographical memory, so that, when it is cued, the person knows that the event belongs to the past and that he/she is not in current danger. And we know that, when this is achieved in a clinical setting, post-traumatic distress substantially decreases.

Given the extensive level of knowledge that exists, why then is there so little consensus in our field, such that after nearly 50 years we appear to be ignorant about so many fundamental issues? I do not claim to have a good answer, but I think it is a question we must all grapple with.

I think that a major source of the problem lies in the discrepancy between the ICD and DSM conceptualizations of post-traumatic stress. I recently had the pleasure of collaborating with a molecular biologist from Ukraine who works in a clinic for wounded Ukrainian soldiers. He had no previous experience with PTSD but, being faced with so many people who had been traumatized, was interested in whether it might be possible to identify biological markers for PTSD, in order to more efficiently identify soldiers with, or at risk of, this condition, and then possibly develop novel treatments. He asked me what he thought was a simple question: "What's the best way to assess PTSD?". I found myself in the unfortunate position of having to explain that it depends on which version of PTSD he wanted to assess. After he picked his jaw up off the floor, I then had to explain to him the thorny issues related to assessment and how reviewers for leading psychiatric journals might respond to different assessment methods. The molecular biologist's confusion and irritation by this exchange was matched only by my embarrassment.

As a paid-up, card-carrying scientician[5], I fully recognize the dangers of ideological homogeneity and attempts to establish scientific consensus via authoritative declarations[6], and I appreciate the value of researchers independently pursuing truth using different models and methods. Nevertheless, I think that, for our field to progress, we have to settle on an agreed-upon diagnostic model for trauma-related psychopathology.

I am reminded here of G. Box's famous aphorism that "all models are wrong, but some are useful"[7]. Nowhere is this truer than for psychiatric diagnoses. Surely nobody believes that DSM-5 PTSD, for example, represents something real. At best, our diagnostic models approximate real phenomena in a way that can be useful. They provide a common language for clinicians and researchers; they guide basic and applied research in a systematic way; they provide a framework for determining who needs care; and they help evaluate the efficacy of treatment.

Since our diagnostic models are not true, what is their point if they are not useful? My view is that the current situation of having two different diagnostic models of trauma-related psychopathology is severely undermining the usefulness of this approach, and is leading to a situation where we are unable to answer basic questions such as "What is a trauma?" and "How many trauma-related disorders are there?".

J. Swift[8], and later S. Freud[9], warned of the narcissism of minor differences. While many of us in the field might place great importance on whether the DSM or ICD provides a more accurate account of trauma-related psychopathology, consider it from the perspective of my molecular biologist friend in Ukraine. It is the narcissism of infinitesimally minor differences. It is time for us to get past it and come to a shared description of reality that is useful, and in doing so we may be able to break our illusion.

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DOI:10.1002/wps.21274

The paradox of the biopsychological and sociocultural levels in post-traumatic stress disorder

It is fascinating to see how the field of post-traumatic stress disorder (PTSD) has evolved over the past 50 years. The team of authors led by C. Brewin[1] – comprising psychologists, epidemiologists, psychiatrists, and intervention researchers – provides a comprehensive analysis of the significant developments in this field and the underlying empirical evidence.

I would like to enumerate a few points on which I am in complete agreement with the authors. First, there is now an accepted set of different phenotypes of PTSD, which includes the "classic" PTSD known for several decades, complex PTSD, a severe dissociative condition, and other phenotypes that have been linked to childhood trauma. Second, the diagnosis should rely on the pattern of symptoms and resulting disabilities rather than on definitions of a trauma criterion, as is still often the case when diagnosing PTSD to this day. Third, delayed PTSD is essentially based on an altered stress sensitivity, and the patients display isolated

post-traumatic symptoms prior to the full development of the condition. On all these points, the authors' thorough presentation deserves gratitude and dissemination in the professional community.

Brewin et al's extension of the core psychopathology theory of PTSD from disturbed memory to identity changes is also noteworthy. However, a core phenomenon of trauma-related disorders should also be highlighted, which we refer to as the biopsychological-sociocultural paradox (in brief, the fact that traumatic experiences mostly disrupt biopsychological processes, while sociocultural processes usually foster recovery).

In the field of biology, numerous studies have documented the existence of deficits and vulnerabilities related to PTSD in a multitude of regulatory systems and circuits. In the field of psychological processes, empirical research has initially focused on memory changes and then on identity impairments. In the clinical setting, this is evidenced by a focus on the core symptoms of patients' suffering, including re-experiencing, avoidance and the persistent (physiological) sense of threat.

The paradox is that the most effective antidote for all these biopsychological disturbances is social support for those affected[2]. There is sufficient evidence from multiple studies to confirm that appropriate social support for victims or survivors can effectively reduce the impact of trauma-related disorders[3]. This phenomenon can be observed clinically in the shorter recovery times of socially well-connected and culturally integrated patients in treatment facilities[4].

It is worth noting that not all the various factors in the biopsychological areas are exclusively pathogenic. To give a few examples, there are protective factors such as a larger hippocampal volume or, in the psychological realm, the range of less avoidant coping strategies. Nevertheless, seeking social support of others – friends, family or members of one's cultural community – consistently yields greater protective effects than factors in the biological and psychological areas.

The apparent contradiction between the biopsychological predominance of deficits and the social-interpersonal-cultural predominance of antidotes may be related to the ontological status of PTSD. It could be said that PTSD is a "silent suffering" of individuals: after traumatization, patients do not usually complain to others about their suffering. Those who have experienced such distress might find it normal and inevitable[5,6]. Some have suggested that this may be one reason why this mental disorder was "discovered" so late compared to depression, psychosis and anxiety disorders. It is possible that, in these other conditions, behaviors, facial expressions and body postures signal to social partners that one is "ill". The philosophical basis of the embodiment of mental disorders recently described in this journal[7] may be therefore comparatively less pronounced in PTSD.

The cultural psychology of PTSD, with its admittedly not yet very advanced research program, suggests that PTSD could be a primarily "social disease". This, of course, does not undermine the suffering experienced by those afflicted with this disorder. However, this assertion is consistent with findings from prevention and treatment research, as discussed in the paper by Brewin et al. According to this, current preventive programs place a strong emphasis on dyadic or group cohesion aspects.

What are the most pressing transcultural issues for reducing suffering after trauma in the future? In my view, it would be beneficial to first consider why there is such a low utilization of PTSD treatment services in cultures other than the European-North American (Global North) ones. Even in these Global North cultures, there are differences. In large groups of affected people, there is no perception of needing help. For example, after the 9/11 attacks in New York, the quickly established outpatient mental health emergency help centers had only a few requests from people seeking help. Could it be that there are different cultural scripts of post-traumatic suffering that go far beyond the symptom descriptions of the DSM and ICD? Many individuals who have experienced trauma have a self-perception of being "broken" or having "a kink in their lifeline"[8].

The provision of lists of cultural syndromes and idioms of distress for consequences of trauma, as mentioned by Brewin et al, could be improved from a scientific standpoint. A key question is how such divergent cultural idioms arise, and how they can be integrated into an overarching, systematic context. In light of the above, it seems reasonable to suggest that transcultural research that takes into account global matrices of values, norms and traditions may be a logical choice. For instance, a study conducted in Rwanda with traumatized individuals, many of whom were survivors of the genocide against the Tutsis in the 1990s, indicated that the values of not showing suffering and maintaining self- and community reputation, as well as *Ubuntu* (in short, humanity towards others), apparently mediate the expression of suffering[9].

After a thorough examination of the social and cultural factors influencing the expression of post-traumatic suffering and the utilization of specialized assistance, it may be possible to place the field of treatment on a more nuanced social and cultural foundation. Brewin et al's paper correctly emphasizes the significant potential of community-based interventions, particularly in addressing health disparities.

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DOI:10.1002/wps.21275

Reducing the burden of PTSD through digital interventions and development of sequential precision treatment rules

Brewin et al[1] provide a comprehensive, thoughtful and up-to-date review of the conceptualization, diagnosis, prevention and treatment of post-traumatic stress disorder (PTSD). Despite the controversies that surround the evolving definitions of traumatic events and criteria for PTSD, there is no doubt about the societal burden and deleterious impact on population health of post-traumatic psychological distress[2]. Given the reportedly high prevalence of PTSD[1] and the widespread occurrence of trauma exposure – an estimated 70% of the global population has experienced any traumatic event and 30% has been exposed to four or more[3] – there are not enough human and financial resources across the globe to realistically treat all those with PTSD, let alone the whole continuum of post-traumatic psychological distress. Furthermore, the majority of those who meet criteria for PTSD never seek treatment, given the stigma associated with mental health in general and some traumas in particular (i.e., rape), and a variety of barriers, both logistical (e.g., time, location) and attitudinal (e.g., beliefs about psychological or pharmacological treatments)[2].

Therefore, to really impact the global burden of PTSD, we not only need novel interventions, but mostly novel modalities of delivering interventions, that are scalable, accessible and acceptable to the target population. Internet and mobile-based interventions reduce many barriers. They are scalable, since – once developed – they require fewer specialized human resources: there are self-directed versions that require no human resources, and supported versions that require less specialized human resources and/or less time per client than traditional in-person modalities. Digital modalities can increase accessibility because generally they can be used at any time in any place where the user has Internet access. Even in low- or middle-income countries, the population often has greater access to Internet (through mobile phones) than to mental health treatment centers. Finally, digital modalities may reduce barriers related to stigma, as they are often anonymous and match the often-cited reason for not seeking help, the individual wanting to deal with the problem on his/her own[2], thus increasing empowerment of self-care.

While the literature on the effectiveness of Internet and mobile-based interventions for PTSD is growing and promising, for differing levels of support[4,5], this is only one small step on the road to substantially reduce the global burden of this disorder. There is a great deal of heterogeneity of treatment response even to well-established treatment options. And certainly, digital intervention modalities do not work for all, due to differences in digital literacy, Internet access, motivation, and other yet-to-be determined factors.

Therefore, a further step to reducing the burden of PTSD is ideally to use pragmatic precision-treatment modelling to create individualized treatment allocation rules to predict in individual patients which treatment modality will work best, and, given equal probability of success, to provide the optimal treatment at the lowest cost or resource intensity.

To my knowledge, no precision treatment rules of this nature have been developed yet for PTSD, but they are emerging for other disorders. For example, in the development of a precision treatment model for university students with depression, we found that 28% were more or equally helped by a self-guided digital cognitive behavioral treatment (CBT) than the guided version of the intervention, and precision treatment rules based on pre-treatment allocation characteristics can predict which treatment is best for whom[6]. A challenge for the field is that the development of precision treatment rules depends upon large sample sizes, pooling samples from multiple studies with comparable measurements and designs, or trial emulation with large observable samples which are iteratively tested with pragmatic clinical trials[7].

An even further step along this path to reduce the global burden of PTSD is not only to identify the right treatment for the right person, but the right treatment for the right person at the right time or in the right order. This can be achieved using an iterative staged approach to precision treatment, whereby algorithms are developed to determine the optimal first-line treatment for each individual and, if not successful, which treatment option to offer next and so on. These algorithms can be developed by conducting sequential multiple assignment randomized trials (SMART)[8], wherein participants are randomly assigned to a treatment type/modality in the first stage and then, depending on treatment outcome, randomly assigned to further treatments in subsequent stages, resulting in precision treatment based on the individual's pre-treatment characteristics and treatment response.

One example is an ongoing SMART for cancer survivors with PTSD symptoms in which participants are randomized in stage 1 to a self-guided app or treatment as usual. Non-responders of both arms are then re-randomized to an increased intensity modality (the app with a clinical guide or a telephone-administered CBT). This approach will therefore provide treatment decision rules based on the four possible sequences[9]. Such models could also be developed for preventive interventions in trauma-exposed individuals.

While guided Internet-based trauma-focused CBT is currently given a lower-strength recommendation by the International Society for Traumatic Stress Studies (ISTSS) and the UK National Institute for Health and Care Excellence (NICE), from a public health perspective a treatment with a smaller effect size but applicable to many more people may go further to reduce PTSD burden globally than a treatment with a larger effect size given to only a few.

Brewin et al[1] set the stage for future directions. Extending these, a strategic research plan to develop sequential precision treatment rules to determine the optimal first-line modality of preventive intervention and/or treatment (with a range of scalable interventions including digital ones) at the lowest intensity or cost for different people, based on pre-treatment characteristics and initial

treatment response, could impact population health and reduce global suffering from PTSD.

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DOI:10.1002/wps.21276

No two traumas are alike, and neither are two presentations of PTSD

Significant advances have been made in our understanding of post-traumatic stress disorder (PTSD), and in translating an overwhelming body of research evidence into clinical practice. However, it is time for researchers and clinicians to pause and reflect on whether true progress has been made. Brewin et al[1] convincingly distill the complexity of defining, assessing, diagnosing, predicting, preventing and treating PTSD in diverse populations, across several countries, in varying socio-political-cultural and societal-structural contexts, and at different life stages.

The review juxtaposes the rapid and exponential growth of knowledge on trauma, PTSD and complex PTSD against the significant knowledge gaps (and possibly "blind spots") that remain. It brings into sharp focus the need for accelerated research and consensus building on a core set of evidence-informed and integrated phenotypes and biotypes, in pursuit of categorical and dimensional solutions to parsing out PTSD heterogeneity, and intervening timeously and effectively. Fine-grained characterization of PTSD phenotypes and biotypes could propel collective global efforts and pave the way for the development of tailored, measurement-based and personalized interventions for adults and youth with PTSD – interventions that yield higher response and remission rates than the current ones.

Trauma is ubiquitous, but it is also individual and personal, and its impact and attributions are highly variable. Prevalence rates of PTSD vary considerably by population, demography, social determinants, and ascertainment method. Several decades of research have taught us that the relationship between the nature of a traumatic event (e.g., single or repeated, interpersonal or non-interpersonal, intentional or non-intentional), the peri-traumatic responses it triggers, and the resultant PTSD is non-linear, and, at an individual patient level, may follow a convoluted trajectory. Similarly, evidence – also gathered over decades – on acute stress disorder, first introduced in the DSM-IV as a distinctive early-after-trauma diagnosis and retained in the DSM-5, has been disappointing with regards to its diagnostic utility in predicting PTSD[2,3].

Despite an abundant literature on pre-trauma, peri-trauma and post-trauma risk and protective factors, our ability to predict PTSD and apply biological markers (e.g., genotypic, epigenetic, transcriptomic, endocrine, immune) to stratify trauma-exposed individuals by risk remains very limited. Moreover, low- and middle-income country populations are disproportionately under-represented in longitudinal neurobiological studies that aim to track biological signatures alongside PTSD symptom trajectories[4]. Also central to the challenge is the astounding within-group heterogeneity in PTSD (in symptom patterning, illness course, and treatment outcome) and the high comorbidity with a wide range of psychiatric disorders and physical illnesses.

It is plausible that symptom-based subtypes and biotypes could incrementally refine classification and treatment of PTSD. To date, significant empirical strides have been made in delineating the dissociative subtype, the only one recognized in the DSM-5, which has a point prevalence of 38.1% in children and adolescents with a diagnosis of PTSD, and a unique symptom, neurobiological and treatment response profile that is underpinned by fairly robust evidence[5,6]. There is still ongoing debate about whether dissociation is a somewhat common phenomenon in PTSD and a marker of PTSD severity, or whether its occurrence is limited to a more circumscribed subgroup of people with the diagnosis. The specificity of the dissociative subtype needs further interrogation, beyond the Global North, and in culturally diverse settings and PTSD populations where dissociative phenomena might be linked to somatization and other culture-bound phenomena.

In the vein of delineating unique PTSD symptom profiles that could inform more targeted, personalized treatments, few studies have sought to map the type of index trauma to PTSD symptom clusters in a concerted fashion. Notable is a recent investigation of 4,069 veterans from the 2019-2020 National Health and Resilience in Veterans Study, which applied an alternative phenotypic model to the DSM-5 and ICD-11 symptom structure to plot the relationship of different traumas (categorized into interpersonal violence, combat/captivity, disaster/accident, and illness/injury) to PTSD symptoms[7]. The resulting eight-symptom PTSD phenotype model comprised internally-generated intrusions (e.g., distressing traumatic memories), externally-generated intrusions (e.g., emotional reactivity to trauma cues), avoidance, negative affect, anhedonia, externalizing behaviors, and anxious and dysphoric arousal. Findings of discriminable symptom profiles between veterans who experienced interpersonal violence or combat/captivity versus those who experienced illness/injury or disaster/accident are encouraging. However, the cross-sectional design of the study precludes addressing the question of whether these trauma-symptom profiles hold out over time in individuals with chronic PTSD. Moreover,

these findings will have to be replicated in other trauma-exposed populations, and the biopsychosocial mechanisms that underlie different trauma-PTSD symptom phenotypes will also require deep exploration.

The field has for a long time invested in large-scale and costly efforts to identify clinically valid, affordable and scalable PTSD biomarkers that can aid screening and timely intervention, and lead to better outcomes. Several susceptibility and diagnostic markers, and some predictive and therapeutic biomarkers, have been evaluated, including polygenic risk scores and regional brain structural morphology. However, these markers require replication and testing in large samples and across populations before their potential clinical utility can be realized[8].

The prospect of employing single biomarkers in PTSD is out of question, and discovery of biomarker panels that have the requisite reliability, specificity, sensitivity and reproducibility – and are cost-effective and feasible to employ at point-of-care – is still some way off. For predictive biomarkers, multiple sampling commencing early after trauma and extending beyond a year to account for the evolving dynamics of PTSD symptoms is arguably the best way to map resilient, chronic, delayed onset, and recovery trajectories, and enhance our understanding of causal pathways. For predictors of treatment response and normalization of biological perturbations with treatment, trials that compare psychotherapies, pharmacotherapies and combination treatments are needed. In addition, innovative strategies, such as biomarker-stratified designs (to address the question of what is the best treatment for all patients with PTSD as well as for biomarker-defined PTSD patient subgroups) and biomarker enrichment designs (to address the question of what is the best treatment in biomarker-positive patients with PTSD), will serve to improve efficiency and precision. Though appealing, these designs are hugely challenging to apply.

Generative artificial intelligence tools may fast change this landscape, with benefits that extend beyond identifying novel predictors of PTSD treatment outcomes, to bolstering treatment fidelity and boosting patient engagement[9]. However, these tools also raise a host of ethical, social and legal considerations that clinicians at the coalface of caring for patients with PTSD will be compelled to grapple with.

Finally, in seeking to transform scientific endeavors to prevent, diagnose and treat PTSD, it behooves us to remember that no two traumas and no two presentations of PTSD are alike. The art of providing individual-level care should always sit alongside our science.

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DOI:10.1002/wps.21277

Socioeconomic inequalities in mortality associated with mental disorders: a population-based cohort study

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Mental disorders are associated with elevated mortality rates and reduced life expectancy. However, it is unclear whether these associations differ by socioeconomic position (SEP). The aim of this study was to explore comprehensively the role of individual-level SEP in the associations between specific types of mental disorders and mortality (due to all causes, and to natural or external causes), presenting both relative and absolute measures. This was a cohort study including all residents in Denmark on January 1, 2000, following them up until December 31, 2020. Information on mental disorders, SEP (income percentile, categorized into low, <20%; medium, 20-79%; and high, ≥80%), and mortality was obtained from nationwide registers. We computed the average reduction in life expectancy for those with mental disorders, relative and absolute differences in mortality rates, and proportional attributable fractions. Subgroup analyses by sex and age groups were performed. Overall, 5,316,626 individuals (2,689,749 females and 2,626,877 males) were followed up for 95.2 million person-years. People with mental disorders had a shorter average life expectancy than the general population regardless of SEP (70.9-77.0 vs. 77.2-85.1 years, depending on income percentile). Among individuals with a mental disorder, the subgroup in the top 3% of the income distribution had the longest average life expectancy (77.0 years), and this estimate was lower than the shortest life expectancy in the general Danish population (77.2 years for individuals in the bottom 6% income distribution). The mortality rate differences were larger in the low-income than the high-income group (19.6 vs. 13.3 per 1,000 person-years). For natural causes of death, a socioeconomic gradient for differences in life expectancy and mortality rates was observed across most diagnoses, both sexes, and all age groups. For external causes, no such gradient was observed. In the low-SEP group, 10.1% of all deaths and 23.7% of those related to external causes were attributable to mental disorders, compared with 3.5% and 8.7% in the high-SEP group. Thus, our data indicate that people with mental disorders have a shorter life expectancy even than people with the lowest SEP in the general population. The socioeconomic gradients in mortality rates due to natural causes highlight a greater need for coordinated care of physical diseases in people with mental disorders and low SEP.

Key words: Mortality, mental disorders, socioeconomic inequalities, life expectancy, natural causes of death

(World Psychiatry 2025;24:92–102)

People with mental disorders experience excess mortality, indicated by elevated mortality rates and shorter life expectancy than the general population[1,2]. The life expectancy for men and women with any mental disorder in Denmark has been estimated to be, respectively, 10.2 and 7.3 years shorter than the general population[2]. People with mental disorders are at higher risk of dying from suicide or other external causes of death. However, most excess mortality in this population is attributable to physical diseases, including cardiovascular, infectious and respiratory diseases, neoplasms and diabetes mellitus[2].

Over the past decades, improvements in life expectancy have been observed in most countries. However, people with mental disorders have not benefitted from this to the same extent as the rest of the population[3]. In fact, evidence suggests that the life expectancy gap might be increasing, especially for deaths related to physical diseases[4,5]. Given the impact of mental disorders on the society, it is crucial to understand the risk factors contributing to the elevated risk of premature mortality in people with these disorders.

There is clear evidence of the link between socioeconomic position (SEP) and mental disorders[6]. Low SEP is associated with an elevated risk of almost all mental disorders, including schizophrenia, bipolar disorder and depression[7-9], with the notable exception of eating disorders[10]. Moreover, a large body of literature has consistently reported higher mortality rates among individuals with low rather than high SEP in the general population[11,12]. A Norwegian register-based study estimated a life expectancy gap of 13.8 years for men and 8.4 years for women between people with the highest and lowest income percentile[12]. The mechanisms underlying the above associations include behavioral (i.e., tobacco, diet, and alcohol use), psychosocial, and distal (e.g., access to resources) factors[13]. There is a need to understand the interplay between mental disorders and SEP in relation to subsequent mortality.

A recent systematic review[14] reported similar associations between mental disorders and mortality in relative terms across SEP levels. However, the underlying mortality rates (yet not reported in the literature) in people with vs. without mental disorders might differ by SEP, which could imply differences in absolute terms. Providing absolute in addition to relative measures will facilitate data interpretation from a public health perspective and might help identify subgroups at the highest risk, allowing preventive and treatment measures to be more effectively targeted.

Furthermore, very few studies have examined the associations between specific mental disorder types (e.g., schizophrenia or bipolar disorder) and mortality. Given that each mental disorder type may have its own unique set of risk factors for cause-specific mortality, it is important to examine if the impact of SEP on these associations differs across various disorder types. In addition, most studies have examined all-cause mortality or suicides, but have not considered natural causes of death separately. Finally, studies providing sex- and age-specific mortality estimates are

lacking, even though these demographic factors are strongly associated with SEP, mental disorders and mortality.

The main aim of this study was to use nationwide register data covering the entire Danish population to investigate the absolute and relative associations between a diagnosis of any mental disorder and subsequent mortality (due to all causes, and to natural or external causes) according to individual-level SEP. Additionally, we aimed to examine these associations with regard to seven specific types of mental disorders (organic disorders, substance use disorders, schizophrenia and related disorders, bipolar disorder, depression, anxiety-related disorders, and personality disorders), and with regard to potential age and sex differences.

Several social determinants, including SEP, stand out as the most modifiable risk factors for early interventions, indicating a great potential to prevent the onset of mental disorders, or improve their prognosis[6]. Indeed, one of the United Nations Sustainable Development Goals is to reduce socioeconomic inequality in access to mental health services[15]. The results of this study can inform more targeted interventions in an often stigmatized and marginalized population.

METHODS

Study design and population

We conducted a population-based cohort study including all individuals living in Denmark on January 1, 2000, followed up until December 31, 2020. The protocol and analysis plan were preregistered on Open Science Framework (https://osf.io/h7ja6).

The study population was identified by the Danish Civil Registration System[16,17], which holds information on legal sex and date of birth, linkage to parents, continually updated information on vital status, and a unique personal identification number that can be used to link information from various national registers. A flow diagram of the study population is provided in the supplementary information.

The study was registered with the Danish Data Protection Agency at Aarhus University (no. 2016-051-000001-2587) and approved by Statistics Denmark and the Danish Health Data Authority. According to Danish law, informed consent and ethical approval are not required for register-based studies. All data were de-identified and not recognizable at an individual level.

Information on mental disorders

Information on mental disorders was obtained from the Danish Psychiatric Central Research Register[18], which includes admissions to psychiatric inpatient facilities since 1969, and visits to outpatient psychiatric facilities and emergency departments since 1995. The ICD-8 was used until 1993, and the ICD-10 from 1994 onward. We considered a broad category of any mental disorder (ICD-10 codes: F00-F99), and seven specific types of mental disorders: organic disorders (F00-F09), substance use disorders (F10-F19), schizophrenia and related disorders (F20-F29), bipolar disorder (F30-F31), depression (F32-F33), anxiety-related disorders (F40-F48), and personality disorders (F60).

Mental disorders were treated as time-varying exposures. Therefore, each individual was considered unexposed until the first diagnosis of a specific disorder; subsequently, individuals were considered exposed to the relevant mental disorder. Individuals diagnosed during the 31-year period from 1969 through 1999 (prevalent cases at the start of follow-up) were continually counted as exposed during the observation period. For those diagnosed at or after January 1, 2000 (incident cases), the date of diagnosis for each disorder was defined as the date of first contact (inpatient, outpatient or emergency visit). People with more than one disorder were considered exposed to each type in the respective analyses, and onset depended on the date of first diagnosis for the disorder of interest.

All-cause and cause-specific mortality

Information on the dates and underlying causes of death was obtained from the Danish Register of Causes of Death[19], and identified according to ICD-10 codes. Underlying causes of death were categorized into external causes (suicides, accidents and homicides) and natural causes (all other causes).

Measurement of individual SEP

We used income as a proxy of individual SEP, which was delineated from the Income Statistics Register[20]. We defined this proxy as the household annual equated disposable income, which is the household annual income after taxes and interest expenses, accounting for household size[20]. We then computed the mean over the three years before 2000 (i.e., 1997-1999). For individuals aged 30 years or younger, we took the maximum value between household income of the index individual and the average of the parents.

We ranked income in percentiles within people of the same age and sex living in Denmark on January 1, 2000 (i.e., the general population). In some analyses, we divided income into three groups: low-income (<20% of the income distribution), medium-income (20-79%), and high-income (≥80%). Individuals with negative income values (less than 1%) were excluded, to avoid potential misclassification (people with negative income in Denmark have an average high net worth).

Statistical analysis

For all analyses, follow-up started on January 1, 2000, or at the minimum possible age of onset of mental disorder (see supplementary information), whichever occurred later. It ended on the date of death, emigration from Denmark, or December 31, 2020, whichever occurred first.

Differences in estimated average life expectancy between people with mental disorders and the general population according to SEP were computed by calculating excess life years lost (LYLs), and were further decomposed into specific causes of death by using a competing risks model[21-23].

We applied Poisson regression models to estimate mortality rate ratios with 95% confidence intervals (CIs), by comparing people with versus without mental disorders according to SEP. Since the Poisson distribution assumes constant event rates over time, we divided the time period into 1-year intervals. The final models included an interaction term between mental disorders and SEP, and adjustment for age and sex (see also supplementary information).

From these models, we calculated predicted mortality rates and mortality rate differences with 95% CIs, comparing people with versus without mental disorders according to SEP. We additionally calculated population attributable fractions[24], aiming to measure the proportional reduction in deaths that would occur in the hypothetical case in which people with mental disorders were to have the same mortality rates as those without mental disorders in each SEP group (i.e., elimination of mental disorders while all other risk factors for mortality remain unchanged).

Pre-defined subgroup analyses were performed by age group (≤30, 31-65, and >65 years) and sex (female and male). We conducted three pre-defined sensitivity analyses. First, we restricted the analysis to incident cases of mental disorders, to attenuate the potential survival bias caused by including prevalent cases who survived until January 1, 2000, and to focus on the differential consequences of newly diagnosed mental disorders across SEP groups. Second, we used educational attainment instead of income as a proxy indicator to account for different aspects of SEP. Third, we assessed income five years before baseline, still applying the mean over three preceding years (e.g., measuring income in year 1995 as the average values across years 1992-1994), to assess an influence of "downward social selection"[25], wherein baseline income is influenced by the prodromal phase of mental disorders (before the first diagnosis).

We conducted analyses to additionally adjust for physical diseases at baseline, which were assessed by adapting the Nordic Multimorbidity Index[26], using data from the Danish National Patient Register[27,28] and the Danish National Prescription Registry[29] (see also supplementary information).

Data are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[30].

RESULTS

The cohort consisted of 5,316,626 individuals – 2,689,749 females (50.6%) and 2,626,877 males (49.4%) – with a median age at baseline of 38.3 years (interquartile range, IQR: 21.1-55.7), who contributed a total of 95.2 million person-years between January 1, 2000 and December 31, 2020.

Among these individuals, we identified 268,070 (5.0%) with pre-existing mental disorders (prevalent cases) and 499,561 (9.4%) diagnosed during follow-up (incident cases). The proportions of both prevalent and incident mental disorders were higher in the low-income (9.6% and 12.2%) than the medium-income (4.4% and 9.3%) and high-income (2.5% and 7.0%) groups, and similar patterns were observed when looking at income percentiles (see Figure 1). During the 21-year follow up period, we observed 1,127,811 (21.2%) deaths – 1,080,232 (20.3%) due to natural causes and 47,579 (0.9%) due to external causes. Detailed cohort characteristics are presented in Table 1.

Life expectancy and mortality rates in people with mental disorders according to SEP level

The estimated average life expectancy was shorter among people diagnosed with a mental disorder than those in the gen-

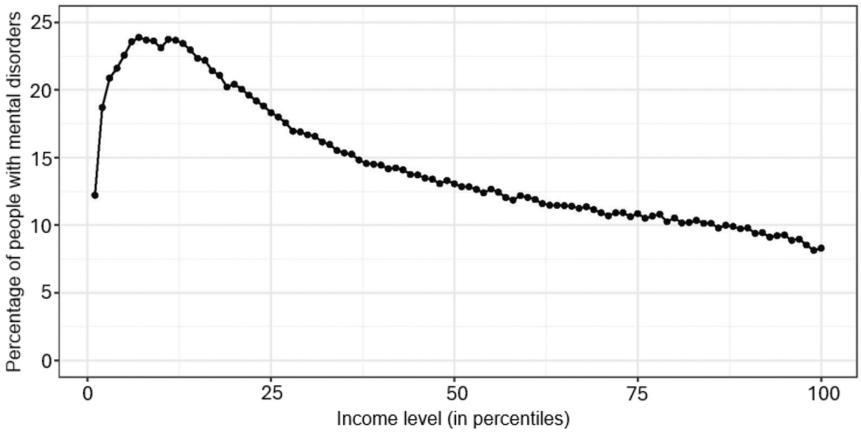

Figure 1 Percentage of people with mental disorders according to baseline income levels in percentiles in Denmark, 2000-2020. The dots represent the percentage of people with mental disorders at each income percentile.

eral population with similar income levels (70.9-77.0 vs. 77.2-85.1 years, depending on income percentile). Among individuals with a mental disorder, the subgroup in the top 3% of the income distribution had the longest average life expectancy (77.0 years). This estimate was lower than the shortest life expectancy in the general Danish population (77.2 years, observed for individuals in the bottom 6% income distribution) (see Figure 2).

The mortality rates were higher in people diagnosed with a mental disorder than in those undiagnosed, across income levels: 34.2 (95% CI: 34.0-34.5) vs. 14.7 (95% CI: 14.6-14.7) per 1,000 person-years in the low-income group; 25.3 (95% CI: 25.1-25.4) vs. 10.7 (95% CI: 10.7-10.8) per 1,000 person-years in the medium-income group; and 21.5 (95% CI: 21.3-21.7) vs. 8.2 (95% CI: 8.2-8.3) per 1,000 person-years in the high-income group (see Table 2).

We found little evidence of heterogeneity in relative measures of mortality across levels of SEP for those with versus without mental disorders: the mortality rate ratios for all-cause mortality were 2.3 (95% CI: 2.3-2.4), 2.4 (95% CI: 2.3-2.4), and 2.6 (95% CI: 2.6-2.7) in the low-, medium- and high-income groups, respectively. However, on the absolute scale, the mortality rate differences were larger for people belonging to the low-income group (19.6 per 1,000 person-years, 95% CI: 19.3-19.8) than in the medium-income (14.5, 95% CI: 14.4-14.7) and high-income (13.3, 95% CI: 13.0-13.5) groups (see Table 2).

Table 1 Characteristics of the study population

		Baseline income category		
	Overall	**Low-income**	**Medium-income**	**High-income**
Number of subjects	5,316,626	1,063,371	3,189,837	1,063,418
Age at baseline, years (median, IQR)	38.3 (21.1-55.7)	38.3 (21.1-55.7)	38.3 (21.1-55.7)	38.3 (21.1-55.7)
Sex, N (%)				
Male	2,626,877 (49.4)	525,399 (49.4)	1,576,058 (49.4)	525,420 (49.4)
Female	2,689,749 (50.6)	537,972 (50.6)	1,613,779 (50.6)	537,998 (50.6)
Highest achieved education at baseline, N (%)				
Low (ISCED level 0-2)	1,379,866 (26.0)	447,020 (42.0)	815,494 (25.6)	117,352 (11.0)
Medium (ISCED level 3-5)	2,440,102 (45.9)	418,931 (39.4)	1,588,007 (49.8)	433,164 (40.7)
High (ISCED level 6-8)	1,206,288 (22.7)	117,100 (11.0)	625,956 (19.6)	463,232 (43.6)
Missing	290,370 (5.5)	80,320 (7.6)	160,380 (5.0)	49,670 (4.7)
Mental disorders, N (%)				
Any prevalent and incident diagnosis	767,631 (14.4)	231,679 (21.8)	434,845 (13.6)	101,107 (9.5)
Incident cases during follow-up	499,561 (9.4)	129,878 (12.2)	295,201 (9.3)	74,482 (7.0)
Organic disorders	125,525 (2.4)	31,574 (3.0)	73,824 (2.3)	20,127 (1.9)
Incident cases during follow-up	100,855 (1.9)	22,548 (2.1)	60,851 (1.9)	17,456 (1.6)
Substance use disorders	157,472 (3.0)	66,975 (6.3)	77,163 (2.4)	13,334 (1.3)
Incident cases during follow-up	86,984 (1.6)	30,116 (2.8)	47,433 (1.5)	9,435 (0.9)
Schizophrenia and related disorders	106,208 (2.0)	42,999 (4.0)	53,603 (1.7)	9,606 (0.9)
Incident cases during follow-up	56,125 (1.1)	21,014 (2.0)	28,793 (0.9)	6,318 (0.6)
Bipolar disorder	39,189 (0.7)	11,450 (1.1)	22,192 (0.7)	5,547 (0.5)
Incident cases during follow-up	25,753 (0.5)	6,947 (0.7)	14,840 (0.5)	3,966 (0.4)
Depression	244,822 (4.6)	67,256 (6.3)	143,268 (4.5)	34,298 (3.2)
Incident cases during follow-up	178,115 (3.4)	46,419 (4.4)	105,573 (3.3)	26,123 (2.5)
Anxiety-related disorders	352,288 (6.6)	111,067 (10.4)	198,541 (6.2)	42,680 (4.0)
Incident cases during follow-up	255,220 (4.8)	73,797 (6.9)	147,816 (4.6)	33,607 (3.2)
Personality disorders	144,660 (2.7)	53,830 (5.1)	77,322 (2.4)	13,508 (1.3)
Incident cases during follow-up	68,901 (1.3)	21,338 (2.0)	39,826 (1.2)	7,737 (0.7)
Mortality during follow-up, N (%)				
All-cause mortality	1,127,811 (21.2)	274,062 (25.8)	665,671 (20.9)	188,078 (17.7)
Natural causes	1,080,232 (20.3)	260,488 (24.5)	638,916 (20.0)	180,828 (17.0)
External causes	47,579 (0.9)	13,574 (1.3)	26,755 (0.8)	7,250 (0.7)

IQR – interquartile range, ISCED – International Standard Classification of Education

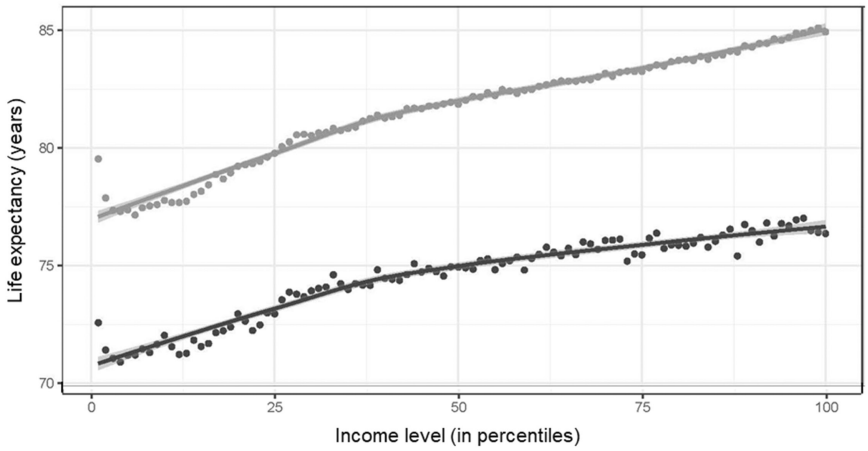

Figure 2 Average life expectancy for people with mental disorders (black) and the general Danish population (grey) according to baseline income levels in percentiles. The solid lines represent values estimated by locally weighted scatterplot smoothing.

The estimated proportional fraction of deaths attributable to any mental disorder was 10.1% (95% CI: 10.0-10.2) in the low-income group, 5.1% (95% CI: 5.1-5.2) in the medium-income group, and 3.5% (95% CI: 3.5-3.5) in the high-income group (see Figure 3).

Contributions of causes of death to the differences in mortality according to SEP level

For natural causes of death, the mortality rate differences were 17.3 per 1,000 person-years (95% CI: 17.1-17.6) in the low-income group; 13.1 per 1,000 person-years (95% CI: 13.0-13.3) in the medium-income group; and 12.0 per 1,000 person-years (95% CI: 11.8-12.2) in the high-income group. For external causes of death, the corresponding mortality rate differences were 2.1 (95% CI: 2.1-2.2), 1.5 (95% CI: 1.4-1.5), and 1.4 (95% CI: 1.3-1.5) (see Table 2).

For external causes of death, the estimated proportional fraction of deaths attributable to any mental disorder showed a socioeconomic gradient that was larger than for all-cause mortality: 23.7% (95% CI: 23.4-23.9) for the low-income group; 11.6% (95% CI: 11.5-11.7) for the medium-income group; and 8.7% (95% CI: 8.6-8.8) for the high-income group (see Figure 3).

Patterns across specific mental disorder types, sex and age groups, and physical diseases

All types of mental disorders were associated with lower life expectancy and higher mortality rates than those observed in the general population, regardless of income. The largest gaps were observed in people with substance use disorders: in these people, the mortality rate differences were, respectively, 43.5 per 1,000 person-years (95% CI: 42.8-44.2) in the low-income group, 28.0 per 1,000 person-years (95% CI: 27.5-28.5) in the medium-income group, and 22.4 per 1,000 person-years (95% CI: 21.4-23.3) in the high-income group (see Table 2).

The socioeconomic patterns in mortality measures for specific types of mental disorders were similar to those for any mental disorder, with the exception of organic disorders, for which the mortality rate differences were similar across income groups: 22.3 per 1,000 person-years (95% CI: 21.8-22.8) in the low-income group, 21.1 per 1,000 person-years (95% CI: 20.8-21.4) in the medium-income group, and 21.2 per 1,000 person-years (95% CI: 20.7-21.6) in the high-income group (see Table 2).

Men showed a greater reduction than women in the life expectancy associated with a diagnosis of any mental disorder, regardless of income: 7.2 years (95% CI: 7.1-7.3) vs. 5.7 years (95% CI: 5.6-5.8) in the low-income group, 8.6 years (95% CI: 8.5-8.7) vs. 6.3 years (95% CI: 6.2-6.4) in the medium-income group, and 9.6 years (95% CI: 9.4-9.9) vs. 6.7 years (95% CI: 6.5-6.9) in the high-income group (see also supplementary information).

For natural causes of death, a socioeconomic gradient for differences in mortality rates was observed in both sexes: 21.1 per 1,000 person-years (95% CI: 20.7-21.5) for men and 14.5 per 1,000 person-years (95% CI: 14.2-14.8) for women in the low-income group; 15.0 (95% CI: 14.7-15.2) and 11.8 (95% CI: 11.6-12.0) in the medium-income group; 13.6 (95% CI: 13.2-14.0) and 10.8 (95% CI: 10.5-11.1) in the high-income group.

The pattern of socioeconomic differences in mortality measures was largely the same across age groups, although mortality rate differences were less pronounced among individuals younger than 30 years (see supplementary information).

The mortality rate differences further adjusted for physical diseases at baseline were slightly attenuated compared with the main analyses, but the overall socioeconomic patterns remained similar (see supplementary information). All sensitivity analyses provided results broadly comparable to those from the main analyses (see supplementary information).

Table 2 Mortality rates related to mental disorders according to baseline income categories

	Mortality rates per 1,000 person-years (95% CI)		
	People diagnosed with a mental disorder	**People without a diagnosis**	**Mortality rate difference**
Any mental disorder			
All-cause mortality			
Low	34.2 (34.0-34.5)	14.7 (14.6-14.7)	19.6 (19.3-19.8)
Medium	25.3 (25.1-25.4)	10.7 (10.7-10.8)	14.5 (14.4-14.7)
High	21.5 (21.3-21.7)	8.2 (8.2-8.3)	13.3 (13.0-13.5)
Natural causes			
Low	31.5 (31.2-31.7)	14.1 (14.1-14.2)	17.3 (17.1-17.6)
Medium	23.5 (23.4-23.6)	10.4 (10.4-10.4)	13.1 (13.0-13.3)
High	19.9 (19.7-20.2)	7.9 (7.9-8.0)	12.0 (11.8-12.2)
External causes			
Low	2.7 (2.6-2.7)	0.5 (0.5-0.5)	2.1 (2.1-2.2)
Medium	1.8 (1.8-1.8)	0.4 (0.4-0.4)	1.5 (1.4-1.5)
High	1.7 (1.6-1.7)	0.3 (0.3-0.3)	1.4 (1.3-1.5)
Organic disorders			
All-cause mortality			
Low	38.7 (38.3-39.2)	16.4 (16.4-16.5)	22.3 (21.8-22.8)
Medium	32.5 (32.2-32.7)	11.4 (11.3-11.4)	21.1 (20.8-21.4)
High	29.7 (29.3-30.2)	8.6 (8.5-8.6)	21.2 (20.7-21.6)
Natural causes			
Low	36.7 (36.3-37.2)	15.6 (15.6-15.7)	21.1 (20.6-21.6)
Medium	31.0 (30.7-31.3)	10.9 (10.9-10.9)	20.1 (19.8-20.4)
High	28.4 (28.0-28.9)	8.2 (8.2-8.3)	20.2 (19.8-20.6)
External causes			
Low	2.1 (2.0-2.3)	0.8 (0.8-0.8)	1.3 (1.2-1.5)
Medium	1.5 (1.5-1.6)	0.5 (0.5-0.5)	1.1 (1.0-1.1)
High	1.4 (1.2-1.5)	0.3 (0.3-0.4)	1.0 (0.9-1.1)
Substance use disorders			
All-cause mortality			
Low	59.5 (58.8-60.2)	16.0 (15.9-16.1)	43.5 (42.8-44.2)
Medium	39.7 (39.2-40.2)	11.7 (11.7-11.7)	28.0 (27.5-28.5)
High	31.3 (30.4-32.2)	8.9 (8.9-9.0)	22.4 (21.4-23.3)
Natural causes			
Low	52.6 (51.9-53.2)	15.4 (15.3-15.4)	37.2 (36.6-37.9)
Medium	35.0 (34.5-35.4)	11.3 (11.2-11.3)	23.7 (23.2-24.2)
High	27.2 (26.3-28.1)	8.6 (8.6-8.6)	18.6 (17.7-19.5)
External causes			
Low	6.0 (5.8-6.2)	0.6 (0.6-0.6)	5.3 (5.1-5.5)
Medium	4.4 (4.2-4.5)	0.4 (0.4-0.4)	4.0 (3.8-4.1)
High	4.2 (3.8-4.5)	0.3 (0.3-0.3)	3.8 (3.5-4.2)

Table 2 Mortality rates related to mental disorders according to baseline income categories *(continued)*

	Mortality rates per 1,000 person-years (95% CI)		
	People diagnosed with a mental disorder	**People without a diagnosis**	**Mortality rate difference**
Schizophrenia and related disorders			
All-cause mortality			
Low	38.8 (38.2-39.4)	16.8 (16.7-16.9)	22.0 (21.4-22.6)
Medium	29.0 (28.5-29.4)	11.9 (11.8-11.9)	17.1 (16.7-17.6)
High	21.0 (20.2-21.9)	9.0 (9.0-9.1)	12.0 (11.2-12.8)
Natural causes			
Low	34.4 (33.8-35.0)	16.1 (16.0-16.1)	18.4 (17.8-19.0)
Medium	26.0 (25.6-26.4)	11.4 (11.4-11.4)	14.6 (14.2-15.0)
High	18.2 (17.4-19.0)	8.7 (8.6-8.7)	9.5 (8.8-10.3)
External causes			
Low	3.9 (3.7-4.1)	0.7 (0.7-0.8)	3.2 (3.0-3.4)
Medium	2.9 (2.7-3.0)	0.5 (0.5-0.5)	2.4 (2.3-2.6)
High	2.9 (2.6-3.2)	0.4 (0.3-0.4)	2.5 (2.2-2.9)
Bipolar disorder			
All-cause mortality			
Low	35.1 (34.0-36.2)	17.2 (17.1-17.3)	17.9 (16.8-19.0)
Medium	26.1 (25.5-26.8)	12.0 (11.9-12.0)	14.2 (13.5-14.8)
High	19.4 (18.4-20.4)	9.1 (9.0-9.1)	10.4 (9.4-11.3)
Natural causes			
Low	31.3 (30.3-32.3)	16.4 (16.3-16.4)	14.9 (13.9-16.0)
Medium	23.2 (22.7-23.8)	11.5 (11.5-11.5)	11.8 (11.2-12.3)
High	17.2 (16.3-18.1)	8.7 (8.7-8.7)	8.5 (7.6-9.4)
External causes			
Low	3.9 (3.6-4.3)	0.8 (0.8-0.8)	3.3 (2.8-3.5)
Medium	3.1 (2.9-3.4)	0.5 (0.5-0.5)	2.7 (2.4-2.9)
High	2.5 (2.1-2.9)	0.4 (0.4-0.4)	2.2 (1.8-2.6)
Depression			
All-cause mortality			
Low	28.3 (27.9-28.7)	16.8 (16.8-16.9)	11.5 (11.1-11.9)
Medium	21.5 (21.3-21.7)	11.7 (11.7-11.7)	9.8 (9.6-10.0)
High	17.6 (17.2-17.9)	8.9 (8.8-8.9)	8.7 (8.4-9.1)
Natural causes			
Low	25.8 (25.4-26.1)	16.1 (16.0-16.1)	9.7 (9.3-10.1)
Medium	19.6 (19.4-19.8)	11.3 (11.2-11.3)	8.3 (8.1-8.5)
High	15.8 (15.5-16.2)	8.5 (8.5-8.6)	7.3 (7.0-7.6)
External causes			
Low	2.7 (2.6-2.8)	0.8 (0.7-0.8)	1.9 (1.8-2.1)
Medium	2.1 (2.0-2.2)	0.4 (0.4-0.4)	1.7 (1.6-1.8)
High	2.0 (1.9-2.1)	0.3 (0.3-0.3)	1.7 (1.6-1.8)

Table 2 Mortality rates related to mental disorders according to baseline income categories *(continued)*

	Mortality rates per 1,000 person-years (95% CI)		
	People diagnosed with a mental disorder	**People without a diagnosis**	**Mortality rate difference**
Anxiety-related disorders			
All-cause mortality			
Low	33.0 (32.5-33.4)	16.6 (16.5-16.7)	16.4 (15.9-16.8)
Medium	23.0 (22.7-23.2)	11.7 (11.7-11.8)	11.2 (11.0-11.5)
High	17.9 (17.4-18.3)	8.9 (8.9-9.0)	8.9 (8.5-9.4)
Natural causes			
Low	29.5 (29.1-29.9)	15.9 (15.8-15.9)	13.6 (13.2-14.0)
Medium	20.6 (20.4-20.8)	11.3 (11.3-11.3)	9.3 (9.1-9.5)
High	15.6 (15.2-16.0)	8.6 (8.6-8.6)	7.0 (6.6-7.4)
External causes			
Low	3.1 (3.0-3.2)	0.7 (0.7-0.7)	2.4 (2.3-2.5)
Medium	2.3 (2.2-2.3)	0.4 (0.4-0.4)	1.8 (1.8-1.9)
High	2.2 (2.1-2.4)	0.3 (0.3-0.3)	1.9 (1.7-2.1)
Personality disorders			
All-cause mortality			
Low	36.3 (35.8-36.9)	16.7 (16.7-16.8)	19.6 (19.1-20.2)
Medium	23.3 (22.9-23.6)	11.9 (11.8-11.9)	11.4 (11.1-11.8)
High	16.6 (15.9-17.2)	9.0 (9.0-9.1)	7.5 (7.0-8.2)
Natural causes			
Low	32.4 (31.9-32.9)	16.0 (15.9-16.1)	16.4 (16.0-16.9)
Medium	20.8 (20.5-21.1)	11.4 (11.4-11.4)	9.4 (9.1-9.7)
High	14.5 (13.9-15.0)	8.7 (8.6-8.7)	5.8 (5.2-6.4)
External causes			
Low	3.6 (3.5-3.8)	0.7 (0.7-0.8)	2.9 (2.7-3.1)
Medium	2.5 (2.4-2.6)	0.5 (0.4-0.5)	2.0 (1.9-2.2)
High	2.2 (2.0-2.4)	0.4 (0.3-0.4)	1.9 (1.6-2.1)

DISCUSSION

This population-based study, using 21-year longitudinal data concerning the entire population in Denmark (5.3 million), provides a comprehensive description of socioeconomic differences in life expectancy and mortality rates in people with mental disorders. The association between mental disorders and mortality is well documented[2,3], but our study extended this evidence by exploring several aspects that had not been previously considered[14], including differences in absolute and relative measures of mortality according to SEP, and considering both external and natural causes of death, different types of mental disorders, and variations according to sex and age.

Overall, our findings indicate that people with mental disorders have a life expectancy 6-8 years shorter than the general population at comparable income levels. Mortality rate differences increase as income decreases. Notably, people with a mental disorder and the highest income level still have higher mortality rates than those in the general population with the lowest income level.

Although studies have examined specific disorders (primarily schizophrenia and depression), our results provide what is, to our knowledge, the first evidence that people with all examined types of mental disorders have a shorter life expectancy for all causes and natural causes, regardless of SEP. These patterns were observed in both men and women, and across all age groups. Deaths due to natural causes had the greatest contribution to the mortality rate differences for people with mental disorders in the lowest SEP group, but this disparity decreased with increasing SEP.

In the analyses with adjustment for prior physical diseases, the overall findings were unchanged. However, it is important to note that mental disorders typically have their onset at a younger age than most physical diseases, and the importance of these latter diseases for natural causes of death might be more relevant after the onset of a mental disorder (i.e., physical diseases would be on

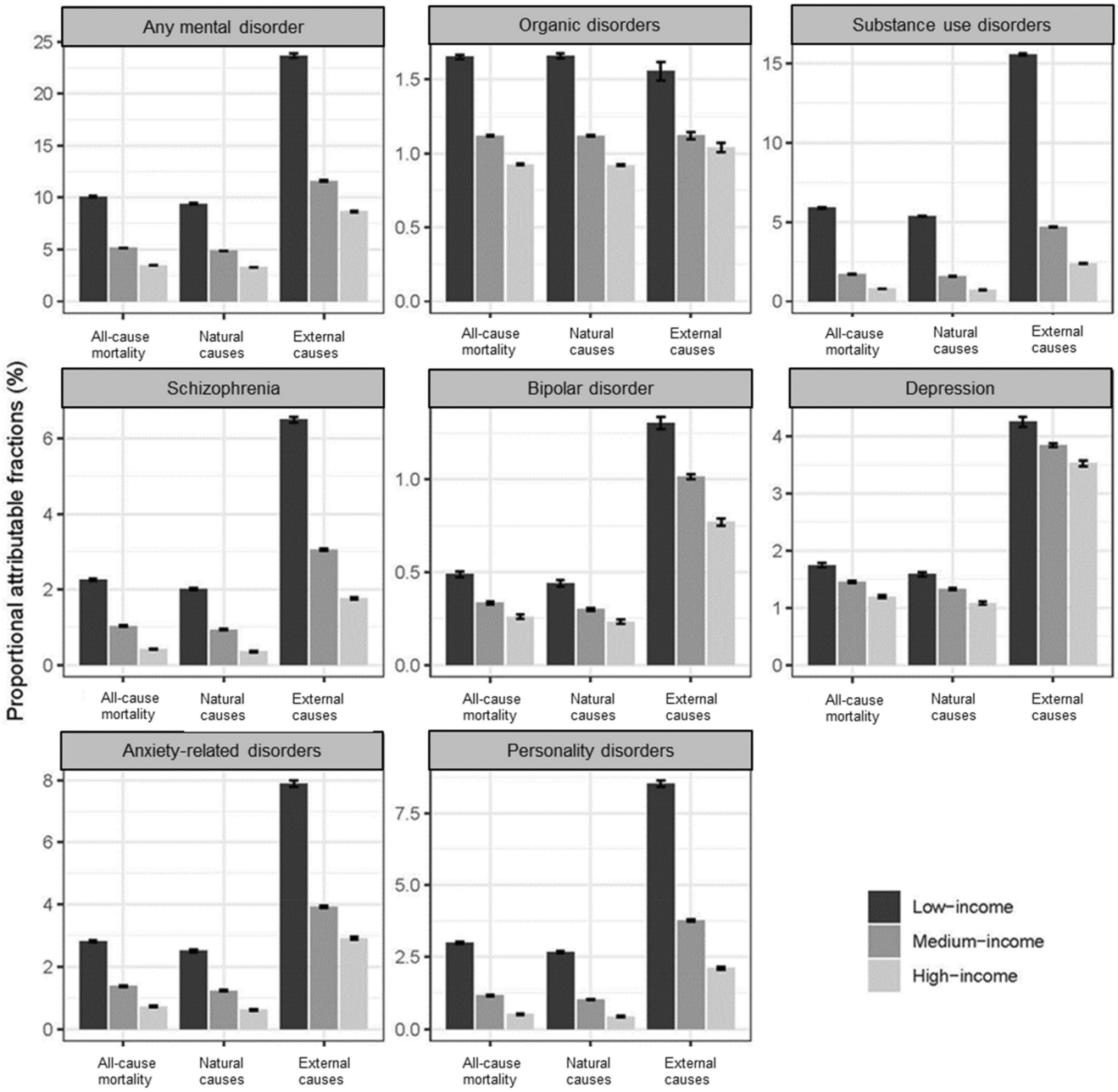

Figure 3 Proportions of all-cause and cause-specific mortality attributable to each type of mental disorder, according to baseline income categories

the pathway between mental disorders and mortality)[31]. Other possible mediators are the inadequate health literacy[32] and the limited access to medical care[33]. One previous study[33] has indicated a social gradient favoring people with high SEP in mental health services in all areas of Denmark, which may potentially aggravate socioeconomic disparities in mortality among individuals with mental disorders. The impact of SEP on access to mental health services could be even higher in countries which, differently from Denmark, do not have free health care at the point of access.

For external causes, the differences in mortality rates observed herein were similar across SEP groups. This finding is broadly consistent with a few previous studies[14], although only one study has provided absolute mortality estimates. In that study[34], the authors found that people in Western China diagnosed with schizophrenia with medium-to-high education levels had six more years lost due to suicide than those who had low education levels. The reason for this finding might be a greater mental health self-stigma among people with higher SEP, leading to delayed diagnosis and treatment[35].

One notable exception from the general socioeconomic pattern was observed for organic disorders, which showed similar mortal-

ity rates for people diagnosed across SEP groups. These disorders typically have an onset at older ages and thus might have minimal relationships (if any) with income, due to pension schemes set before retirement age. Additionally, people surviving to older ages have greater homogeneity in health-related characteristics than younger people[36].

The use of population-based register data allowed us to capture SEP information for all residents, and collect detailed, accurate information on both mental disorder diagnoses and mortality[37-39]. However, this study has some limitations. First, people with mental disorders were identified according to diagnostic information from secondary health care settings; thus, our findings might not be applicable to less severe mental disorders that do not require psychiatrist visits, or are treated in primary care[40]. Additionally, the register data do not contain information on disease course, severity or recovery; thus, we considered mental disorders as homogeneous chronic conditions. Moreover, bias related to left truncation occurs in register-based research when individuals had a diagnosis prior to the start of the available data period, and this limitation is likely more important in the older population.

Second, SEP might have been subject to misclassification. For retired individuals, tax-reported income might not be a valid representation of the available monetary resources[41]. Third, SEP was measured at a single time point for all individuals; therefore, our results cannot offer insights into dynamic changes in inequalities over time. Finally, our findings related to socioeconomic inequalities are likely to be generalizable to countries in which similar welfare systems exist, but less generalizable to low- and medium-income countries, and countries without universal health care, in which the scale of inequalities could be even larger.

We believe that our findings will help inform health care planning and clinical decision-making in several ways. Most importantly, they clearly show that people with mental disorders and low SEP are at the highest risk of deaths from natural causes. The coexistence of mental disorders and physical diseases is a common clinical problem and a challenge for health care systems worldwide[42]. There is a pressing need for integrated strategies to manage these comorbidities in health care systems[43], and it is essential to ensure an inclusive, accessible and effective approach for those with low SEP.

Our study also has important research implications. First, when examining excess mortality in people with mental disorders, it is necessary to account for socioeconomic factors, and to consider natural and external causes of death separately, as our results show different patterns for these causes. Future studies could examine more detailed causes of death. Second, most studies to date exclusively report excess mortality using relative measures of association (e.g., odds, risk or hazard ratios)[14]. To reduce reporting biases, improve transparency and enhance the implications for evidence-based policies and clinical practice, future research should follow the existing recommendations[44] by reporting socioeconomic inequalities in both absolute and relative scales.

In conclusion, people diagnosed with mental disorders have higher mortality rates and shorter life expectancy than even the general population with the lowest SEP levels. The elevated absolute differences in mortality rates due to natural causes in the low SEP group highlight the greater need for coordinated care of physical comorbidities for people with mental disorders and low SEP. Future research is needed to understand the underlying mechanisms and potential differential SEP roles in various causes of death.

ACKNOWLEDGEMENTS

This project was supported by Independent Research Fund Denmark (grant no. 1030-00085B). O. Plana-Ripoll also received funding from Independent Research Fund Denmark (grant no. 2066-00009B) and the Lundbeck Foundation (grant no. R345-2020-1588). C. Hakulinen was supported by the Research Council of Finland (Academy Research Fellowship 354237) and the European Union (ERC, MENTALNET, 101040247). The funders had no role in the design and conduct of the study, analyses, interpretation of data, or decision to submit the manuscript for publication. Supplementary information on this study is available at https://osf.io/h7ja6.

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DOI:10.1002/wps.21278

Excess cardiometabolic risk in children and adolescents initiating antipsychotic treatment compared to young adults: results from a nationwide cohort study

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Antipsychotic treatment is associated with cardiometabolic risks that may be especially detrimental to children and adolescents. In this Danish population-based cohort study, we included individuals with psychiatric diagnoses who initiated antipsychotics in 2000-2021 at age 6-31 years. We assessed the risk of cardiometabolic adverse events up to 10 years following incident exposure to antipsychotics, compared to age- and sex-matched unexposed individuals with psychiatric diagnoses. Cox regression models were used to calculate hazard ratios (HRs) after adjustment using high-dimensional propensity scores, including age, sex, calendar time, hospital diagnoses, and prescription drug use. HRs were compared between incident exposure in youths (6-17 years) and young adults (18-31 years), and between incident exposure in children (6-11 years) and adolescents (12-17 years). The total cohort consisted of 335,093 individuals, including 36,092 subjects exposed to antipsychotics (children and adolescents: 8,547, mean follow-up: 6.8±3.2 years; young adults: 27,545, mean follow-up: 6.5±3.4 years) and 299,001 age-, sex- and calendar-matched unexposed subjects. The incidence rate of cardiometabolic events was higher for young adults initiating antipsychotics than for children and adolescents (23.2 vs. 14.1 events/1,000 person-years). However, the adjusted excess risk of cardiometabolic events was significantly higher in exposed compared to unexposed children and adolescents (HR=1.87, 95% CI: 1.71-2.05) than in exposed compared to unexposed young adults (HR=1.46, 95% CI: 1.40-1.51) (p<0.001). The excess risk of cardiometabolic events was even higher when antipsychotic treatment was initiated before age 12 years (HR=2.44; 95% CI: 1.99-2.98) than at age 12-17 years (HR=1.69, 95% CI: 1.52-1.87) (p=0.012). Concerning specific cardiometabolic outcomes, there was an effect of age at antipsychotic initiation on the risks of metabolic syndrome (p=0.011) and obesity (p<0.001), that were higher among children and adolescents than young adults. Thus, initiation of antipsychotic treatment before age 18 years is associated with an excess risk of cardiometabolic events compared to age- and sex-matched youths with psychiatric disorders but unexposed to antipsychotics. The excess cardiometabolic risk is significantly higher than that of individuals who start antipsychotic treatment in early adulthood, and significantly higher for treatment onset in childhood compared to adolescence. On the basis of these findings, recommendations are provided about the use of antipsychotics in children and adolescents.

Key words: Cardiometabolic adverse events, antipsychotics, children, adolescents, excess risk, metabolic syndrome, obesity

(World Psychiatry 2025;24:103–112)

The incidence of diagnosed mental disorders in children and adolescents ("youths") is rising[1,2]. This leads, in this age group, to a higher global health burden[1] and an increased utilization of psychotropic drugs, including antipsychotics[3,4], as reflected in various international studies (e.g., from Japan[5], the US[6-8], the UK[9] and Denmark[10]).

The increased use of antipsychotics in youths may partly reflect appropriate treatment, following efficacy data and approved indications such as schizophrenia, bipolar mania, bipolar depression, disruptive behavior disorders, and Tourette's syndrome[11-22]. However, off-label use of these medications among youths is considerable[23,24]. For example, they may be used to target agitation, irritability or self-injurious behavior in children and adolescents with conditions such as intellectual disability and autism spectrum disorders[3].

In a study including inpatients and outpatients below age 18 years from Denmark, 95.6% of antipsychotic prescriptions were off-label, primarily with lower age than indicated, but also with other indications than approved, and to a lesser degree with higher dosages or longer treatment duration than approved[24].

The adverse effects of antipsychotics are possibly enhanced in children and adolescents[25-32], and their insufficient monitoring in clinical care[33-36] has caused concern about the increasing and/or long-term use of these medications in youths[37-41].

Weight gain and metabolic abnormalities are among the most concerning antipsychotic-related adverse effects, due to the potentially life-shortening consequences of cardiometabolic disorders[42-45]. Antipsychotic-induced weight gain is very common, although to varying degrees and depending on the specific antipsychotic[46,47]. In children and adolescents, considerable weight gain has been observed not only with antipsychotics traditionally regarded as having high risk of cardiometabolic side effects (e.g., olanzapine), but also with those considered to have a lower risk (e.g., aripiprazole)[48-50].

Along with the physical impact of antipsychotic-related side effects, there is also an impact on mental well-being and functionality that youths and their carers have voiced as a potentially impairing aspect of their living with a mental disorder[51], such as feeling

stigmatized by slowed physical mobility or being bullied for obesity. These effects can lead to decreased medication adherence, even when the antipsychotic treatment is effective[52,53].

The above concerns about weight gain and metabolic abnormalities are mirrored by reports indicating that body mass index (BMI) in childhood and adolescence is a strong predictor of BMI as well as coronary heart disease in adulthood[54]. Notably, the risk of diabetes mellitus or coronary heart disease in adulthood remains significantly higher in people who have been overweight or obese as children or adolescents even after weight loss or normalization of body weight, compared to individuals without abnormal body weight status during development[55].

In this context, children and adolescents treated with antipsychotics have a 2.5-3-fold increased risk for type 2 diabetes mellitus compared with age-matched general population samples, with such risk still being 1.8-2.0 fold higher compared to youths with mental disorders but without antipsychotic exposure[56]. Moreover, brains of youths with first-episode psychosis receiving antipsychotic treatment, as measured by magnetic resonance imaging scans, have been reported to age by one additional month per year for each additionally gained BMI point[57].

On the basis of this evidence, a general increase in use of antipsychotics among youths[7,8], even at lower doses, is concerning. Mental disorders are detected increasingly at an earlier age[58], hopefully improving prognosis, but in parallel enhancing the potential long-term risks of medications.

The hypothesis of an increased excess population-adjusted risk for cardiometabolic events following antipsychotic exposure during youth versus adulthood can only be tested in large-scale prospective database studies. Accordingly, in a Danish nationwide register-based cohort study, we compared cardiometabolic events between exposed individuals who initiated antipsychotic treatment at different time points in life and unexposed individuals, considering a large number of potential covariates. Additionally, we examined outcomes in relation to different exposure levels.

METHODS

We conducted a nationwide cohort study, using Danish health care registers, to examine the risk of cardiometabolic events with initiation of antipsychotics in childhood or adolescence (6-17 years) versus in early adulthood (18-31 years). The study is reported in accordance with the RECORD-PE guidelines[59].

Data sources

We used nationwide Danish health care register data covering the period between January 1, 2000 and December 31, 2021. Data on the use of antipsychotics and other prescription drugs were obtained from the Danish National Prescription Register, which contains information on all prescription drugs collected at community pharmacies in Denmark from 1994 onwards[60]. Information on somatic and psychiatric diagnoses was derived from the Danish National Patient Register, that holds information on recorded inpatient and outpatient diagnoses from 1995 onwards[61]. Information on vital status, cause of death, and sociodemographic factors was collected from the Danish Cause of Death Register and the registers of Statistics Denmark[62,63] (see also supplementary information).

The use of de-identified data for this project was approved by the Capital Region of Denmark (P-2022-307) and Statistics Denmark (706672).

Study population

Exposed individuals were 6-31 years old at their first prescription fill for an antipsychotic drug ("index date") and had ≥1 recorded mental disorder according to the ICD-10 prior to this incident prescription fill. We excluded individuals with diagnoses of malignant neoplasms, tuberculosis and/or human immunodeficiency virus (HIV) infection before the index date, as these diseases or their treatments may elevate the risk of later cardiovascular disorders.

We created a control group of individuals with mental disorders, but without antipsychotic use ("unexposed"). For each exposed individual, we randomly selected up to 10 unexposed individuals of the same sex and birth-year using risk-set sampling (i.e., allowing for controls to become cases later). The index date of the exposed individuals was used as the index date for the corresponding unexposed individuals. The control group was required to fulfill the same inclusion and exclusion criteria as exposed individuals (except for antipsychotic prescription fills). Specific diagnostic codes used in the selection of the cohort are provided in the supplementary information.

Outcomes

The primary outcome was any cardiometabolic event, defined by either first occurrence of a relevant diagnosis in the Danish National Patient Register (e.g., obesity, ischemic heart disease, stroke, diabetes) or a prescription fill for an associated relevant medication in the Danish National Prescription Register (e.g., glucose- or lipid-lowering drug). Secondary outcomes were clusters of the individual outcomes (e.g., heart disease), and death from cardiovascular causes. Codes used for outcome definitions are provided in the supplementary information.

Antipsychotic exposure

To estimate the duration of antipsychotic exposure, the coverage of a given prescription was estimated for each individual using the PRE2DUP algorithm[64]. As antipsychotics are generally supplied during hospital admissions, the number of hospital days was subtracted from the interval between prescriptions filled at community pharmacies, to avoid underestimation of the

average dose. Intervals between prescription fills were adjusted using expert-defined values for plausible maximum/minimum average daily doses, if they resulted in average doses higher/lower than these plausible values (e.g., average doses of quetiapine above 1,200 mg/day or lower than 12.5 mg/day)[64].

For analyses of the cardiometabolic risk with various types of antipsychotics, we classified them as having low risk (e.g., haloperidol, ziprasidone, lurasidone, aripiprazole, cariprazine, brexpiprazole) versus high risk (e.g., levomepromazine, chlorprothixene, clozapine, olanzapine) of weight gain and metabolic disturbances[49]. Antipsychotic polypharmacy was defined as concomitant use of ≥2 antipsychotics for ≥60 days.

Cumulative dose was expressed as defined daily doses (DDDs) according to the World Health Organization's ATC/DDD-system[65]. As an example, one DDD equals 5 mg risperidone, 10 mg olanzapine, or 400 mg quetiapine.

Follow-up

Individuals were followed up from day 31 after the index date (to avoid events potentially unrelated to treatment) until they experienced the outcome, emigrated, died, had reached 10 years of consecutive follow-up, or reached the end of data availability (December 31, 2021), whichever came first. Additionally, individuals in the unexposed group were censored if and when they filled a prescription for an antipsychotic drug.

Statistical analysis

To control for potential confounders before assessing the impact of antipsychotic treatment and exposure age on outcomes, we used propensity-score weighting. We employed a high-dimensional propensity score algorithm to identify the 100 most influential covariates regarding potential bias[66]. The algorithm assessed all hospital diagnoses and prescription fills in the 365 days preceding the index date. Hereafter, propensity scores were estimated using a logistic regression model including sex, age, year of cohort entry, and these 100 covariates (see supplementary information for specific covariates). After trimming the non-overlapping parts of the propensity-score distribution, fine-stratification weights were calculated by constructing ten propensity-score strata and weighting the unexposed individuals according to the distribution of the exposed individuals within these strata (see also supplementary information). Covariate balance was assessed using standardized mean differences (SMDs), with SMDs ≤0.2 indicating adequate balance[67].

We determined various baseline characteristics of the study population, including the most frequent psychiatric diagnoses and filled non-antipsychotic psychotropic drugs. Next, we assessed crude incidence rates of cardiometabolic events among the exposed and unexposed individuals. We then calculated hazard ratios (HRs) with 95% confidence intervals (CIs) using Cox proportional hazard regression models adjusted for baseline confounders using the fine-stratification weights. HRs were estimated separately for each age group (6-17 and 18-31 years), and a potential effect of age at antipsychotic initiation was tested in a model including an interaction term between antipsychotic exposure and age group.

We conducted five sensitivity analyses to identify factors potentially affecting our results: a) requiring ≥1 additional prescription fill for an antipsychotic within 180 days of the index date, to reduce exposure misclassification from minimal or no exposure to antipsychotics; b) requiring ≥12 months of steady treatment with antipsychotics after the index date (with follow-up starting at day 366), to further reduce exposure misclassification; c) restricting follow-up to time-on-treatment plus an additional follow-up of ≥6 months to capture outcomes potentially related to treatment, but first identified/diagnosed closely after the treatment discontinuation; d) using propensity-score matching instead of weighting to assess the impact of this data analysis choice; and e) restricting maximum follow-up from 10 to 1, 2 and 5 years to assess the impact of follow-up on outcomes. All analyses were adjusted for baseline confounders using fine-stratification weights/propensity scores (see also supplementary information).

In subgroup analyses, we tested the potential influence of sex (male/female), initiation of treatment in childhood vs. adolescence (6-11 vs. 12-17 years), having a schizophrenia-spectrum diagnosis, and recent inpatient contacts. The latter two analyses were conducted *post-hoc*, as the exposed and unexposed groups differed on these characteristics.

To further examine the importance of exposure levels of antipsychotics for the development of cardiometabolic events, we also conducted a case-control study nested within the cohort of individuals exposed to antipsychotic drugs. We used conditional logistic regression analyses to estimate odds ratios (ORs) for the outcomes based on various exposure levels. This included cumulative duration of exposure, cumulative DDDs, use of antipsychotics with high risk of weight gain and metabolic deviations, and exposure to antipsychotic polypharmacy. We estimated ORs separately for individuals aged 6-17 years and 18-31 years at antipsychotic initiation. A potential effect of age at antipsychotic initiation was tested by including a case-age group interaction term in the logistic regression models.

Analyses were adjusted for age, sex and calendar year by matching; and additionally adjusted for family income (in the year before the index date), family history of cardiometabolic outcomes, and use of other psychotropic medications associated with weight gain (valproic acid, lithium, paroxetine, mirtazapine, and tricyclic antidepressants) or weight loss (topiramate, zonisamide, bupropion, stimulants, and atomoxetine). All analyses were conducted using STATA, release 18.0 (StataCorp, College Station, TX, USA).

RESULTS

The total cohort included 335,093 individuals, of whom 36,092 were exposed to antipsychotics and 299,001 were unexposed. Among the exposed individuals, 8,547 were aged 6-17 years and 27,545 were aged 18-31 years (see Figure 1).

The total follow-up in the cohort was 1,901,579 person-years, including 236,311 person-years among individuals exposed to antipsychotics and 1,665,268 person-years in the unexposed population. The mean duration of follow-up was 6.8±3.2 years among youths exposed to antipsychotics and 6.5±3.4 years among exposed young adults. The most common reason for censoring was end of data availability (see supplementary information).

All baseline characteristics were reasonably balanced between exposed and unexposed individuals after fine-stratification weighting, except that the former were more likely to have had recent inpatient contacts (40.2% vs. 17.1%) (see Table 1). In the exposed group, the most common psychiatric diagnosis before the index date was major depressive disorder (N=6,734, 18.6%), followed by personality disorders (N=4,388, 12.1%), substance use disorders (N=4,431, 12.3%), schizophrenia and other psychoses (N=3,845, 10.6%), anxiety disorders (N=3,163, 8.8%), attention-deficit hyperactivity disorder (N=3,101, 8.6%), autism (N=2,630, 7.3%), eating disorders (N=1,236, 3.4%), bipolar disorder (N=1,159, 3.2%), intellectual disability (N=1,153, 3.2%), and post-traumatic stress disorder (N=536, 1.5%).

The antipsychotics most frequently used among youths were quetiapine (N=3,732, 43.7%), risperidone (N=3,573, 41.8%), chlorprothixene (N=2,979, 34.8%), aripiprazole (N=2,752, 32.2%) and olanzapine (N=1,202, 14.1%). The antipsychotics most frequently used among adults were the same: quetiapine (N=16,803, 61.0%), chlorprothixene (N=9,841, 35.7%), risperidone (N=5,782, 21.0%), olanzapine (N=5,219, 18.9%) and aripiprazole (N=4,878, 17.7%) (see also supplementary information).

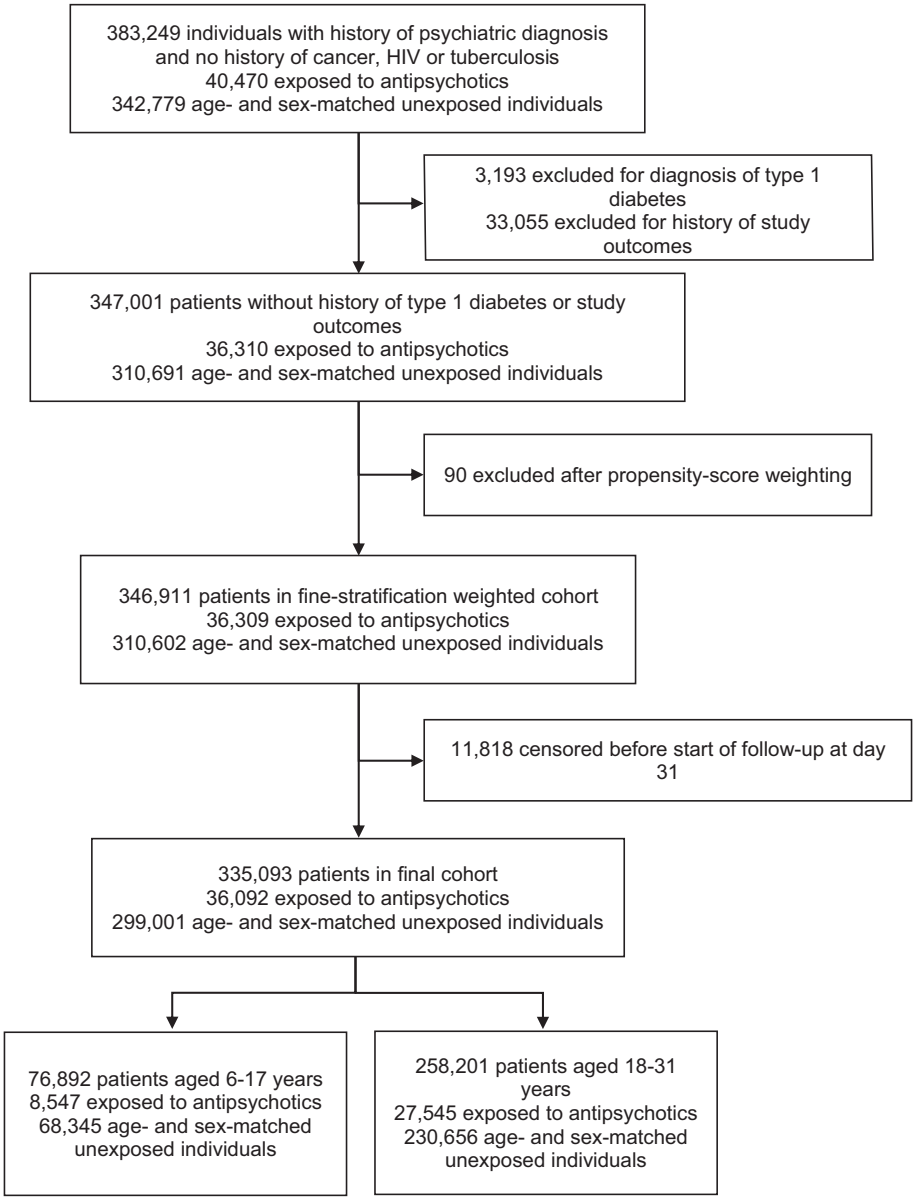

Figure 1 Flow chart of cohort selection

Table 1 Selected baseline characteristics of participants exposed and unexposed to antipsychotics

			Standardized mean difference	
	Exposed (N=36,092)	Unexposed (N=299,001)	Before weighting	After weighting
Sex, N (%)				
Males, N (%)	18,504 (51.3)	152,578 (51.0)		
Females, N (%)	17,588 (48.7)	146,423 (49.0)	<0.01	0.01
Age (years)				
Median (IQR)	22 (18-26)	22 (18-27)	0.04	0.03
6-11 years, N (%)	1,803 (5.0)	15,328 (5.1)	0.01	0.03
12-17 years, N (%)	6,744 (18.7)	53,025 (17.7)	0.02	0.03
18-23 years, N (%)	13,419 (37.2)	107,160 (35.8)	0.03	0.01
24-31 years, N (%)	14,126 (39.1)	123,512 (41.3)	0.04	0.02
Family income, N (%)				
1st quartile (lowest)	12,478 (34.6)	75,473 (25.2)	0.20	0.13
2nd quartile	8,711 (24.1)	72,728 (24.3)	0.00	0.02
3rd quartile	7,463 (20.7)	73,084 (24.4)	0.09	0.05
4th quartile (highest)	7,440 (20.6)	77,716 (26.0)	0.13	0.11
Year of cohort entry, N (%)				
2000-2003	4,613 (12.8)	39,122 (13.1)	0.01	0.02
2004-2009	8,436 (23.4)	67,197 (22.5)	0.02	0.01
2010-2015	11,639 (32.2)	91,501 (30.6)	0.04	0.01
2016-2021	11,404 (31.6)	101,181 (33.8)	0.05	0.01
Psychotropic drug use before index-date, N (%)				
Antidepressants	13,514 (37.4)	43,199 (14.4)	0.54	0.03
Anxiolytics	3,724 (10.3)	8,106 (2.7)	0.31	0.04
Hypnotics	6,244 (17.3)	14,763 (4.9)	0.40	0.02
Lithium	227 (0.6)	316 (0.1)	0.09	0.05
Antiepileptics	2,409 (6.7)	8,103 (2.7)	0.19	<0.01
Stimulants	3,994 (11.1)	20,273 (6.8)	0.15	0.09
Drugs used in addictive disorders	834 (2.3)	2,241 (0.7)	0.13	0.07
Other drug use before index date, N (%)				
Glucocorticoids	513 (1.4)	4,079 (1.4)	<0.01	0.02
Thyroid therapy	181 (0.5)	1,511 (0.5)	<0.01	0.01
Smoking before index date, N (%)	2,803 (7.8)	20,175 (6.7)	0.04	<0.01
Alcohol misuse before index date, N (%)	2,060 (5.7)	12,241 (4.1)	0.07	0.04
Health care use before index date, N (%)				
Inpatient contacts	14,504 (40.2)	51,199 (17.1)	0.53	0.19
Outpatient contacts	17,435 (48.3)	86,598 (29.0)	0.41	0.04
Emergency room visits	21,905 (60.7)	111,873 (37.4)	0.48	0.07

IQR – interquartile range

Risk of any cardiometabolic event

Among the 6-17-year-old youths exposed to incident antipsychotic use, 813 had recorded cardiometabolic events, representing a crude incidence rate of 14.1 events/1,000 person-years of follow-up, compared to 6.4 events/1,000 person-years among unexposed youths. Both unadjusted and adjusted HRs indicated an association between antipsychotic initiation and cardiometabolic events, compared to non-use (adjusted HR, aHR=1.87, 95% CI: 1.71-2.05) (see Table 2). This association persisted when

Table 2 Associations between initiation of antipsychotics in youth versus early adulthood and cardiometabolic events

	Exposed			Unexposed				
	Total (N)	Events (N)	IR (events/1,000 PY)	Total (N)	Events (N)	IR (events/1,000 PY)	Hazard ratio (95% CI)	Test for interaction with age group (p value)
Primary analysis								
Crude								
6-17 years	8,547	813	14.1	68,345	2,277	6.4	2.16 (1.99-2.34)	<0.001
18-31 years	27,545	4,140	23.2	230,656	18,054	13.8	1.68 (1.62-1.73)	
Adjusted after fine-stratification weighting								
6-17 years	8,547	813	14.1	68,345	2,277	6.4	1.87 (1.71-2.05)	<0.001
18-31 years	27,545	4140	23.2	230,656	18,054	13.8	1.46 (1.40-1.51)	
Sensitivity analyses								
Restricting to individuals with >1 prescription								
6-17 years	7,935	718	13.8	63,341	2,133	6.5	1.83 (1.66-2.02)	<0.001
18-31 years	25,841	3,759	23.4	214,755	16,916	13.9	1.47 (1.41-1.53)	
Restricting to individuals with ≥12 months of exposure								
6-17 years	1,187	133	17.0	59,126	1,955	6.5	2.23 (1.86-2.68)	0.002
18-31 years	3,802	682	26.6	200,612	15,617	14.0	1.66 (1.53-1.80)	
Restricting follow-up to time-on-treatment								
6-17 years	8,547	388	16.3	68,345	2,277	6.4	2.21 (1.96-2.49)	<0.001
18-31 years	27,544	1,767	27.3	230,656	18,054	13.8	1.74 (1.65-1.84)	
Propensity-score matched cohort								
6-17 years	8,459	802	14.0	7,431	237	7.8	1.79 (1.55-2.07)	0.016
18-31 years	27,270	4,090	23.1	23,148	1,584	15.6	1.47 (1.39-1.56)	
Subgroup analyses (6-17 years only)								
Sex								
Male	4,724	324	9.8	38,864	847	3.9	2.01 (1.74-2.32)	0.28
Female	3,823	489	19.8	29,481	1,430	10.3	1.56 (1.38-1.77)	
Age at initiation								
6-11 years	1,803	169	12.7	15,328	445	4.7	2.44 (1.99-2.98)	0.012
12-17 years	6,744	644	14.5	53,017	1,832	7.0	1.69 (1.52-1.87)	
Schizophrenia-spectrum diagnosis								
Yes	636	81	17.7	507	5	7.2	2.24 (0.91-5.57)	0.7
No	7,911	732	13.7	67,838	2,272	6.4	1.83 (1.66-2.02)	
History of inpatient contacts								
Yes	2,918	322	16.4	9,409	439	10.2	1.62 (1.36-1.93)	0.37
No	5,629	491	12.8	58,936	1,838	5.9	1.89 (1.69-2.11)	

IR – incidence rate, PY – person-years

restricting the cohort to individuals with high-level exposure, defined as refilling prescriptions within the first six months (aHR=1.83, 95% CI: 1.66-2.02), or continuous use of antipsychotics for 12 months following the index date (aHR=2.23, 95% CI: 1.86-2.68).

The incidence rate of cardiometabolic events was higher overall in antipsychotic-exposed young adults than in antipsychotic-exposed youths (23.2 vs. 14.1 events/1,000 person-years). However, the excess risk of cardiometabolic events was significantly higher in exposed youths (aHR=1.87, 95% CI: 1.71-2.05) than in exposed young adults (aHR=1.46, 95% CI: 1.40-1.51) (p<0.001). This finding remained consistent across all sensitivity analyses (see Table 2).

The risk of cardiometabolic events was higher when antipsychotic treatment was initiated before adolescence (6-11 years) than during adolescence (12-17 years) (aHR=2.44, 95% CI: 1.99-2.98 vs. aHR=1.69, 95% CI: 1.52-1.87; p=0.012). The risk did not vary between the sexes or other predefined subgroups (see Table 2).

The risk of cardiometabolic events was higher in exposed youths than in exposed young adults filling prescriptions for antipsychotics at 1 year (aHR=2.16, 95% CI: 1.71-2.73 vs. aHR=1.39, 95% CI: 1.25-1.55; p<0.001); 2 years (aHR=2.00, 95% CI: 1.68-2.37 vs. aHR=1.42, 95% CI: 1.31-1.53, p<0.001); 5 years (aHR=1.96, 95% CI: 1.74-2.20 vs. aHR=1.43, 95% CI: 1.36-1.50, p<0.001) and 10 years (aHR=1.87, 95% CI: 1.71-2.05 vs. aHR=1.46, 95% CI: 1.40-1.51, p<0.001) of follow-up (see supplementary information).

Concerning specific cardiometabolic outcomes, there was an effect of age at antipsychotic initiation on the risks of metabolic syndrome (p=0.011) and obesity (p<0.001), that were higher among youths than young adults (see also supplementary information).

Antipsychotic exposure levels

There was a significant relationship between the cumulative duration of antipsychotic treatment and the risk of cardiometabolic events in both age groups (see Table 3). The risk of cardiometabolic events increased with the cumulative duration of antipsychotic treatment in youths (test for trend: p<0.001). A cumulative duration of 3-5 years was also associated with an increased risk (adjusted OR, aOR=1.29, 95% CI: 1.06-1.58, p=0.013), as well as a cumulative duration >5 years (aOR=1.34, 95% CI: 1.05-1.71, p=0.017). In adults, an increased risk was observed already at 1-2 years of cumulative duration, persisting for all durations (p<0.001) (see Table 3).

A similar pattern was seen when assessing the cumulative dose of antipsychotics (see Table 3). Cumulative doses of >500 DDDs were associated with an increased risk of metabolic events in youths (aOR=1.87, 95% CI: 1.22-2.87, p=0.004), with evidence of increasing risk with increasing doses (test for trend: p<0.001). In adults, this trend was evident already at cumulative doses of 100-200 DDDs (p=0.04), and the test for trend was likewise significant (p<0.001).

An increased risk of cardiometabolic events was seen among youths exposed to antipsychotics with high risk for weight gain and metabolic deviations (aOR=1.36, 95% CI: 1.14-1.62), antipsychotics with low risk (aOR=1.78, 95% CI: 1.53-2.07), and antipsychotic polypharmacy (aOR=1.77, 95% CI: 1.48-2.11). Risks of similar magnitude were, however, also seen among young adults at similar exposure levels (see Table 3).

DISCUSSION

This study revealed an excess risk of cardiometabolic events in individuals who initiated antipsychotic treatment at age 6-17 years compared to unexposed individuals with psychiatric disorders matched by age and sex. This excess risk was higher than in individuals initiating antipsychotics in young adulthood (age 18-31 years) compared to their matched controls. The excess risk observed for youths at an average follow-up of 6.8 years was remarkably stable when considering a wide range of potential confounders and different exposure levels, and after performing various sensitivity analyses; and was driven by an increased risk of metabolic syndrome and obesity. Initiation of antipsychotic treatment in childhood (6-11 years) additionally increased the risk of cardiometabolic events compared to initiation in adolescence (12-17 years).

Additionally, we observed a dose-response relationship, in which a duration of antipsychotic treatment higher than five years significantly increased the risk of cardiometabolic events in youths. This finding indicates that long-term treatment in youths is particularly harmful, but could also reflect the fact that they are more likely to receive low-dose (off-label) treatments that have adverse effects emerging over time.

There is evidence that individuals initiating antipsychotics in childhood or adolescence often have more severe psychiatric disorders[68]. Nevertheless, the use of antipsychotics at such an early age needs to be considered in the context of psychosocial interventions that have been shown to avert, reduce or shorten this use, especially in youths with behavioral and externalizing problems where these medications are commonly administered[15,69-73].

The results of this study are novel and unique. Previous analyses of the association between antipsychotic use and cardiometabolic events mainly relied on observations in adults[46], did not directly compare initiation during childhood or adolescence versus adulthood[74], or did not compare exposure to antipsychotics with non-exposure, resulting in a lack of data on developmental stage-based risk for cardiometabolic events. Therefore, our findings – obtained from a large and generalizable nationwide database with long-term follow-up, using careful propensity-score weighting and yielding robust confirmation across various sensitivity analyses – represent a substantial gain in knowledge.

These results raise considerable concern. First, both metabolic syndrome and obesity are established risk factors for distal coronary heart disease, cerebrovascular events and other severe physical outcomes[49,75]. Second, weight gained during antipsychotic treatment is difficult to lose, even after switching to a medication with lower risk or after stopping antipsychotics altogether[76,77]. Third, obesity during childhood and adolescence predicts obesity and cor-

Table 3 Associations between various antipsychotic drug exposure levels in youth versus early adulthood and cardiometabolic events

	Initiation 6-17 years				Initiation 18-31 years				Test for interaction with age group (p value)
	Cases	Controls	Adjusted OR (95% CI)	p	Cases	Controls	Adjusted OR (95% CI)	p	
Subjects, N	827	17,620			4,206	82,675			
Cumulative duration (years)									
<1	308	7,461	1 (reference)		1,777	40,635	1 (reference)		
1-2	109	2,328	1.09 (0.86-1.39)	0.46	580	10,903	1.25 (1.13-1.38)	<0.001	
3-5	211	4,288	1.29 (1.06-1.58)	0.013	1,012	17,085	1.44 (1.32-1.57)	<0.001	
>5	199	3,543	1.34 (1.05-1.71)	0.017	837	14,052	1.46 (1.33-1.61)	<0.001	
Test for trend				<0.001				<0.001	
Cumulative dose (DDD)									
<10	61	1,513	1 (reference)		252	5,953	1 (reference)		
10-19	101	2,760	0.88 (0.58-1.33)	0.55	679	18,088	0.86 (0.72-1.02)	0.083	
20-49	122	2,963	0.94 (0.63-1.40)	0.75	610	14,027	0.96 (0.81-1.15)	0.69	
50-99	89	2,303	1.30 (0.86-1.96)	0.22	469	9,548	1.12 (0.92-1.36)	0.24	
100-200	106	2,019	1.50 (0.99-2.26)	0.055	425	8,553	1.24 (1.01-1.53)	0.04	
200-500	108	2,325	1.11 (0.72-1.71)	0.63	502	9,333	1.44 (1.19-1.74)	<0.001	
>500	240	3,737	1.87 (1.22-2.87)	0.004	1,269	17,173	1.77 (1.51-2.07)	<0.001	
Test for trend				<0.001				<0.001	
Specific exposures									
Use of high-risk antipsychotic	275	4,950	1.36 (1.14-1.62)	<0.001	1,501	24,607	1.37 (1.28-1.46)	<0.001	0.36
Only use of low-risk antipsychotic	351	5,113	1.78 (1.53-2.07)	<0.001	1,034	14,393	1.59 (1.48-1.71)	<0.001	0.11
Antipsychotic polypharmacy	249	3,493	1.77 (1.48-2.11)	<0.001	1,114	14,653	1.77 (1.64-1.90)	<0.001	0.16

DDD – defined daily dose, OR – odds ratio (adjusted for sex, age, calendar year, family income, family history of metabolic outcomes, use of psychotropic drugs associated with weight loss, and use of psychotropic drugs associated with weight gain)

onary heart disease in adulthood, even if normal weight is recaptured[54,55]. Finally, youths treated with antipsychotics may be reluctant to engage in metabolic monitoring[78], and clinicians' screening approach towards this age group is often unsystematic[79], highlighting the need for improved monitoring practices as part of usual care[33,80].

Results from this study underscore that antipsychotic treatment in children and adolescents should only be initiated: a) after careful consideration of indication, expected benefits and potential side effects; b) when lower-risk treatment options have been exhausted and proven insufficient; c) in conjunction with healthy lifestyle education and, possibly, healthy lifestyle intervention; d) using antipsychotics with lower cardiometabolic risk, first and only for as long and at doses as clinically needed; e) with close monitoring of efficacy and safety, including cardiometabolic risk assessment prior to antipsychotic initiation and routinely thereafter[28,33,81-84]. Furthermore, when cardiometabolic risk factors or abnormalities are identified, switching to a lower-risk antipsychotic or a non-antipsychotic treatment option should be considered inasmuch as possible, healthy lifestyle interventions should be implemented, and medications reducing the cardiometabolic risk – such as metformin and lipid lowering agents – may need to be added.

Among the strengths of the present study are the nationwide cohort design and the completeness of the samples due to free access of patients to national mental health care. In addition, we compared individuals with psychiatric disorders and incident use of antipsychotics not to "healthy controls", but to individuals with psychiatric disorders who were naïve to antipsychotics but not to other psychotropic drugs. However, some limitations must be considered: database studies lack information on disease severity and healthy lifestyle behaviors; and, despite weighting and extensive propensity-score matching, we cannot exclude residual confounding. However, this confounding would apply to all antipsychotic-treated groups, independent of age.

In conclusion, children and adolescents treated with even low-dose antipsychotics have an excess risk for obesity and metabolic syndrome compared to non-exposed age-matched individuals with psychiatric disorders, which is significantly higher than that of adults treated with antipsychotics relative to their age-matched controls. Given the serious long-term consequences of cardiometabolic events, these results warrant additional concern and caution regarding antipsychotic exposure during development than that suggested by a recent study reporting increased mortality related to high-dose antipsychotic treatment in adults but not

in youths[85].

The results of our study have direct clinical relevance, indicating that antipsychotic prescribing in youths should be restricted to on-label or medically unavoidable clinical scenarios; lower cardiometabolic risk antipsychotics should be prioritized whenever possible; monitoring of adverse cardiovascular effects should be conducted routinely; and cardiometabolic abnormalities and risk factors should be targeted and addressed proactively.

ACKNOWLEDGEMENTS

C.U. Correll and H.-C. Steinhausen contributed equally to this work. Supplementary information on this study is available at https://osf.io/d4xch/.

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DOI:10.1002/wps.21279

Augmenting trauma-focused cognitive behavior therapy for post-traumatic stress disorder with memory specificity training: a randomized controlled trial

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Although trauma-focused cognitive behavior therapy (TF-CBT) is the recommended treatment for post-traumatic stress disorder (PTSD), up to one-half of patients do not respond to this intervention. There is an urgent need to develop new strategies to improve treatment response. Training people to recall specific positive memories may augment treatment gains in TF-CBT. We conducted a controlled trial in Australia with current or former first responders (including police, firefighters and paramedics) with PTSD, who were randomized on a 1:1 basis to 12 weekly 90-min individual sessions of either TF-CBT combined with memory specificity training (TF-CBT/MT) or TF-CBT alone. The primary outcome was change in PTSD severity independently assessed at baseline, post-treatment, and six months after treatment (primary outcome timepoint). Secondary outcomes included measures of depression, trauma-related cognitions, alcohol use, and quality of life. Between October 2021 and May 2023, fifty participants were randomized to TF-CBT/MT, and fifty to TF-CBT alone. Most participants were males (71.0%) and the mean age was 46.8±9.9 years. At the 6-month assessment, participants receiving TF-CBT/MT showed a greater reduction of PTSD severity than those randomized to TF-CBT alone (mean difference: 9.2, 95% CI: 3.2-15.1, p=0.003), indicating a large effect size (0.9, 95% CI: 0.1-1.6). Participants receiving TF-CBT/MT also had greater reductions in alcohol use (mean difference: 5.3, 95% CI: 1.5-9.2, p=0.007; effect size: 0.8, 95% CI: 0.2-1.4) and self-blame cognitions (mean difference: 0.8, 95% CI: 0.2-1.4, p=0.008; effect size: 0.5, 95% CI: 0.1-0.9). These data suggest that memory specificity training adds significantly to the effect of standard TF-CBT in reducing PTSD severity. This approach can offer a simple and easy to implement strategy to augment treatment for PTSD patients.

Key words: Post-traumatic stress disorder, trauma-focused cognitive behavior therapy, memory specificity training, augmentation, treatment response, trauma-related cognitions

(World Psychiatry 2025;24:113–119)

Post-traumatic stress disorder (PTSD) is the most common psychiatric condition to arise after traumatic events, affecting approximately 5.6% of trauma-exposed people in their lifetime[1]. Trauma-focused cognitive behavior therapy (TF-CBT), which encompasses a range of treatments variably including exposure to one's trauma memory and cognitive reframing of excessively negative appraisals, is the frontline treatment for this disorder.

Despite the success of TF-CBT, between one-third and one-half of PTSD patients do not respond optimally to this treatment[2]. This situation, which has persisted for several decades, has led to much attention on new strategies to improve treatment response[3]. Most of these attempts have focused on modulating extinction processes, which are proposed to underpin core mechanisms of TF-CBT[4]. Despite the promise of these strategies, they have yielded only modest gains over standard TF-CBT[5].

An alternate approach to augmenting TF-CBT is enhancing a person's capacity to retrieve specific personal memories. There is considerable evidence that retrieval of autobiographical memories tends to be more overgeneral in people with PTSD[6]. This form of recall involves retrieval of abstract categories of events without being able to focus on highly specific instances of personal memories.

Overgeneral retrieval of autobiographical memories adversely affects people with a range of psychiatric disorders, because it promotes rumination, limits social functioning, can promote general beliefs that are maladaptive, and increases risk for suicidality[7,8]. This overgeneral retrieval has been shown to be a risk factor for ongoing PTSD, impeding problem-solving and planning for the future, and being associated with rumination about negative events[9,10].

For these reasons, strategies have been developed to train people with psychiatric disorders, particularly depression, to retrieve more specific memories. One initial variant involved training participants to systematically rehearse retrieving personal positive and negative memories with episodic detail, including temporal and contextual specificity[11]. This form of training focused primarily on people with depression, with early evidence showing effectiveness in reducing depressive symptoms[12].

One pilot trial has also shown that memory specificity training may have benefit in reducing PTSD symptoms[13]. This initial finding accords with accumulating evidence that accessing positive memories is linked to reduced avoidance and more adaptive post-traumatic appraisals[14,15]. Subsequent variants of this intervention which have trained people to be flexible in specific and general retrieval have also shown to be effective in reducing PTSD symptoms[16].

The goal of this trial was to evaluate the extent to which a form of memory specificity training focused on promoting retrieval of positive autobiographical memories could augment the clinical benefit of TF-CBT in people with PTSD. The training aimed to produce a shift towards retrieving memories that can: a) promote more adaptive views of the self, which can be compromised in PTSD[3,17], and b) facilitate positive affect, which has additional benefits in reducing anxiety[18].

The trial focused on first responders – including police, firefighters and paramedics – because these personnel have particularly high rates of PTSD[19], and tend to ruminate on negative personal memories[20]. We hypothesized that combined TF-CBT and

memory training treatment (TF-CBT/MT) would achieve greater PTSD severity reduction than TF-CBT alone.

METHODS

Study design and participants

In this randomized, parallel, controlled trial, first responders who met DSM-5 diagnostic criteria for PTSD were randomly assigned to either TF-CBT/MT or TF-CBT alone on a 1:1 basis. Assessments were conducted by independent psychologists who were blinded to the treatment condition of participants. The primary outcome was PTSD severity, and the primary outcome timepoint was the 6-month assessment.

Participants were recruited in Sydney (Australia) by referral, online advertising, and notices in first responder publications. Potential participants were initially screened during a telephone intake by a psychologist to determine eligibility, and suitable participants subsequently received a baseline assessment by a clinical psychologist.

Inclusion criteria were: a) aged at least 18 years, b) meeting DSM-5 diagnostic criteria for PTSD, c) being a current or former first responder, and d) being proficient in English. Exclusion criteria were: a) severe suicidal risk (reporting suicidal plan and intent), b) presence of psychosis, and c) substance dependence. At baseline assessment, major depressive disorder, anxiety disorders and substance use disorders were assessed using the Mini-International Neuropsychiatric Interview (MINI, version 5.5)[21].

The trial was approved by the University of New South Wales Human Research Ethics Committee (HC210804), and prospectively registered on Australian and New Zealand Clinical Trials Registry (ACTRN12621001442897). No changes were made to the protocol during the trial.

Randomization and masking

Participants were assigned to either TF-CBT/MT or TF-CBT alone by randomization on a 1:1 ratio, in blocks of four, by personnel who were independent of the trial using a computerized software that generated random number sequences. Randomization was not stratified. Assignment to one of the treatment conditions was e-mailed to a trial coordinator, and the relevant therapist was informed of the participant's treatment condition. All assessors were masked to treatment condition. To index the success of blinding, the assessors were asked to guess the participants' treatment condition at each assessment.

Interventions

Following explanation of the rationale of the study and written informed consent, participants completed the Credibility/Expectancy Questionnaire[22], a 6-item measure that asks respondents to rate on 10-point scales their confidence in the treatment they will receive and the perceived logic of the treatment.

Therapy comprised 12 weekly 90-min individual sessions, and was modelled on previous TF-CBT programs for first responders[23]. It was conducted by master's or doctoral level clinical psychologists, who were trained to use treatment manuals and received weekly supervision from the principal investigator. Both treatment manuals are available in the supplementary information.

The TF-CBT/MT condition commenced with a session of psychoeducation about PTSD and the rationale for TF-CBT, and a slow breathing exercise. In this first session, training retrieval of specific memories was started by coaching participants into recalling a neutral memory in response to a cue word (e.g., "bicycle") in highly specific detail, including where and when it occurred, all perceptual experiences attached to the event, and any other contextual details. This was then repeated for positive memories

Table 1 Baseline characteristics of participants in the trial

	TF-CBT/MT (N=50)	TF-CBT (N=50)
Age, years (mean±SD)	45.7±9.1	45.8±10.8
Male, N (%)	37 (74.0)	34 (68.0)
Education, years (mean±SD)	14.4±3.2	14.6±2.6
Time working as first responder, years (mean±SD)	20.1±9.8	18.9±10.7
Time since trauma, months (mean±SD)	103.2±99.8	76.4±75.0
Relationship status, N (%)		
Married/de facto	35 (70.0)	35 (70.0)
Divorced/separated	10 (20.0)	9 (18.0)
Widowed	0	1 (2.0)
Single	5 (10.0)	5 (10.0)
Ethnicity, N (%)		
White	43 (86.0)	40 (80.0)
Asian	1 (2.0)	3 (6.0)
Indigenous	3 (6.0)	7 (14.0)
Other	3 (6.0)	0
Profession, N (%)		
Police	30 (60.0)	29 (58.0)
Firefighter	13 (26.0)	13 (26.0)
Paramedic	7 (14.0)	8 (16.0)
Major depressive disorder, N (%)	32 (64.0)	28 (56.0)
Anxiety disorder, N (%)	12 (24.0)	12 (24.0)
Substance use disorder, N (%)	11 (22.0)	6 (12.0)
On antidepressant, N (%)	18 (36.0)	20 (40.0)
Credibility/Expectancy Questionnaire total score (mean±SD)	37.0±9.4	39.5±7.2

TF-CBT/MT – trauma-focused cognitive behavior therapy combined with memory specificity training, TF-CBT – trauma-focused cognitive behavior therapy alone

to cue words (e.g., "happy"). When participants delivered general memories, they were given corrective suggestions to deliver more specific detail. This was followed by providing participants with a workbook to practice retrieval of positive memories between sessions.

Memory training was continued in sessions 2-11. Session 2 also introduced labelling of emotions and cognitive reframing, and commenced monitoring of daily thoughts. Session 3 introduced challenging of maladaptive trauma-related thoughts, which continued in sessions 4-9. Session 3 also introduced skills training to assist participants with specific problems they may be experiencing (e.g., anger, panic, depression, sleep difficulties), and this continued in sessions 4-9. These skills were taught because previous trials with emergency service personnel indicated that they benefit from treatment addressing comorbidity issues common in this population[23]. Session 4 also introduced *in vivo* exposure to avoided situations.

Session 5 introduced imaginal exposure to the trauma memory, comprising 30 min of reliving of the traumatic event. This was continued in sessions 6-10. Sessions 10-11 reviewed all previously taught strategies. Session 12 focused on relapse prevention, including how strategies learnt in treatment would be applied to future stressors or exacerbation of symptoms.

The TF-CBT condition was identical to TF-CBT/MT, except that there was no memory specificity training. In this condition, the time allocated to memory training in TF-CBT/MT was assigned to

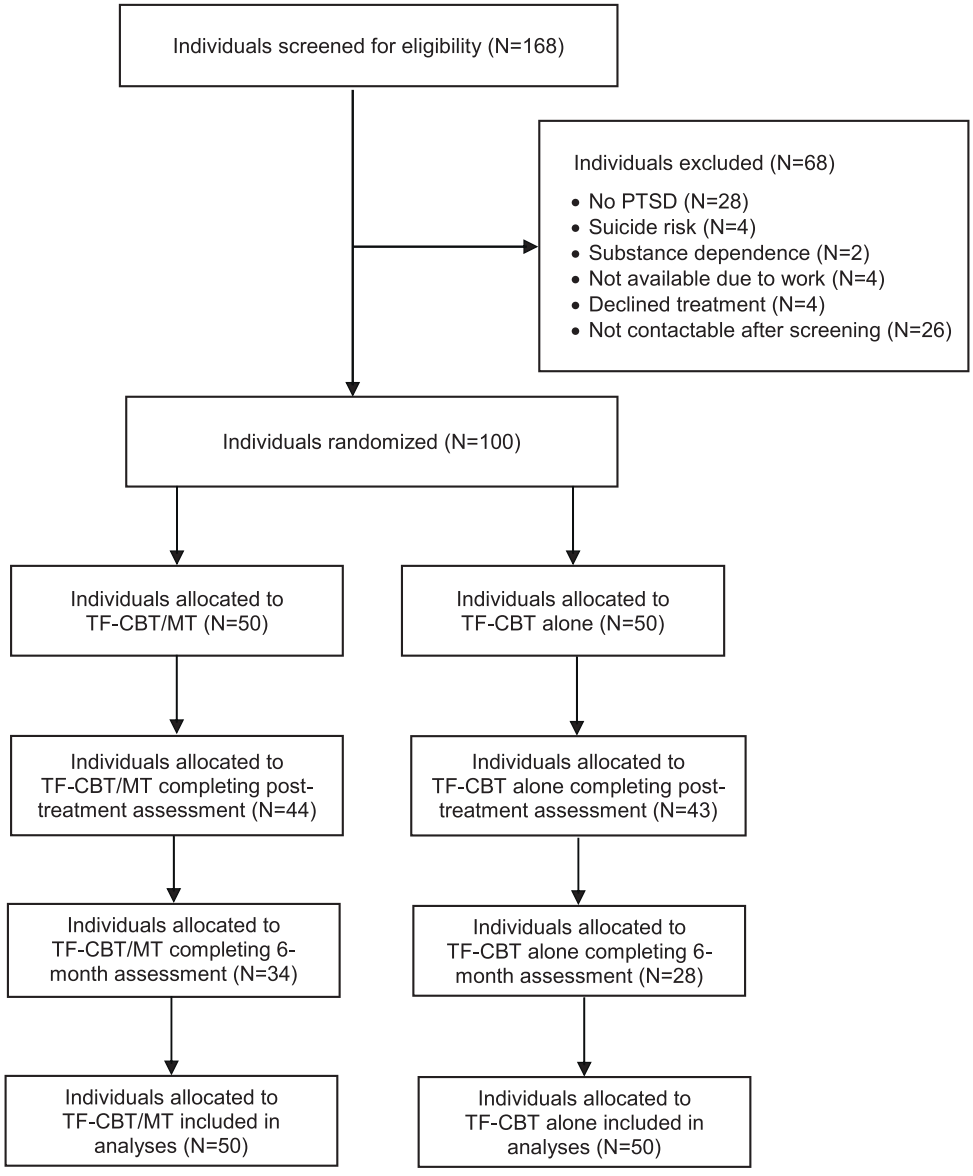

Figure 1 CONSORT flow diagram. TF-CBT – trauma-focused cognitive behavior therapy, TF-CBT/MT – TF-CBT combined with memory specificity training.

non-directive counseling.

To assess treatment fidelity, audio recordings of 10% of sessions were randomly selected and rated by an independent clinical psychologist who was blinded to treatment condition. This rater assessed the presence or absence of each of 61 treatment components across sessions, and evaluated quality of the therapy on a 7-point scale (0 = unacceptable, 6 = extremely good). The mean quality ratings were 5.2±0.8 for TF-CBT/MT and 5.1±1.1 for TF-CBT. No participants in the TF-CBT condition received memory specificity training.

An independent data monitoring committee reviewed adverse events occurring during the trial. No interim analyses were conducted.

Outcomes

The primary outcome was change in PTSD severity, as measured by the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)[24]. This is a structured clinical interview that indexes

Table 2 Results from linear mixed model analyses of primary and secondary outcomes

		Estimated marginal mean (95% CI)		Mixed model analysis		
Outcome measure		**TF-CBT/MT (N=50)**	**TF-CBT (N=50)**	**Difference in estimated means (95%CI)**	**p**	**Effect size (95% CI)**
PTSD severity (CAPS)	Baseline	39.5 (36.8-42.1)	36.6 (33.9-39.3)			
	Post-treatment	15.2 (11.7-18.8)	18.6 (15.0-22.2)	6.3 (1.6-11.0)	0.01	0.6 (0.1-1.0)
	6-month	17.9 (13.7-22.2)	21.8 (17.3-26.4)	9.2 (3.2-15.1)	0.003	0.9 (0.1-1.6)
Depression (BDI-2)	Baseline	29.9 (27.3-32.6)	29.3 (26.5-32.1)			
	Post-treatment	14.5 (11.2-17.9)	18.1 (14.5-21.7)	4.2 (−6.8 to 9.1)	0.09	0.4 (−0.6 to 0.9)
	6-month	19.4 (15.2-23.7)	21.5 (16.7-26.3)	2.7 (−3.7 to 9.0)	0.40	0.2 (−0.3 to 0.8)
Alcohol use (AUDIT)	Baseline	8.5 (6.6-10.4)	7.4 (5.5-9.5)			
	Post-treatment	7.4 (5.8-9.1)	6.2 (4.5-7.9)	−0.2 (−2.0 to 1.7)	0.87	0.0 (−0.3 to 0.3)
	6-month	4.7 (2.5-7.0)	9.0 (6.9-11.0)	5.3 (1.5-9.2)	0.007	0.8 (0.2-1.4)
Trauma-related cognitions (PTCI), Self	Baseline	4.1 (6.3-7.4)	4.0 (3.7-4.3)			
	Post-treatment	3.0 (2.5-3.4)	3.2 (2.7-3.6)	0.3 (−0.2 to 0.8)	0.26	0.2 (−0.2 to 0.7)
	6-month	3.3 (2.8-3.7)	3.3 (2.8-3.8)	0.1 (−0.4 to 0.6)	0.74	0.1 (−0.3 to 0.5)
Trauma-related cognitions (PTCI), World	Baseline	5.2 (4.8-5.5)	4.8 (4.4-5.2)			
	Post-treatment	4.2 (3.7-4.7)	4.1 (3.7-4.6)	0.3 (−0.2 to 0.8)	0.20	0.2 (−0.2 to 0.5)
	6-month	4.2 (3.7-4.7)	4.1 (3.6-4.6)	0.3 (−0.3 to 0.9)	0.31	0.2 (−0.2 to 0.6)
Trauma-related cognitions (PTCI), Self-blame	Baseline	3.1 (2.7-3.5)	2.4 (2.0-2.9)			
	Post-treatment	2.3 (1.9-2.7)	2.4 (2.0-2.8)	0.8 (0.2-1.4)	0.01	0.5 (0.1-1.0)
	6-month	2.3 (1.9-2.7)	2.4 (1.9-2.7)	0.8 (0.2-1.4)	0.008	0.5 (0.1-0.9)
Quality of life (WHOQOL-BREF), Physical	Baseline	3.1 (2.9-3.2)	2.9 (2.8-3.1)			
	Post-treatment	3.6 (3.4-3.8)	3.2 (3.0-3.5)	−0.2 (−0.4 to 0.1)	0.16	−0.3 (−0.6 to 0.1)
	6-month	3.5 (3.3-3.7)	3.1 (2.9-3.4)	−0.2 (−0.5 to 0.1)	0.22	−0.3 (−0.7 to 0.1)
Quality of life (WHOQOL-BREF), Psychological	Baseline	2.7 (2.6-2.8)	2.7 (2.6-2.9)			
	Post-treatment	2.9 (2.7-3.1)	2.9 (2.7-3.2)	−0.2 (−0.4 to 0.1)	0.25	−0.3 (−0.7 to 0.2)
	6-month	3.5 (3.3-3.7)	2.8 (2.6-3.0)	−0.1 (−0.4 to 0.1)	0.22	−0.2 (−0.8 to 0.2)
Quality of life (WHOQOL-BREF), Social relationships	Baseline	2.8 (2.6-3.0)	2.9 (2.6-3.1)			
	Post-treatment	3.2 (3.0-3.5)	3.2 (3.0-3.4)	−0.1 (−0.4 to 0.2)	0.47	−0.1 (−0.5 to 0.3)
	6-month	3.0 (2.7-3.3)	3.2 (2.8-3.5)	0.1 (−0.3 to 0.5)	0.50	0.2 (−0.4 to 0.6)
Quality of life (WHOQOL-BREF), Environment	Baseline	3.5 (3.4-3.7)	3.5 (3.4-3.7)			
	Post-treatment	3.8 (3.7-4.0)	3.7 (3.5-3.8)	−0.2 (−0.4 to 0.0)	0.06	−0.3 (−0.7 to 0.0)
	6-month	3.7 (3.5-3.9)	3.7 (3.4-3.9)	0.0 (−0.3 to 0.2)	0.80	0.0 (−0.5 to 0.3)

TF-CBT/MT – trauma-focused cognitive behavior therapy combined with memory specificity training, TF-CBT – trauma-focused cognitive behavior therapy alone, CAPS-5 – Clinician-Administered PTSD Scale for DSM-5, BDI-2 – Beck Depression Inventory-2, AUDIT – Alcohol Use Disorders Identification Test, PTCI – Posttraumatic Cognitions Inventory, WHOQOL-BREF – World Health Organization Quality of Life - Brief Version

the 20 symptoms described by the DSM-5 criteria for PTSD, with each symptom rated for severity and frequency in the past month on 5-point (0-4) scales (score range: 0-80; higher scores indicate greater PTSD severity). The CAPS-5 has strong inter-rater reliability (.91), test-retest reliability (.78), and internal consistency (.88)[24].

Among secondary outcomes, depression was assessed by the Beck Depression Inventory-2 (BDI-2)[25], which is a 21-item self-report measure of depression in the past two weeks (score range: 0-63; higher scores indicate more severe depression). Trauma-related cognitions were assessed by the Posttraumatic Cognitions Inventory (PTCI)[26], which is a 36-item self-report scale that measures maladaptive appraisals commonly associated with PTSD (negative cognitions about self, negative cognitions about the world, and self-blame; score ranges: 21-147, 7-49 and 5-35, respectively; higher scores indicate more maladaptive appraisals). Participants are asked to respond on how they currently think, without reference to a timeframe.

Quality of life was assessed using the World Health Organization Quality of Life – Brief Version (WHOQOL-BREF)[27], which assesses quality of life across four domains of functioning in the past two weeks, with higher scores indicating better functioning (physical health: score range 7-35; psychological: score range 6-30; social relationships: score range 3-15; environment: score range 0-40). Alcohol use was assessed by the Alcohol Use Disorders Identification Test (AUDIT)[28], which is a 10-item self-report scale providing an overall severity score of alcohol use in the past month (score range: 0-40; higher scores indicate greater alcohol use).

Statistical analyses

We determined that, in order to have 90% power (with alpha = 0.05, two-sided) to detect a between-treatment effect at 6-month follow-up equivalent to a large effect size of 0.8, 35 participants per group would be needed. This effect size was based on a previous pilot trial of a variant of memory specificity training in PTSD, which found a large effect size[13]. On the expectation that 30% of participants would not be retained for the follow-up assessment, it was estimated that 100 participants (50 per group) would be required.

We focused on intent-to-treat analyses. Using SPSS (Version 28.0), hierarchical linear models were applied to assess differential changes in PTSD severity between treatment arms, because this allows the number of observations to vary between participants and handles missing data by using maximum likelihood estimation methods. All missing data were assumed to be random, because the participants who were and were not retained at 6 months did not differ in terms of baseline characteristics (see supplementary information). Models included time-of-assessment point, treatment condition, and their interaction.

Fixed (intervention, time of assessment) effects and their interactions were entered in unstructured models to determine the relative effects of the treatments assessed at baseline, post-treatment, and 6-month follow-up. This approach uses maximum likelihood estimation to derive estimated means, and calculate the differences between conditions in the estimated means relative to baseline levels. Fixed effects parameters were tested using the Wald test (t-test, $p<0.05$, two-sided) and 95% confidence intervals (CIs). Cohen's d effect sizes were calculated by dividing the difference in change between treatment arms relative to baseline by the pooled standard deviations.

To assess the robustness of this approach, secondary analyses were conducted which focused only on participants who completed the 6-month assessment. Noting the possible effects of time working as a first responder, analyses were repeated using this variable as a covariate.

RESULTS

Participants

Between October 2021 and May 2023 (with final follow-up assessments completed in November 2023), 100 participants were enrolled into the trial. Participants in the two arms did not differ at baseline on any sociodemographic characteristic or psychopathology measure (see Table 1). The mean number of intervention sessions attended did not differ between participants in the TF-CBT/MT (10.2±3.4) vs. TF-CBT alone (10.6±2.7) conditions ($t_{98}=0.7$, $p=0.48$).

Figure 1 summarizes the participant flow. There were 100 participants randomized to either TF-CBT/MT (N=50) or TF-CBT alone (N=50). Most participants completed the post-treatment (87, 87.0%), and 6-month assessment (62, 62.0%). The other participants were not contactable for these assessments. Participants who were and were not retained at 6-month assessment did not differ on any pre-treatment variable (see supplementary information).

Blinding efficacy

Assessors correctly guessed the treatment condition within chance levels, for participants in TF-CBT/MT and TF-CBT arms, at both post-treatment (51.6% and 50.0%, respectively) and 6-month follow-up (51.6% and 54.2%, respectively). This pattern indicates that assessors were actually blind to treatment condition at each assessment.

Primary outcome

Both treatments displayed a marked reduction in PTSD symptoms at the 6-month assessment (mean difference: 18.0, 95% CI: 15.1-21.0, $p<0.001$), with a large effect size (1.9, 95% CI: 1.6-2.2).

Participants receiving TF-CBT/MT showed a greater reduction in PTSD severity on the CAPS-5 than those randomized to TF-CBT alone, at both post-treatment (mean difference: 6.3, 95% CI: 1.6-11.0, $p=0.01$) and 6-month follow-up (mean difference: 9.2,

95% CI: 3.2-15.1, p=0.003) (see Table 2). The difference at 6-month assessment indicated a large effect size (0.9, 95% CI: 0.1-1.6).

Analysis of participants who completed the post-treatment assessment indicated no difference in rates of meeting PTSD diagnostic criteria between the TF-CBT/MT (6, 13.6%) and the TF-CBT (10, 23.2%) arms. Although there was a trend for fewer participants in TF-CBT/MT (6, 17.6%) than in TF-CBT (10, 35.7%) condition to meet PTSD criteria at the 6-month follow-up, this difference was not significant (χ^2=2.6, p=0.11). The number needed to treat at follow-up was 5.4.

Secondary outcomes

TF-CBT/MT resulted in a greater reduction of alcohol use at the 6-month assessment (mean difference: 5.3, 95% CI: 1.5-9.2, p=0.007) than TF-CBT alone, with a large effect size (0.8, 95% CI: 0.2-1.4). There was also a greater reduction in self-blame cognitions in the former group (mean difference: 0.8, 95% CI: 0.2-1.4, p=0.008), with a moderate effect size (0.5, 95% CI: 0.1- 0.9). There were no significant differences in terms of depression, other forms of post-traumatic appraisals, or quality of life between the two groups (see Table 2).

Secondary analyses

Secondary analyses focusing only on participants who completed the 6-month follow-up replicated the intent-to-treat findings that TF-CBT/MT led to greater reductions in PTSD severity and self-blame relative to TF-CBT. The intent-to-treat finding that TF-CBT/MT led to less alcohol use than TF-CBT was not observed in this analysis (see supplementary information). Consistent with the primary analyses, there were no significant differences on other secondary outcomes.

When controlling for number of years served as a first responder, the same pattern of findings was observed as in the primary analyses, with TF-CBT/MT resulting in greater reductions in PTSD severity, alcohol use, and self-blame than TF-CBT (see supplementary information).

There was one adverse event reported. A participant in the TF-CBT arm asked to not continue treatment because of an increase in nightmares.

DISCUSSION

In this trial, both TF-CBT conditions were associated with significant reductions in PTSD severity, which is consistent with previous reports of a positive impact of TF-CBT in first responders[23]. The major finding, however, was that augmenting TF-CBT with memory specificity training for positive memories significantly enhanced reduction of PTSD symptoms relative to standard TF-CBT. This is in line with previous reports of the efficacy of memory specificity training in mitigating anxiety and mood symptoms[29], as well as with pilot evidence of an amelioration of PTSD symptoms[13]. However, this is the first trial to show that this strategy can increase the treatment gains of TF-CBT in individuals with PTSD.

The utility of memory specificity training which focuses on positive memories for enhancing the effects of TF-CBT can be understood in the context of evidence that PTSD is characterized by overgeneral retrieval of memories[6]. It has been proposed that promoting more specific retrieval of autobiographical memories can reduce rumination, improve social functioning, reduce maladaptive appraisals, and boost self-esteem[15]. It is noteworthy that TF-CBT/MT resulted in greater reductions of self-blame appraisals than TF-CBT, which supports the proposal that memory specificity training can alleviate negative cognitions about oneself[17].

We observed that TF-CBT/MT resulted in a greater reduction of alcohol use. This finding appears to be a function of TF-CBT participants' alcohol use increasing over the 6-month follow-up, whilst alcohol use decreased in the TF-CBT/MT arm. It is possible that, as PTSD symptoms decreased over the six months after treatment, participants had a weaker motivation to self-medicate with alcohol. There is indeed abundant evidence that changes in PTSD severity influence alcohol use[30]. Although TF-CBT alone also resulted in a reduction in PTSD severity, it is possible that this level of symptom reduction was not sufficient to trigger a decrease in alcohol use. We note that this finding was not replicated in the secondary analysis including only those who completed the 6-month assessment. Thus, we regard the finding as tentative.

TF-CBT/MT did not reduce depressive symptoms more than TF-CBT alone, which may appear not to be in line with previous reports that memory specificity training can alleviate depressive symptoms[12]. However, it should be considered that the training implemented in this trial was not as comprehensive as the programs that have been shown to reduce depression. It is also known that reductions in depression can often occur as a result of TF-CBT alone[31], and it is worth noting that depression decreased significantly in both TF-CBT/MT and TF-CBT arms in this trial. It is possible that the gains produced by memory specificity training were not sufficient to augment the benefits of reduced PTSD symptoms achieved by patients in both treatment arms.

In terms of trial limitations, we note that three-quarters of the sample were male, so that generalizability to females requires further evaluation. Second, we cannot definitively conclude that TF-CBT led to PTSD reduction, because the design lacked a no-treatment or placebo condition. Third, whereas 87% of the sample was retained at the post-treatment assessment, only 62% was assessed at the 6-month follow-up. However, there were no baseline differences between those who were and were not retained at follow-up, and the number of retained participants was larger than in most previous PTSD trials[32]. It is possible that attrition did not occur at random, and this raises questions concerning the symptom trajectories of those lost to attrition. Fourth, we acknowledge that it was not possible to blind therapists and participants concerning their assigned treatment condition, and accordingly we cannot rule out expectancy effects impacting the outcomes. Fifth, this trial focused on first responders, and results need to be replicated in other PTSD populations.

In conclusion, this study represents the first demonstration that integrating memory specificity training for positive personal memories with TF-CBT can augment the effects of this frontline treatment. In the context of up to one-half of PTSD patients not responding to TF-CBT[2], it is important for clinicians to consider auxiliary strategies that can promote better treatment response. Training patients to retrieve positive autobiographical memories is a relatively simple strategy, and this promising technique can be readily implemented into clinical practice.

ACKNOWLEDGEMENTS

This study was supported by an Australian Research Council Linkage grant (no. LP180100393), co-funded by ICARE Insurance and Employers Mutual Limited (EML), and by a National Health and Medical Research Council Investigator grant (no. 2033928). Supplementary information on this study is available at https://osf.io/ft3jw.

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DOI:10.1002/wps.21280

Effectiveness of a stepped-care programme of WHO psychological interventions in a population of migrants: results from the RESPOND randomized controlled trial

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Migrant populations – including labour migrants, undocumented migrants, asylum seekers, refugees, internationally displaced persons, and other populations on the move – are exposed to a variety of stressors that affect their mental health. We designed and tested the effectiveness of a stepped-care programme consisting of two scalable psychological interventions developed by the World Health Organization (WHO) and locally adapted for migrant populations. A parallel-group randomized controlled trial was conducted in Italy. We recruited migrant adults (≥18 years) with psychological distress (score of at least 16 on the Kessler Psychological Distress Scale, K10). The experimental arm received psychological first aid (PFA) and a stepped-care programme consisting of two WHO interventions adapted for this population group: first, Doing What Matters in Times of Stress (DWM) and, for participants who still reported significant levels of psychological distress after DWM, Problem Management Plus (PM+). Each intervention lasted 5-6 weeks and was delivered remotely by lay facilitators. The control arm received PFA and care as usual (CAU). The primary outcome was the change in symptoms of depression and anxiety from baseline to week 21 after randomization, measured by the Patient Health Questionnaire Anxiety and Depression Scale (PHQ-ADS). Between December 14, 2021 and April 18, 2023, 108 migrants were randomized to the stepped-care intervention and 109 to CAU. Analysis of the primary outcome revealed that participants receiving the stepped-care programme showed a greater reduction in anxiety and depression symptoms compared to those receiving CAU (coefficient: –3.460, standard error, SE: 1.050, p=0.001) at week 21. The same difference was observed at week 7 (coefficient: –3.742, SE=1.008, p<0.001) and week 14 (coefficient: –6.381, SE=1.039, p<0.001). The stepped-care programme was also associated with a greater improvement of depression and anxiety symptoms assessed separately at all timepoints, of post-traumatic stress disorder symptoms at weeks 14 and 21, and of self-assessed problems, function and well-being at all timepoints. No serious adverse events occurred. This study provides evidence supporting the stepped-care delivery of DWM and PM+ for migrant population groups with elevated distress. As these interventions are low-intensity, transdiagnostic and task-shifting, they are highly scalable. Existing evidence-based guidelines and implementation packages should be updated accordingly.

Key words: Migrants, psychological distress, WHO psychosocial interventions, Problem Management Plus, anxiety, depression, stepped-care model

(World Psychiatry 2025;24:120–130)

Migration has been a common phenomenon for centuries. The term "migrant" typically encompasses many different groups: labour migrants, undocumented migrants, asylum seekers, refugees, internally displaced individuals, and other populations on the move[1].

According to the International Organization for Migration, there were about 281 million international migrants worldwide in 2021, marking a 27% increase compared to the 221 million migrants in 2010. Migrants represent a total of 3.6% of the world's population. Many migrants arrive in Europe through Italy, with 34,000 new arrivals in 2020 and almost 60,000 in 2021[2].

Migrant population groups are exposed to various risk factors for mental health conditions. These include discrepancies between expectations and actual achievements, inadequate support systems, challenges in adaptation and acculturation processes, along with financial, administrative and legal hurdles throughout and after the migration trajectory[3]. Among migrants, forcibly displaced people – such as refugees and asylum seekers – face additional severe stressors, including the loss of their homes and possessions, and other traumatic events such as bombings, threats, imprisonment and torture.

In recent years, there has been a growing number of randomized controlled trials (RCTs) exploring the benefits of psychosocial interventions targeting psychological symptoms in migrant populations[4]. A systematic review of 52 studies (including 26 RCTs) identified a significant effect of psychological interventions in reducing depression, anxiety and somatization symptoms[5]. These results align with those of a scoping review of mixed-methods studies, which indicated a positive effect of psychosocial interventions on participants' mental health, mainly through a reduction in depressive symptoms and an improvement in social functioning[6].

However, implementing the above interventions necessitates extensive training, a significant time for delivery, staff members with a background in mental health, and a robust monitoring and supervision framework. Moreover, it involves face-to-face individual delivery in most instances. As these characteristics are barriers to implementation, the World Health Organization (WHO) has de-

veloped a stress management intervention named Self Help Plus (SH+)[7], and a brief intervention based on cognitive-behavioral and problem-solving strategies called Problem Management Plus (PM+)[8]. A guided self-help programme based on the SH+ course, called Doing What Matters in Times of Stress (DWM), is also available and has been adapted to be delivered as a mobile-supported website[9].

SH+, PM+ and DWM are designed to be scalable, transdiagnostic and task-shifting. They have been tested as stand-alone interventions in diverse populations, including health care staff, asylum seekers, refugees, international migrants, involuntarily displaced people, and individuals exposed to armed conflicts, natural disasters, and health stressors such as the COVID-19 pandemic[10-14]. Studies have generally found benefits in mental health outcomes, though the effectiveness of interventions may diminish over time[15]. One study conducted among health care staff with COVID-19-related distress combined DWM and PM+ into a stepped-care programme compatible with fully remote training, delivery and supervision[16]. The stepped-care programme was found to be feasible. It resulted in clinically significant reductions in symptoms of anxiety, depression and post-traumatic stress disorder (PTSD)[17], suggesting that it may be potentially beneficial in other populations exposed to adversity.

Against this background, the present study examined the efficacy of DWM and PM+ delivered as a stepped-care programme in reducing anxiety and depression symptoms in a sample of migrants with elevated psychological distress.

METHODS

Study design

We conducted a parallel-group RCT in Italy. The trial protocol was published and registered in clinicaltrials.gov (NCT04993534)[18]. No changes were made to the design after the trial started. The Ethics Committee of the University of Verona approved the project. Written informed consent was mandatory for all participants. In accordance with the Declaration of Helsinki, participants' confidentiality was preserved, and the contents of the recruitment and follow-up forms were not disclosed to any third party.

An Ethics and Data Advisory Board monitored the study and provided expert advice on data management and all ethical, legal and societal issues related to the project. The Consolidated Standards of Reporting Social and Psychological intervention Trials (CONSORT-SPI) statement was followed in reporting trial results[19]. Participant recruitment occurred from December 14, 2021 to April 18, 2023.

Participants were adult migrants recruited through: a) key stakeholders such as non-governmental organizations (NGOs) located in Italy; b) other community-based organizations offering legal and/or social and/or psychosocial support to this vulnerable group; or c) social media and "word of mouth" (i.e., investigators proactively approached local organizations providing social, health and/or legal support to migrant populations, including refugees and asylum seekers, to identify potentially eligible participants).

Interested individuals were informed (in English, Italian or French), using an easily accessible terminology, about the nature and scope of the study. A research assistant explained details of the study and provided study materials. Participants meeting the inclusion criteria were randomized to receive psychological first aid (PFA) combined with the adapted stepped-care DWM/PM+ intervention, or to receive PFA and care as usual (CAU) alone. After the screening at T0, participants were assessed at baseline before random allocation (T1) (one week after the screening), and after randomization at week 7 (T2), week 14 (T3), and week 21 (T4) (primary endpoint).

Inclusion and exclusion criteria

Participants were included if they met the following criteria: a) aged 18 years or older; b) being a migrant resettled in Italy temporarily or permanently (including labour migrants, undocumented migrants, asylum seekers, refugees, internationally displaced persons, or other persons on the move); c) having elevated levels of psychological distress (score of at least 16 on Kessler Psychological Distress Scale, K10[20]); d) sufficient mastery of English, Italian or French (written and spoken); e) oral and written informed consent before entering the study.

Individuals who met the inclusion criteria were excluded from participation if they met any of the following criteria: a) acute medical conditions requiring hospitalization; b) imminent suicide risk or expressed acute needs or safeguarding risks that required immediate follow-up; c) severe mental disorder (e.g., psychotic disorder); d) severe cognitive impairment (e.g., severe learning difficulties or dementia); e) initiated, stopped or significantly modified psychiatric drug treatment over the previous two months; f) receiving specialized psychological treatment at enrolment (e.g., cognitive-behavioral therapy, eye movement desensitization and reprocessing); g) planning to permanently move back to their home country before the last quantitative follow-up assessment (T4).

Randomization and masking

Randomization was coordinated by the WHO Collaborating Centre at the University of Verona. The electronic software Castor Electronic Data Capture (EDC) generated the randomization schedule, employing a variable block randomization method[21]. Research team members involved in recruitment could access the web-based software to randomize each newly enrolled participant, but were not able to access the randomization list and were not aware of the block size. The Castor EDC software allowed random allocation only after the main information on the enrolled participant was entered, upon verification of the inclusion criteria. After random allocation, the software produced a unique identification number for each participant.

Masking participants and research staff was not feasible, due to the nature of the intervention programme. However, the statistician performing the analyses was masked to participant allocation status through pseudo-blinding using coded groups. The trial statistician was not involved in determining participants' eligibility, administering the intervention, measuring the outcomes, or entering data.

Experimental and control intervention

All participants initially received a phone call of up to 15-20 min where intervention helpers provided information on which group they were allocated to, as well as on specific resources and supports they could access following the principles of PFA.

PFA is a WHO-developed support strategy that involves human, supportive and practical help for individuals who have been affected by humanitarian crises[22]. It consists of a conversation during which the helper provides non-intrusive practical care and support, assesses needs and concerns, helps people to address basic needs (e.g., information), listens to people without pressuring them to talk, comforts them and helps them calm down; and helps them to connect to information, services and social support[22,23].

Participants allocated to the control arm received PFA and CAU, which could include community care, social/legal support, and psychoeducation on general distress and personal and community resources.

Participants allocated to the intervention arm received PFA, CAU and the stepped-care program, which included DWM and – for participants who reported significant levels of psychological distress after DWM (score of at least 16 on the K10 scale) – PM+.

After allocation, participants in the intervention arm were assigned to a helper who provided ongoing support over the phone, assisting with practical exercises and explaining key concepts of DWM. After an initial welcome call, participants received a message with login details to access the DWM course. As a result of the local adaptation process, reported elsewhere[24], we transformed DWM into a mobile-friendly website and adapted some content to reflect barriers or stress triggers that might affect migrant populations in Italy.

The DWM course was delivered over a period of 5-6 weeks, with new modules released every week. Helpers scheduled weekly support calls lasting approximately 15 min each, and provided motivation and support in using DWM. Participants who did not want to receive phone calls could contact their helpers using the messaging system available on the website. The DWM course is based on acceptance and commitment therapy techniques (e.g., acting on values, making room for difficult thoughts and feelings, keeping attention and curiosity), along with audio recordings to support practice[24]. Participants were reminded of the sessions through text messages, in accordance with the WHO manual for delivery of the intervention.

After 5-7 days from DWM completion (T2), an assessment was made of the criterion for stepping up to PM+, i.e. significant levels of psychological distress as measured by the K10 scale (score of at least 16). The PM+ intervention, culturally and contextually adapted according to WHO protocols, was administered by trained helpers without a formal background in mental health[25], over a period of 5-6 weeks.

The PM+ protocol provides five different behavioral strategies: stress management, problem-solving techniques, behavioral activation, promoting social support, and maintaining the effects. The cultural adaptation of the intervention was conducted through ten online meetings over a 6-month period between the staff of the University of Verona, WHO officers, and representatives of other sites of the RESPOND Consortium.

Both DWM and PM+ interventions had an online format and were delivered in Italian, English or French. The intervention manuals are available on the WHO website (www.who.int). A detailed description of the interventions delivered during the trial (PFA, CAU, DWM and PM+) is provided in the supplementary information.

Helpers were bilingual (Italian/English or Italian/French) and received training in Italian on PFA, DWM and PM+ according to WHO protocols and manuals[26]. The training was conducted by master trainers based at the University of Verona (clinical psychologists trained by WHO officers and/or experts with long experience in delivering WHO interventions). Details on the training activities are provided in the supplementary information. Intervention supervision was provided for DWM and PM+ helpers by clinical psychologists, who were available to address questions, as well as to provide debriefing after sessions. If necessary, additional training and consultation were available. Fidelity was checked by the intervention supervisor, who was not involved in the delivery of interventions, observed at least 10% of DWM sessions, and listened to at least 10% of recorded PM+ sessions.

Participants in both arms received: a) baseline and follow-up assessments according to the study schedule, b) information about freely available health and social services, and c) links to community networks providing support for migrant populations.

Measures

Participants completed online questionnaires, using the Castor EDC software[21], at T0 (screening for eligibility); T1 (baseline assessment, before random allocation); T2 (week 7 after randomization); T3 (week 14 after randomization); and T4 (week 21 after randomization).

Screening for eligibility was conducted using the K10. This is a ten-item self-report questionnaire to screen broadly for psychological distress experienced in the past 30 days[20]. Each item is scored from 1 ("none of the time") to 5 ("all of the time"). Scores of the ten items are then summed, yielding a minimum score of 10 and a maximum score of 50. The K10 has robust psychometric properties and strong discriminatory power to distinguish DSM-IV cases from non-cases[20]. Suicidality was explored by the "Assessment of suicidal thoughts" risk tool from PM+. The possible presence of a severe mental disorder or cognitive impairment was assessed using the PM+ tool "Impairments possibly due to severe

mental, neurological or substance use disorders".

The primary study outcome was the change in symptoms of depression and anxiety from baseline to week 21 after randomization (T4), measured through the combined sum score of the Patient Health Questionnaire-9 (PHQ-9)[27] and the Generalized Anxiety Disorder-7 (GAD-7)[28], previously validated as the Patient Health Questionnaire Anxiety and Depression Scale (PHQ-ADS)[29]. The scale scores range from 0 to 48, with higher scores indicating higher levels of depression and anxiety symptoms.

Secondary measures included the changes in symptoms of anxiety, depression and PTSD, and self-assessed problems, function and well-being, evaluated at all timepoints (T1, T2, T3 and T4). Depression and anxiety symptoms were measured using PHQ-9 and GAD-7, respectively. PTSD symptoms were assessed using the eight-item version of the PTSD Checklist for DSM-5 (PCL-5)[30], which provides scores ranging from 0 to 32, with higher scores indicating higher levels of PTSD symptoms. The instrument is based on the PTSD Checklist - Civilian Version (PCL-C), a DSM-IV-based checklist[31].

Self-assessed problems, function and well-being were measured using the Psychological Outcomes Profiles (PSYCHLOPS)[32], a patient-generated tool consisting of four questions (two for problems, one for function, and one for well-being). Participants are asked to give free text responses to the questions. Responses are scored on an ordinal six-point scale ranging from 0 to 5, producing a maximum score of 20. If both problem questions have been responded, the total score is the sum of the four items. If only the first problem question has been responded, the score of the first question is doubled.

Assessments were completed remotely via secure online links to Castor EDC. Adverse events reported spontaneously by the participants or observed by the research staff were recorded, and any serious adverse events were reported to the Ethics and Data Advisory Board.

Statistical analysis

Based on prior studies on PM+[33,34], we aimed to detect a medium effect size (defined as the square root of the ratio of the variance of the tested effect to its error variance) of 0.3 in the PM+ group at T4, based on the primary composite outcome PHQ-ADS. A power calculation for a repeated measurement design suggested a minimum sample size of N=74 per group (power = 0.95, alpha = 0.05, two-sided) in order to identify an effect at the time of interest. Assuming an attrition rate of 30%, we aimed to include 212 participants (106 in the DWM/PM+ intervention group and 106 in the control group).

All primary and secondary analyses were performed on an intention-to-treat (ITT) basis. The ITT population consisted of all participants randomly assigned to one of the two groups and with data available on at least the baseline assessment. In order to check the robustness of results, all outcomes were additionally analyzed using a per-protocol (PP) approach that included only DWM participants clicking through all the contents of at least three modules and PM+ participants attending at least four sessions.

We calculated the descriptive statistics (mean with SD for interval-level variables, number and percentage for categorical variables) at baseline and for the two intervention arms separately. Arms were compared using standardized mean differences (SMDs).

The primary analysis assessed the intervention effect on the average PHQ-ADS score at each timepoint in the ITT population. To estimate the intervention effect for the timepoints T2, T3 and T4, we employed a linear mixed model for the analysis of PHQ-ADS, which had time as a fixed effect, baseline measurement of PHQ-ADS as a covariate, and subject as a random effect. The model was re-parametrized by constraining the intervention fixed-effect to be 0, and by including a time-intervention interaction at T2 as well. In this way, at each timepoint, the intervention effect was measured as the interaction between time (as a categorical variable) and intervention, with its value at T4 being our outcome of interest.

The interaction effects and confidence intervals (CIs) represent the average difference between the two study arms at each timepoint. We used the mean of the values predicted from the model to calculate the estimated average values for the two study arms in case all participants were assigned to the intervention versus the control arm. In addition, a covariate-adjusted mixed model of the primary outcome was performed by adding covariates showing imbalance at baseline (as measured by a SMD above 0.1 in absolute value). Robust standard errors (SEs) were used in all models.

A secondary analysis of the effect of the intervention on the outcomes was conducted in the PP population, using the same approach as reported above. In addition, a covariate-adjusted mixed model of primary outcome was performed using this population by adding pre-specified covariates at baseline (gender, age, whether the person had at least secondary education; prior trauma expressed as replying "Yes" to at least one item from the Brief Trauma Questionnaire[35]; whether the person had been infected by COVID-19; and the stressor exposure as measured by the Mainz Inventory of Microstressors[36]).

No imputations of missing values at the scale level were made, as multilevel models can deal with missing data in case the missing at random assumption holds[37]. If only some items were missing for a particular scale, we used the corrected item mean substitution method (i.e., the item mean across participants weighted by the subject's mean of completed items)[38], using information from subjects belonging to the same intervention arm for the same follow-up time (estimated values above the maximum or below the minimum admissible value were set to maximum/minimum). As a sensitivity analysis, the analyses for outcomes with partially imputed scales were repeated by excluding such imputed values. To avoid missing values among categorical predictors, a category "missing value" was included.

A linear mixed model with robust SEs, as mentioned for the primary analysis, was carried out to analyze the following secondary outcomes: changes in depressive symptoms (PHQ-9), generalized anxiety symptoms (GAD-7), PTSD symptoms (PCL-5), self-assessed problems, function and well-being (PSYCHLOPS).

Possible interactions between the intervention and specific variables (baseline score on the primary outcome, age, gender, le-

gal status, time since resettlement; whether the person had at least secondary education, was receiving an income, and had ever consulted a mental health professional) were evaluated, by excluding categories with data from less than ten participants. A global test on each variable was implemented and, in case of statistical significance after applying the Benjamini-Hochberg correction[39], statistical significance at each timepoint was evaluated for that variable.

Finally, the loss-to-follow-up rate was compared between the two groups using a chi-square or a Fisher exact test, as appropriate. All analyses were performed using Stata/SE, Release 17.0[40].

RESULTS

After screening 238 potentially eligible participants, 21 were excluded (19 of them had a level of distress lower than the established cut-off; one was on an unstable dose of psychotropic medication; and one refused to participate) (see Figure 1). This left 217 individuals who met the inclusion criteria, consented to be randomized by signing a written informed consent form, and were allocated to either the stepped-care programme (N=108) or CAU (N=109). Only 16.6% of randomized participants were lost to follow-up. The distribution of participants lost to follow-up did not differ between the study groups at any timepoint (see supplementary information).

Selected socio-demographic characteristics of the included participants are shown in Table 1 (see supplementary information for other variables). More than one third of participants were male; the average age was about 36 years in both groups. The majority of participants had at least a secondary education, with almost 40% having an academic education. The country of origin was in Asia/Pacific for 14.8% of them; in Europe or Central Asia for 34.0%; in the Americas or the Caribbean for 26.8%; and in the Middle East or Africa for 24.4%. Most participants were permanent residents in Italy (59.7%), 22.4% had a temporary permit to stay, and 17.9% were refugees or asylum seekers. The reported travel duration to reach Italy was over six months for 16.3% of participants (see Table 1).

Assessment of more than 10% of DWM and PM+ sessions indicated near-perfect fidelity. Only in a few cases (<10) DWM calls were longer than the established duration (i.e., 30 min). We identified minor deviations from the PM+ protocol, due to adaptations for cultural aspects, or specific content that did not totally apply to the problems reported by participants. The total supervision time required for all sessions of DWM and PM+ was 3 hours per helper on average (approximately 12 hours in total).

At T2 (week 7), 32.4% (35/108) of participants allocated to the intervention arm versus 21.1% (23/109) allocated to the control condition reported a clinically significant improvement in distress, as shown by a score below the cutoff of 16 at the K10. In the experimental arm, therefore, 35 participants did not step into PM+. The mean K10 value at T2 was 19.49 (SD=5.91) in the intervention arm and 22.94 (SD=8.13) in the control condition. During the study period, apart from the experimental or control intervention, the mental and physical health care received did not differ between the two groups (see supplementary information).

Differences between study conditions on primary and secondary outcome measures are reported in Table 2. The stepped-care programme led to a significant reduction of anxiety and depression symptoms compared to CAU, as measured by the PHQ-ADS at T4 (coefficient: –3.460, SE=1.050, p=0.001) (primary outcome). The same was observed at the other timepoints (coefficient:

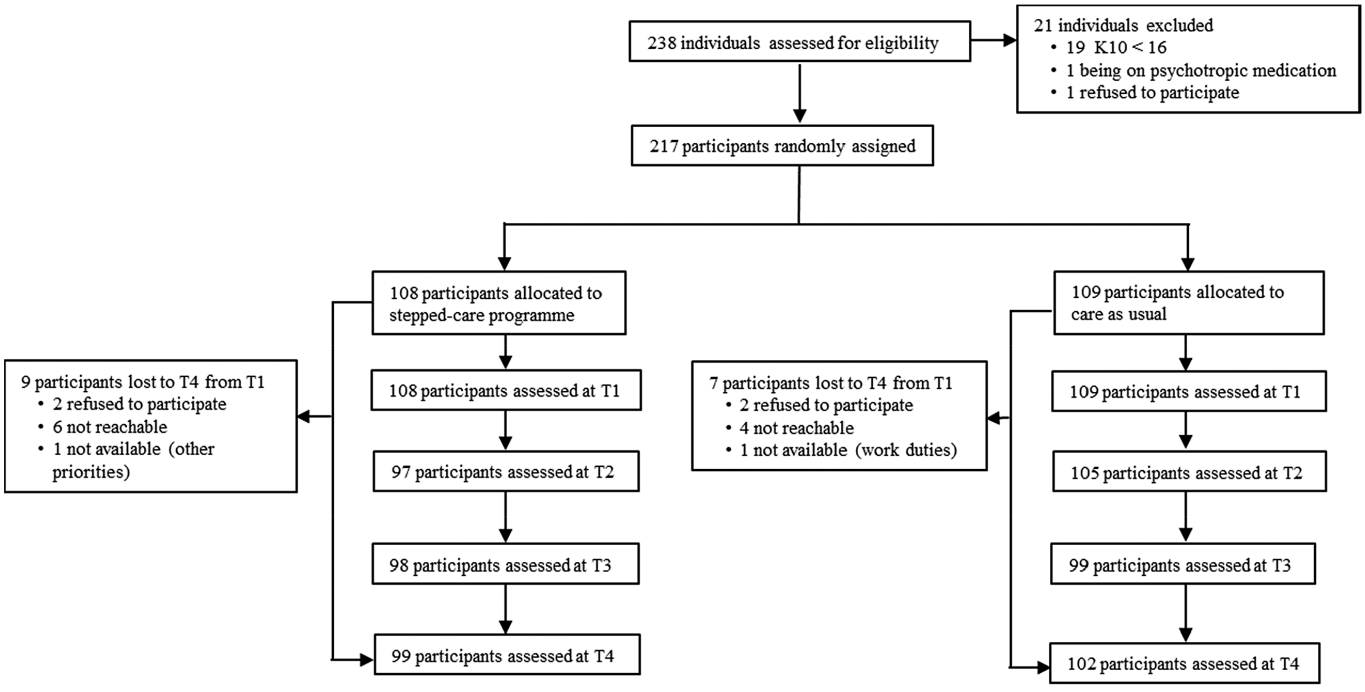

Figure 1 CONSORT-SPI flow diagram. K10 – Kessler Psychological Distress Scale

Table 1 Socio-demographic and clinical characteristics of study participants by treatment allocation

	All participants	Intervention group	Control group	Difference (SE)	SMD
Age (years), mean±SD	35.7±12.5	35.5±13.1	35.9±11.9	–0.414 (1.735)	0.033
Gender (%)					
Female	62.7	68.5	56.9	0.116 (0.065)	**0.241**
Male	36.4	31.5	41.3	–0.098 (0.065)	**0.204**
Other	0.9	0	1.8	–0.018 (0.013)	**0.192**
Education level (%)					
Up to primary school	12.2	8.3	16.0	–0.077 (0.047)	**0.235**
Secondary school	48.5	50.0	47.0	0.030 (0.072)	0.060
University	39.3	41.7	37.0	0.047 (0.070)	0.095
Country of origin (%)					
Asia/Pacific	14.8	17.5	12.3	0.052 (0.049)	**0.146**
Europe or Central Asia	34.0	35.9	32.1	0.038 (0.066)	0.081
America or Caribbean	26.8	23.3	30.2	–0.069 (0.061)	**0.155**
Middle East or Africa	24.4	23.3	25.5	–0.022 (0.060)	0.050
Legal status (%)					
Temporary permit	22.4	22.9	22.0	0.009 (0.060)	0.022
Permanent resident	59.7	64.6	55.0	0.096 (0.070)	**0.195**
Refugee or asylum seeker	17.9	12.5	23.0	–0.105 (0.054)	**0.276**
Travel duration (%)					
Up to six months	83.7	85.4	82.0	0.034 (0.053)	0.092
Over six months	16.3	14.6	18.0	–0.034 (0.053)	
Ever consulted a mental health professional (%)					
Yes	41.5	38.9	44.0	–0.051 (0.071)	**0.102**
No	58.5	61.1	56.0	0.051 (0.071)	
Having an income (%)					
Yes	56.5	60.2	53.1	0.072 (0.072)	**0.144**
No	43.5	39.8	46.9	–0.072 (0.072)	
Measures at baseline, mean±SD					
PHQ-ADS score	19.08±8.69	19.14±8.56	19.02±8.89	–0.119 (1.185)	0.014
PHQ-9 score	10.05±4.93	9.87±4.82	10.22±5.07	–0.350 (0.672)	0.071
GAD-7 score	9.03±4.52	9.15±4.65	8.92±4.43	0.231 (0.616)	0.051
PCL-5 score	11.77±7.23	12.05±7.36	11.49±7.14	0.562 (0.989)	0.075
PSYCHLOPS score	13.304±4.079	13.343±4.276	13.264±3.890	0.079 (0.566)	0.019

SMD – standardized mean difference, SE – standard error, PHQ-ADS – Patient Health Questionnaire Anxiety and Depression Scale, PHQ-9– Patient Health Questionnaire-9, GAD-7 – Generalized Anxiety Disorder-7, PCL-5 – PTSD Checklist for DSM-5, PSYCHLOPS – Psychological Outcomes Profiles. SMD values in bold prints are those above the threshold for imbalance.

–3.742, SE=1.008, p<0.001 at T2; coefficient: –6.381, SE=1.039, p<0.001 at T3). Figure 2 shows the trend over time in the average values of symptoms of depression and anxiety measured by the PHQ-ADS in each of the two groups, with their CIs.

A significant difference was also observed considering depression and anxiety symptoms separately at all timepoints (see Table 2). The stepped-care programme, compared with CAU, was also associated with larger improvements for PTSD symptoms at T3 (coefficient: –3.513, SE=0.827, p<0.001) and T4 (coefficient: –2.523, SE=0.763, p=0.001), and for self-assessed problems, function and well-being at all timepoints (see Table 2).

The results of the ITT analysis were confirmed by the PP analysis (see Table 3). Secondary analyses conducted without any imputations of missing values did not identify any relevant difference with respect to the main analyses (see supplementary information). As the two groups differed on some socio-demographic vari-

Table 2 Results for primary and secondary outcomes at each timepoint (intention-to-treat analysis)

	Intervention Estimated average value (SE)	Control Estimated average value (SE)	Coefficient (SE)	p	Standardized coefficient (SE)
PHQ-ADS score					
T2	12.303 (0.696)	16.045 (0.728)	–3.742 (1.008)	**<0.001**	–0.414 (0.111)
T3	9.112 (0.631)	15.493 (0.825)	–6.381 (1.039)	**<0.001**	–0.705 (0.115)
T4 (primary outcome)	10.625 (0.730)	14.085 (0.755)	–3.460 (1.050)	**0.001**	–0.382 (0.116)
PHQ-9 score					
T2	6.769 (0.390)	8.414 (0.400)	–1.645 (0.560)	**0.003**	–0.324 (0.110)
T3	5.123 (0.368)	8.300 (0.502)	–3.177 (0.623)	**<0.001**	–0.625 (0.123)
T4	5.978 (0.418)	7.292 (0.420)	–1.314 (0.593)	**0.027**	–0.258 (0.117)
GAD-7 score					
T2	5.537 (0.336)	7.621 (0.391)	–2.085 (0.516)	**<0.001**	–0.471 (0.117)
T3	3.995 (0.308)	7.193 (‘0.423)	–3.198 (0.523)	**<0.001**	–0.723 (0.118)
T4	4.652 (0.348)	6.783 (0.400)	–2.131 (0.531)	**<0.001**	–0.482 (0.120)
PCL-5 score					
T2	8.422 (0.630)	10.056 (0.568)	–1.633 (0.849)	0.054	–0.235 (0.122)
T3	6.079 (0.540)	9.592 (0.625)	–3.513 (0.827)	**<0.001**	–0.506 (0.119)
T4	5.994. (0540)	8.517 (0.538)	–2.523 (0.763)	**0.001**	–0.363 (0.110)
PSYCHLOPS score					
T2	8.085 (0.506)	10.234 (0.529)	–2.149 (0.732)	**0.003**	0.392 (0.134)
T3	6.379 (0.520)	9.907 (0.572)	–3.528 (0.773)	**<0.001**	–0.644 (0.141)
T4	5.427 (0.479)	8.995 (0.533)	–3.567 (0.717)	**<0.001**	–0.651 (0.131)

SE – standard error, PHQ-ADS – Patient Health Questionnaire Anxiety and Depression Scale, PHQ-9 – Patient Health Questionnaire-9, GAD-7 – Generalized Anxiety Disorder-7, PCL-5 – PTSD Checklist for DSM-5, PSYCHLOPS – Psychological Outcomes Profiles. Bold prints indicate statistically significant differences.

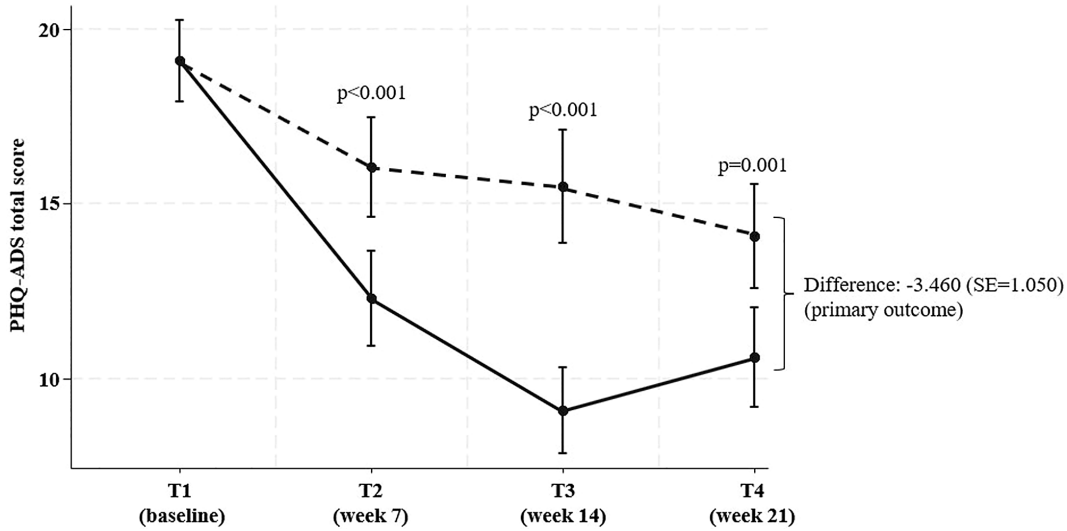

Figure 2 Average PHQ-ADS (Patient Health Questionnaire Anxiety and Depression Scale) total score at different timepoints, with confidence intervals, in intervention (solid line) and control (dotted line) arms (intention-to-treat population). SE – standard error.

ables at baseline, we included these variables in planned regression analyses of the primary outcome, without finding relevant differences in relation to our main analyses (see supplementary information).

We also tested, as planned, for interactions between intervention allocation and potential moderators (baseline score on the

Table 3 Coefficients for primary and secondary outcomes at each timepoint (per-protocol analysis)

	Coefficient (SE)	p
PHQ-ADS score		
T2	–4.215 (1.039)	**<0.001**
T3	–6.982 (1.043)	**<0.001**
T4 (primary outcome)	–4.208 (1.068)	**<0.001**
PHQ-9 score		
T2	–1.948 (0.609)	**0.001**
T3	–3.493 (0.612)	**<0.001**
T4	–1.696 (0.612)	**0.006**
GAD-7 score		
T2	–2.256 (0.542)	**<0.001**
T3	–3.491 (0.545)	**<0.001**
T4	–2.504 (0.545)	**<0.001**
PCL-5 score		
T2	–1.831 (0.828)	**0.027**
T3	–4.088 (0.826)	**<0.001**
T4	–2.930 (0.830)	**<0.001**
PSYCHLOPS score		
T2	–2.606 (0.739)	**<0.001**
T3	–3.796 (0.776)	**<0.001**
T4	–4.044 (0.729)	**<0.001**

SE – standard error, PHQ-ADS – Patient Health Questionnaire Anxiety and Depression Scale, PHQ-9 – Patient Health Questionnaire-9, GAD-7 – Generalized Anxiety Disorder-7, PCL-5 – PTSD Checklist for DSM-5, PSYCHLOPS – Psychological Outcomes Profiles. Bold prints indicate statistically significant values.

primary outcome, age, gender, legal status, time since resettlement; whether the person had at least secondary education, was receiving an income, and had ever consulted a mental health professional). In mixed models built on our main model, by adding such variables and their interaction with intervention allocation as regressors, only the baseline value of the primary outcome measure was statistically significant, and remained so after the Benjamini-Hochberg correction (p=0.006, see Table 4). The effect of the intervention on reducing PHQ-ADS scores was stronger for participants with higher scores at baseline (see supplementary information).

Table 4 Test for interactions of potential moderators with treatment

	Chi-square	p	Adjusted p
Baseline score on the primary outcome	17.17	**0.0007**	**0.006**
Gender	0.71	0.872	0.885
Age	4.48	0.214	0.506
At least secondary education	7.32	0.292	0.506
Legal status	7.06	0.316	0.506
Time since resettlement	3.65	0.302	0.506
Income	1.85	0.605	0.807
Ever consulted a mental health professional	0.65	0.885	0.885

The reported adjusted p values are those following Benjamini-Hochberg correction. Bold prints indicate statistically significant values.

We did not identify any serious adverse event. Six adverse events were identified, all of them regarded as unrelated to study participation (one accidental fall, one suicidal thought, two hospitalizations for a medical condition, two bereavement conditions).

DISCUSSION

In a migrant population with elevated psychological distress, a stepped-care programme combining DWM and PM+ (two WHO-developed, low-intensity, task-shifting psychological interventions) was effective in alleviating anxiety and depressive symptoms.

Efficacy was consistently observed at different timepoints, with coefficients indicating a substantial impact. Improvements were noted in depression and anxiety symptoms separately across all timepoints. Furthermore, the stepped-care programme showed positive effects on PTSD symptoms and self-assessed problems, function and well-being.

Exploratory analyses for heterogeneity did not detect significant interactions between the intervention and potential moderators, except for baseline values of the primary outcome measure. Notably, the intervention effect was more pronounced in participants with higher baseline levels of anxiety and depression, which can be seen as further evidence of its impact. The same finding was reported in a trial of PM+ for Syrian refugees[41] and in a trial testing stepped-care DWM/PM+ in health care workers in Spain[17]. In terms of acceptability, no serious adverse events were detected and very few participants were lost at follow-up. These findings support the programme's effectiveness and suggest its applicability to migrant populations.

The beneficial effects of the stepped-care programme may be related to various factors. DWM, based on acceptance and commitment therapy, aims to increase psychological flexibility and improve coping strategies to deal with adversity. As it is self-administered and only facilitated by trained helpers, it offers the opportunity to practice exercises through an online web/app, and to learn ways of recognizing and managing emotional states[9,42,43]. DWM might have encouraged participants to better adapt to fluctuating situational demands, by helping them to find ways of acting in accordance with their values, even in the face of external difficulties and migration-related stressors[43]. Participants may have acquired and consolidated skills to accommodate and "unhook" from difficult thoughts and feelings, through the integration of mindfulness techniques practiced regularly.

The possibility to move to PM+ for those still experiencing distress after DWM was a practical source of help in identifying and managing problems. PM+ helps people to improve the manage-

ment of practical (e.g., unemployment, interpersonal conflict, poverty) and psychological (e.g., depression, anxiety, grief, fear, feelings of helplessness) problems. Additionally, PM+ ingredients such as behavioral activation and use/strengthening of social support may have contributed to lowering symptoms of common mental disorders. Psychotherapy research indicates that guided Internet-based psychological interventions are influenced by social support to a greater extent than in-person therapy[44,45]. This is attributed to the fact that online interventions heavily depend on self-motivation and the completion of activities even in the absence of direct or long therapist interaction[44,46].

Moreover, the interpersonal dynamics with helpers may have exerted a direct and positive impact on outcomes[47]. These dynamics are particularly important for migrants, because of the potential lack of robust social support and networks in the country of resettlement. A systematic review of 35 RCTs, which examined 33 mental health interventions delivered through a digital format, found that the effects were larger when interventions were complemented with clinical assistance[48]. This underscores the key role of helpers in our trial, especially for PM+.

In addition, the digital format of DWM and PM+ is more flexible than in-person delivery, and could have contributed to increasing attendance, as highlighted by the low number of participants who did not complete the sessions. This, in turn, could have reinforced the effect of the intervention. In previous RCTs testing SH+ delivered in person and in groups to asylum seekers and refugees, we identified high proportions who did not attend the sessions[12,13]. This may reflect the fact that migrants have many competing priorities other than attending mental health-focused interventions, such as meeting basic needs, securing housing, navigating legal procedures, finding a job, and learning a new language[24].

We note some limitations of our study. First, we were inclusive in the definition of migrant participants, with the advantage of identifying a large group of distressed people, including asylum seekers, refugees and people in unstable living conditions. However, factors such as the type and number of stressors, barriers in the host country, availability of social support and sheltering centres, and time since resettlement, might have generated heterogeneity in the sample, with potential impact on the intervention's effect[49]. Nonetheless, when we tested for interactions between intervention allocation and age, gender, education level, time since resettlement, legal status and receiving an income, we found no signal that the effect of the stepped-care programme might differ with respect to these factors. Additionally, the main socio-demographic characteristics of the population group of our trial are aligned with those reported by the International Organization for Migration in relation to international migration flows and migrants resettled in Italy[1]. All this suggests that the stepped-care programme has a potential of uptake across migrant populations beyond this trial.

A second limitation is that a double-blind design was not feasible, and outcome measures were not assessed by masked assessors, but were self-reported. The use of self-reports can introduce variability and reduce the reliability of data, and the participants' overall perception of the intervention may influence how they report outcomes, leading to wrong estimates of effects. In the present study, however, this risk was mitigated by a design in which all participants received a supportive intervention, i.e. PFA. It is therefore likely that participants in both arms had similar perceptions of care. The finding that losses to follow-up were minimal and similarly distributed in the two intervention arms appears to support this consideration. We also observed that the use of social and health care services was similar in the two groups during the study, highlighting a low risk of performance bias.

Third, the study had a relatively short follow-up period. Therefore, we cannot exclude that the positive effects that we observed would diminish over longer follow-up periods. Moreover, our study was not specifically designed to test a stepped-care model against a single intervention. Future studies could usefully examine the stepped-care model versus PM+ or DWM as stand-alone interventions.

Overall, these results significantly expand the existing knowledge on the efficacy of psychological interventions in migrant populations, by showing for the first time that low-intensity, task-shifting interventions with freely accessible manuals may be implemented as a stepped-care programme to alleviate anxiety and depression in migrants with elevated distress. Due to these characteristics, these interventions are uniquely suited for implementation in low-resource settings. Considering that even countries classified as middle- or high-income, such as Italy, may experience significant resource constraints in certain sectors, regions, or for certain populations such as migrants, these interventions may be appropriate for countries at any level of economic development.

Regarding implications for policy makers aiming to scale up these interventions, local adaptation may be a key factor[26,50,51]. It is important to tailor the stepped-care programme to the specific needs and characteristics of the target population. The demographics, cultural norms and unique challenges of the community or group for whom the intervention is intended should be carefully assessed[52-54]. Adaptation may involve translating materials into local languages, considering cultural sensitivities, and incorporating feedback from local stakeholders, to make the intervention accurate, understandable and acceptable.

A second consideration is that the stepped-care programme may be scaled up in parallel or in series with existing services. In the parallel approach, it is introduced alongside the existing services, creating a parallel track for addressing vulnerability to mental health challenges. By introducing parallel interventions, it may be possible to reach more migrant groups, outside the health care sector, ensuring that a broader spectrum of people can access the support that they require. However, there are some challenges associated with parallel implementation: in particular, it can strain resources, as it necessitates separate funding, staffing and infrastructure. This can lead to inefficiencies or duplication of efforts.

In contrast, the series approach involves introducing the stepped-care programme sequentially, for example before or after migrants have received the existing social services. One key advantage of implementing in series is resource efficiency. It maximizes the use of existing infrastructure and personnel before introducing new elements, minimizing duplication of resources. However, the series approach may be less adaptable to evolving needs or chang-

ing circumstances, and it may not accommodate specific, targeted interventions as effectively as the parallel approach.

The scale-up of the stepped-care programme, either in parallel or in series with existing services, needs to be studied using quantitative or mixed approaches, aiming to identify the most cost-effective implementation strategies.

In conclusion, this study provides evidence supporting the effectiveness of the stepped-care delivery of DWM and PM+ in migrant population groups with elevated distress. Existing evidence-based guidelines and implementation packages should be updated accordingly, and applied by various social and health care organizations, to ensure that migrant groups have equitable access to high-quality mental health care.

ACKNOWLEDGEMENTS

This work was supported by the European Commission, Horizon 2020 (grant no. 101016127). The authors are grateful to helpers who facilitated the implementation of DWM, and delivered the PFA and PM+ interventions. Supplementary information on this study is available at https://trng-b2share.eudat.eu/records/11c67c2b492a4dd3a1325c5852b3657c.

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DOI:10.1002/wps.21281

Changing approaches to interventions for autistic adults

The last decade has witnessed many changes in our knowledge of and approaches to autism. While this was initially considered a severe childhood disorder, typically associated with significant intellectual and language impairments, recent research suggests that the majority of autistic individuals (~60%) are of average or higher IQ (≥86), and less than a third have severe cognitive (IQ <50) and communication impairments[1]. Autism is also now recognized as a lifelong condition, although the impact on functioning and the need for intervention varies extensively over time, both across and within individuals.

Probably the greatest change relevant to intervention results from calls by autistic adults, from many different personal and professional backgrounds, for a "de-pathologizing" of the condition. They argue that autism should not be considered as a deficit or disorder, but as an aspect of neurodiversity within human society. There is growing resistance to interventions designed to "manage" autism and a focus, instead, on the environmental factors (individual, social, physical) that affect well-being and quality of life[2]. Consequently, current approaches to research and intervention increasingly involve collaborations between the autistic and non-autistic community to facilitate mutual understanding and promote outcomes that are relevant and meaningful to autistic people[3].

A further significant shift is the recognition that, in adulthood, it is generally not autistic features that prove the main barrier to social inclusion, but poor mental health. Mental health problems – especially anxiety, depression and attention-deficit/hyperactivity disorder – are significantly raised in autism[4]. There is also a heightened risk of suicide. Chronic physical ill-health, too, is significantly more frequent than in the general population, and poor physical and mental health are both associated with an increased risk of premature mortality. Among the many factors affecting mental well-being are failure to find or maintain appropriate employment, and limited access to social and leisure activities or independent accommodation, all leading, in turn, to economic disadvantage, over-dependence on families, stigmatization, victimization, social isolation and low self-esteem.

Among the various psychological interventions for mental health problems in autism, cognitive-behavioral and mindfulness-based techniques appear to be at least moderately effective for reducing anxiety, obsessive-compulsive behaviors, depressive symptoms and social anxiety[5]. The evidence on treatments for severe depression is weaker and few trials have included clinically ill patients. Overall, the quality of many trials is limited, and participant groups are often small and homogeneous (mostly male, relatively young and without intellectual disability). Furthermore, despite calls for autism-specific adaptations of standard techniques to improve treatment effectiveness, currently there are no empirically derived guidelines on how this should be done.

Other trials of psychological interventions have concentrated on social-communication skills, with improvements reported in social cognition, emotional understanding and engagement with peers[6]. However, while some studies report moderate to large effects, others find no significant improvements; few describe the impact on real-life social interactions, and very few include older autistic adults or those with more severe cognitive disabilities. Critics of "social skills training" also highlight lack of attention to the dynamic nature of social interactions – which involve not only the autistic person, but others' perceptions, judgments, reactions and responses.

Alternative approaches in adults have aimed to address problems that affect well-being and quality of life[7]. These include programmes for young autistic adults that foster academic, vocational or work-related skills to aid the transition into employment. Interventions designed to improve daily life skills and/or increase access to leisure programmes suggest that these may reduce stress and improve cognitive and social skills as well as mental health. Specialist supported employment schemes can increase access to work and job retention, resulting in higher job levels, better pay and improved quality of life. These typically focus on ways of minimizing stress caused by excessive social or environmental demands, and educating employers on how to achieve an "autism friendly" workplace[7].

Unfortunately, even in higher income countries, access to such specialist programmes is very limited, and there are few community services available once the intervention scheme ends. Some autistic participants also suggest that these programmes are not always well adapted to meet individual goals. To date, the lack of adequately powered randomized controlled trials, and the wide mix of participants and treatment methods, mean that it is still not possible to identify which specific approaches work best for which individuals, or which are the essential elements of effective programmes.

Collaborations between autistic and non-autistic researchers have also begun to identify many more factors that have a negative impact on well-being. These include the multiple social and environmental barriers experienced by autistic individuals in accessing health services. Sensory sensitivities (e.g., to sounds, textures, smells, food) can also severely limit daily activities, while personal accounts highlight the risk of "autistic burnout" due to the continual stress of attempting to camouflage autistic traits in order to adapt to a "neurotypical" world.

Such difficulties may be better helped by environmental modifications and interventions to improve wider social attitudes, rather than attempting to change autistic individuals themselves. There is a pressing need, too, to recognize, and make accommodations for, the particular assessment, intervention and support needs of autistic women, including their somewhat atypical manifestation of autism traits, and their requirements for better adapted services around pregnancy, parenthood and menopause.

The focus here has been so far on autistic adults who can voice their own concerns and make recommendations for change. However, it is crucial to remember the almost 30% of individuals whose autism is compounded by severe intellectual and communi-

cation disabilities; behavioral difficulties, including self-injury; and life-threatening physical problems such as epilepsy. These individuals are also at greater risk of victimization, abuse and social and economic disadvantage. There has been growing concern that their needs, and those of their carers, could become marginalized in disputes about pathological versus ecological models of autism and whether autism should be viewed as a "difference" rather than a disability.

To address such concerns, the term "profound autism" was proposed to distinguish individuals with high dependency needs from the more verbally and intellectually able autism population[8]. While this term has generated considerable criticism, especially within the neurodiversity movement, it underscores the fact that, for some adults, autism can have a profound negative impact on quality of life. Moreover, because these individuals are rarely involved in research, knowledge about effective interventions is limited, and risks of maltreatment (including excessive use of medication and restraint) are high.

Research is needed to develop economically viable support programmes that can be adapted to individual and cultural circumstances and rolled out within high-, middle- and lower-income countries. Among the most immediate needs are access to ongoing opportunities to develop social, communication and daily-life skills; provision of appropriate occupational, leisure and residential facilities; and practical, social, economic and emotional support for carers.

A current guideline, by autistic writers and researchers, specifies other elements of quality care relevant to adults of all ability levels[9]. These include a focus on promoting autonomy, facilitating communication, tackling environmental and other stressors, removing barriers to access, fighting stigma and discrimination, recognizing distress, providing person-centred care, and ensuring ongoing and autism-specific staff training.

Since all outcomes arise from a "dynamic interaction between the individual and his or her environment that plays out over time"[2], provision of care appropriate for individual needs should be available to all autistic people throughout the lifespan.

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DOI:10.1002/wps.21282

Vulnerability to addictive behaviors: the Associational Memory-Appetitive Systems Relations Model

The concept of behavioral addictions invites controversy, but is slowly penetrating psychiatric consensus. Any addiction involves five components[1]: a) existence of appetitive needs and b) repeated attempts at satiation of these needs through ingestion of a substance or engagement in a behavior (appetitive effects), followed at some point by c) preoccupation with obtaining appetitive effects (e.g., craving, tolerance), d) loss of control over time spent engaged in appetitive effect-related behavior (e.g., duration, relapse), and e) undesired or negative consequences (such as failure to meet work, familial and social obligations; suffering physical injury; emotional turmoil) resulting from continued engagement in the behavior[2].

The fundamental underlying perspective is that addiction involves disruption of appetitive functioning; that is, of behavior directed towards fulfilling specific human psycho-socio-biological needs[3]. It has been theorized that addictive phenomena operate through appetitive mechanisms involving, in part, a misleading, temporary subjective sense of neurobiological fitness[4,5]. This experience may be identified through subjective changes in a) affect (e.g., feelings of joy, or merely improvement of affect), b) level of arousal (e.g., alertness or sedation/calm), or c) cognition (e.g., clarity, enlightenment, or decrease in tempo of stream of thought). One may learn to associate in memory the appetitive need (internal cue) with the contexts (location, time of day, situation) and behavior (e.g., sex, work) that led to its temporary subjective satiation, even though the result may not actually be biologically adaptive.

The Associational Memory-Appetitive Systems Relations Model of addiction describes how appetitive motives may become excessive, atypically elicited, or misdirected[5]. There are four main components of this model.

First, it is acknowledged that addictions (e.g., alcohol use) have a substantial *genetic* component (e.g., between 10 and 50% is accounted for by genetics). The model theorizes that one's appetitive needs are impacted by one's genetics. Individuals with a genetic predisposition to substance or behavioral addictions may have a different physiological reaction when engaging in certain behaviors (e.g., involving valence of subjective reward, dissociation of wanting and liking, or involvement of counteradaptation processes). The neurochemistry of an individual can potentially create an inclination toward maladaptive appetitive functioning. DNA epigenetic processes such as cytosine methylation may impact gene expression in the nucleus accumbens (part of an appetitive motivation pathway) subsequent to initial recreational drug intake and possibly involvement in other addictive behaviors. Prolonged pe-

riods of stress, particularly at a young age (adverse childhood experiences), may lead to disruption in brain reward cascade functioning. Such disruption, in turn, may increase one's vulnerability to addictive behavioral rewards.

Second, the social and physical environmental *settings* that one traverses will impact what information one learns and how one thinks, and may facilitate which behaviors one may select to perform. Daily life social "pushes" (stresses, social influence) and "pulls" (seductions) provide possible avenues of addiction. For example, encouragement by peers to engage in drug use or marketing the "excitement" of local casinos may push or pull one to explore an addictive substance or behavior. Production and distribution routes of various addictive behaviors will impact what is available to the potential "consumer". Accessibility and awareness of nearby addictive behavior will impact which behaviors one will initiate.

Third, one's *lifestyle* inputs also impact what behaviors may "pop" to mind in daily life. A child who grows up with parents who were engaged in addictive behaviors may be relatively likely to tie appetitive needs fulfillment to an addiction-related lifestyle through vicarious learning[3], or else be quite wary to fall victim to such a behavior pattern. In addition, through vicarious experiences, one may learn the vocabulary associated with an addictive behavior (e.g., cannabis "head high" versus a "body high"). That is, one may be socialized and prepared at a young age for entrée into involvement with an addictive behavior later on.

When one contemplates trial of an addictive behavior, it should be mentioned that acquisition skills are needed to be able to engage in the behavior with minimal conflict. This includes behavior-specific conversation initiation skills (i.e., knowing how to meet a "supplier" and acquire the addictive behavior; for example, arranging a purchase of cocaine, or time with a sex worker) and a means of exchange (e.g., money or favors for drugs).

Involvement in different addictions may vary over the course of human development. For example, persons as young as three years of age may suffer from television addiction. Persons as young as eight years of age may become addicted to caffeine. There are many behaviors that could be experienced as appetitive and become addictive (e.g., tobacco, alcohol, and other drug misuse; binge overeating/food addiction; shopping; electronic media-related; love and sex; workaholism; exercise; and gambling)[3]. A large minority or a majority of people have tried at least once engaging in various addictive behaviors (e.g., overeating, alcohol use, overspending). More-than-initial trial of an addictive behavior is partly a function of attraction to that behavior. Attraction-related variables include the social image associated with the behavior (e.g., mentioned in the recovery movement, of being "hip, slick and cool"), what one's peers are engaged in (peer social influence), as well neurobiological effects of engaging in the behavior.

Fourth, it is through the process of *associative learning* that appetitive needs come to be subjectively satiated through adaptive or maladaptive behaviors. Associative learning and memory have been considered in several recent models of addictive behaviors. Cues in an environment that otherwise would be considered innocuous can stand out to be emotionally salient when influenced by motivational states[6]. These cues can range from eating behavior being triggered when seeing fast food sign cues or eating locations, or a drug user becoming excited or agitated when in sight of his/her drug of choice.

Some individuals may not, through deliberate cognition, recognize that their decisional processes are being influenced by maladaptive or extreme reward cues. It has been proposed[7] that appetitive motivation is controlled through a dual process of deliberate, conscious, executive, regulatory cognition interacting with relatively automatic, implicit processes, in response to addiction-related cues. Over time, in part due to relatively automatic prompting by multiple cues, one may experience excessive thoughts about and desire to perform a behavior. In turn, excessive time may be spent to plan and engage in the behavior, and possibly recover from its effects (e.g., from "hangovers"), and less time may be spent on other activities, despite diminishing appetitive effects[1,8]. One is most vulnerable to initial and continued trial of an addictive behavior if the initial consequences are experienced as "filling the gap" in one's sense of well-being (i.e., of being satiated, fulfilled). A widely used saying within the recovery movement is that at first the addiction "does something for the person" and then it "does something to the person".

In conclusion, appetitive needs are instinctually embodied in every human being from birth. For at least the past one hundred years, researchers have been exploring the parameters of appetitive needs in human beings[9]. The interface between one's genetics, social and physical environmental cues, lifestyle situations, development and adaptation (epigenetics and associative learning), and associative memory, may underlie addictive behavior.

There is a lot to be learned from an appetitive needs perspective on what is at the root of an addictive process. Appetitive needs which might be explored include those of dominance/leadership, respect, being part of a herd, providing nurturance or being nurtured, and obtaining pleasure[3,5]. More research is needed to explore a taxonomy of appetitive needs, and how different appetitive needs act as sources of vulnerability factors and may transform into specific addictive behaviors.

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DOI:10.1002/wps.21283

Suicide prevention: what works, what might work, and what does not work

Suicide prevention is a global public health priority, with many countries adopting national suicide prevention strategies over the past 30 years. Global suicide rates decreased by almost one third between 1990 and 2016[1]. Notably, recent data indicate that US rates have markedly defied this trend.

It is difficult to demonstrate that reductions in suicide rates seen in most countries reflect the introduction of national suicide prevention strategies. However, there is evidence regarding some of the specific initiatives that often comprise such strategies, including what is effective and what seems not to work. The suicide prevention field is also rapidly evolving, with many promising approaches still needing fuller evidence.

Modification of access to the means for suicidal acts is the suicide prevention policy for which there is the best evidence of effectiveness. This has ranged from removing access to specific methods to introducing policies for detecting and intervening when individuals may be about to initiate a suicidal act in a public place.

Ingestion of pesticides has been a major means of suicide in many lower-and-middle income countries. With removal of more toxic pesticides in some countries, the most recent data from the World Health Organization (WHO) indicate fewer deaths involving this method. In China, for example, national bans on highly hazardous pesticides in 2008 and 2016 were followed by major reductions in suicides involving pesticides, and a marked decrease in overall national suicide rates[2]. Notably, introduction of safer storage policies for pesticides has not had a similar impact.

Erection of safety barriers on bridges, and other safety measures at public sites frequently used for suicide, have been shown in several studies to reduce deaths at those locations, with limited displacement to other potential nearby sites[3]. There is also support for interventions that encourage help-seeking at such sites[3]. Initiatives to prevent suicides on rail networks are ongoing in several countries, but have less evidence of effectiveness at the moment.

Restricting pack sizes of analgesics commonly used in self-poisoning, or complete removal for particularly toxic drugs, have been found to have a preventive effect. Although more than half of all suicides in the US involve firearms, there has been relatively little effective action to restrict access to guns in that country, probably due to a combination of cultural and commercial factors, together with a strong gun lobby. This is likely to have contributed to suicide rates in the US failing to follow recent global declines.

Dramatic reporting and portrayal of suicides in traditional, social and entertainment media can increase risk of suicidal behavior in those exposed to these influences. The WHO and many countries have developed guidelines aimed at improving how suicide is reported or portrayed. These have generally led to improved quality of suicide-related content, although there is less evidence regarding their potential contribution to reducing suicides. However, public health messaging sharing narratives of survival and modelling help-seeking, especially when done by a celebrity, can have positive effects on both attempts to get help and suicide rates[4].

Several school-based suicide prevention interventions have been developed, with mixed evidence for efficacy in the context of methodological concerns for some studies. There is reasonable support of impacts on suicidal thoughts and behaviors for a European programme focused on mental health literacy and coping skills development, and an American one focused on helping students recognize warning signs and on help-seeking, for both themselves and friends[5].

Broad socioeconomic conditions also contribute to suicide risk and can be leveraged for prevention, with many studies linking macroeconomic policy and suicide rates in both high and lower-and-middle income countries. Increasing employment rates appear to reduce suicide in middle-aged adults. Likewise, increases in social welfare spending, minimum wage, per capita gross domestic product, and investment in active labor market programs, all tend to reduce suicide rates. Strategic spending may also be particularly important in counteracting the effects of economic downturn on suicide rates.

Large proportions of people dying by suicide have psychiatric disorders, especially mood disorders, but also personality, psychotic, substance use or eating disorders. There has been considerable controversy about whether antidepressant treatment helps prevent suicide. A meta-analysis of observational studies found that exposure to selective serotonin reuptake inhibitors was associated with increased risk of suicide death or attempt among adolescents, but somewhat decreased risk among adults, and had a clear protective effect in those aged 65 years and above, although this last finding was based on just two studies[6].

Attention has also focused on the role of mood stabilizers in reducing the high risk of suicide in bipolar disorder. A review of systematic reviews showed substantial evidence that lithium can reduce the occurrence of suicidal acts[7]. The potential role of ketamine, electroconvulsive therapy and clozapine in reducing risk of suicide in specific patient populations requires further substantiation.

Some psychotherapies have shown promising results in reducing self-harm, a much more frequent phenomenon than suicide, that can be more easily studied in clinical trials. These include cognitive behavioral therapy (CBT)-type interventions for people presenting to hospital following self-harm, and dialectical behavior therapy (DBT) for similar presenting people with a history of borderline personality disorder and repeated self-harm[8]. However, interventions effective for prevention of repeated self-harm in children and adolescents other than DBT have not so far been identified. Also, the size of trials required to show an impact of these psychotherapies on suicide is very large.

Historically, a major and understandable focus of prevention efforts in psychiatric services has been to try to identify patients

most at risk of suicide. However, increasing evidence indicates that these efforts are largely ineffective, with prediction estimates being very low, and indeed the majority of suicides occurring in individuals identified as at lower risk[9]. Like population-level efforts, the most effective clinical interventions must be available for as many patients as possible. This approach also aligns with standard clinical practices across medicine, which generally emphasize treatment that lowers risk across an entire group rather than prediction of who will experience a sentinel event (e.g., myocardial infarction).

There is good evidence that safety planning – through which clinician and patient work together to plan and document measures that the patient will take if a crisis is developing – is effective in reducing the occurrence of suicidal acts. This should be offered along with comprehensive biopsychosocial care and therapeutic risk management, including a focus on clinical interventions likely to improve patients' well-being. While requiring further evaluation, this overall approach is likely the optimal strategy for preventing suicide in people with mental disorders[9].

In conclusion, suicide prevention through national strategies and other coordinated actions must include a combination of public health and clinical policies, with the former likely having a greater impact on suicide rates. Population-level interventions should include a focus on decreasing access to the means of suicide, increasing access to information about how to seek help and survive (including via the media and educational programs), and creating economic conditions that decrease stress on populations. Clinical interventions should focus on high-quality, humane care, including safety planning and targeted evidence-based treatment according to the individualized needs of patients.

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DOI:10.1002/wps.21284

The 988 Suicide and Crisis Lifeline in the US: status of evidence on implementation

In July 2022, "988" became the US dialing code for the Suicide and Crisis Lifeline, which replaced what was, since 2005, the National Suicide Prevention Lifeline (NSPL), reachable via "1-800-273-TALK". The transition from a ten to three-digit dialing code – like others widely known and used in the US – was intended to increase awareness and use of the lifeline. Furthermore, by changing the name and marketing of the lifeline from being narrowly focused on suicide to being explicitly inclusive of mental health crisis more broadly, 988 expanded the target population.

Since evaluations of the NSPL suggest that it improved callers' psychological well-being and reduced the incidence of suicide death[1,2], 988 has potential to produce benefits for population mental health in the US. In this piece, written about two years after 988's launch, we provide an overview of extant evidence about 988's implementation. This evidence spans six domains.

First is evidence from administrative data about *988 call volume*. This increased nationally by about 40% (compared to the previous lifeline) to almost 5 million contacts in the first year after the launch. The call volume increased in every state, but the magnitude of the increase differed dramatically between states (e.g., increase of 74% in Wisconsin versus 8% in Texas)[3]. One study also documented wide between-state variation in Google searches for 988[4], which could reflect variation in the intensity of marketing between states. In general, increases in call volume can be interpreted as a promising finding, given that daily increases in NSPL call volume – prompted by a pop song promoting the lifeline – were independently associated with daily reductions in suicide death[2]. Future research should explore whether similar associations between call volume and suicide death (as well as other outcomes, such as emergency department use for mental health crisis) persist in the 988 context.

Second is evidence about the *prevalence and correlates of 988 use*. This evidence comes from surveys conducted with nationally representative probability panels about one year after the launch of the lifeline[5-8]. One of these surveys found that 0.8% (95% CI: 0.5-1.0) of adult respondents had used 988 on behalf of themselves[5]. However, the proportion was 6% (95% CI: 3.6-8.3) among respondents with "serious" past 30-day psychological distress (Kessler K6 score ≥13), compared to 1% (95% CI: 0.4-1.6) of those with moderate distress and 0.2% (95% CI: 0-0.3) among those with no distress. Another survey of US residents aged ≥13 found that 2% had used 988 and that the proportion was 3% among respondents with a history of suicidality/suicide attempt[6]. While these studies shed light on the prevalence of 988 use, future work should explore the incidence of this use and the correlates of repeated use among individual callers.

Third is evidence related to *people's experiences using 988*. These data also come from population-based probability surveys, but should be interpreted with caution, given the small sample sizes (i.e., N<50) of respondents. One of these surveys found that, among respondents who had used 988 on behalf of themselves or a loved one, 68% reported receiving "all" (28%) or "some" (40%) of

"the help they needed", while 14% selected the response "No, did not receive the help needed"[7]. Another survey found that only 29% of adults with serious past 30-day psychological distress who used 988 reported being "very likely" (6-7 on a 7-point scale) to use it in the future if they were experiencing suicidality or a mental health crisis[5]. These data highlight the importance of future research that explores how, and for whom, 988 is or is not satisfying callers' needs and expectations.

Fourth is evidence about *knowledge about and intention to use 988*. About one-year following 988's launch, about half of US adults had heard of 988[5]. This proportion will inevitably increase as time elapses and people are exposed to more marketing and news about the lifeline. Data indicate, however, that not all people who are aware of 988 have intention to use it if they or a loved one need it in the future. One of the aforementioned surveys found that the percentage of respondents who reported being "very likely" to use 988 in a crisis was lower among those with serious (22%; 95% CI: 18-26) and moderate (21%; 95% CI: 18-23) distress than no distress (26%; 95% CI: 25-28)[5]. Another of the surveys found that just 35% of adults reported being "highly likely" to use 988 if they or someone they knew "needed help"[8]. A separate survey found that 26% of respondents had "a great deal of trust" that they would receive the help they needed if they contacted 988 – compared to 37% for contacting 911 (an emergency number for any police, fire or medical help)[7]. Another of the surveys found that 33% of respondents aged ≥13 reported being "likely" (4-5 on 5-point scale) to use 988 if they were "struggling with [their] mental health", and the proportion was 37% among respondents with a history of suicidality/suicide attempt[6]. These findings highlight a need for communications research that can inform marketing and messages which foster positive attitudes towards 988 and intention to use it if needed in the future.

Fifth is evidence related to *988 financing*. Although 988 was created by federal law, states have broad discretion regarding how and the extent to which they fund implementation. Extant data indicate broad between-state heterogeneity in 988 financing. One study found that fiscal year 2022 state per capita expenditures for 988 ranged between $4.73 to $0.30 (mean ± SD: $1.15±1.28)[3]. Surveys of public system leaders also found wide between-state variation in 988 financial readiness. Consistent with state variation in 988 financing and readiness, between-state variation was documented in the extent to which state legislators promulgated the launch of 988 on social media and mentioned the importance of state financing in its implementation success[9]. Variations in state 988 financing offer opportunities for natural experimentation and assessing the effects of different financing approaches and levels of investments.

Sixth is evidence about the *performance of 988 systems*. Numerous metrics of state 988 system performance are available in public reports (e.g., https://988lifeline.org/our-network). In general, these data are promising and indicate that federal and state investments in 988 have enhanced the capacity of lifeline systems. For example, in March 2024, the mean 988 wait time across US states was 21 seconds. The mean in-state answer rate – i.e., the percentage of calls from a state fielded in that state, conceptualized as a quality metric – was 85%. This is an improvement from the NSPL era, despite increases is lifeline demand which require greater staffing capacity. Future research should examine associations between changes in these system-level metrics, population mental health outcomes, and disparities therein.

988 has the ability to save lives and improve population mental health, and has demonstrated early evidence of fulfilling its potential. However, like any population-based intervention, these benefits come with potential risks – such as 988 callers having a suboptimal experience with a counselor that discourages future help-seeking, or being referred to community-based services that they are unable to access. Policy makers and system leaders across the US are making decisions about 988 implementation, and evidence from rigorous research is crucial to informing these decisions.

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DOI:10.1002/wps.21285

The WHO Special Initiative for Mental Health: increasing access to mental health services for millions of people

The World Health Organization (WHO) has consistently documented the global burden of mental, neurological and substance use disorders, and the significant treatment gaps, which are most pronounced in low-resource settings[1]. Despite global targets set for WHO Member States in the Comprehensive Mental Health Action Plan[2], progress has been slow. In 2019, aiming to support countries to work towards targets in that Action Plan, and to demonstrate that transformation of mental health services is achievable, the WHO launched its Special Initiative for Mental Health: Universal Health Coverage for Mental Health[3].

This Special Initiative aims to increase access to mental health services for 100 million more people across 12 countries. It features two strategic actions: a) advancing mental health policy, advocacy and human rights, and b) scaling up interventions and services across community-based, general health and specialist settings. These actions are deliberately broad, to allow for a health system strengthening approach to transform national-level mental health systems and services, as described in WHO's World Mental Health Report[1].

Engaging with ministries of health, service users and other stakeholders, the Special Initiative for Mental Health has walked a multi-year journey in each country. Even though the myriad challenges facing mental health services cannot be addressed under one programme, the Initiative has catalyzed interest and investments, and is building foundations for continued work.

Alongside expressed government readiness for services transformation, the Special Initiative countries were selected to represent each of the WHO six regions. Following baseline situational assessments[4], consultative planning and design work began in 2020 in six countries: Bangladesh, Jordan, Paraguay, the Philippines, Ukraine and Zimbabwe. Implementation of activities commenced later that same year and in early 2021. As financial resources allowed, Ghana, Nepal and Argentina later entered the Initiative. These nine countries are the focus of the Initiative to date.

Based on monitoring data from the nine countries (as of September 2024), access to newly available mental health services, at local levels, has been enabled for nearly 60 million people. Due to data constraints, treatment coverage information is only being tracked from specific services, but is indicating that at least 717,000 children and adults are receiving mental health services, most for the first time. With government in the lead, supported by the WHO, more than 34,000 people have received mental health and psychosocial support training, and over 1,000 organizations have contributed to this success.

The quantitative data show only part of the story, however. Major national-level changes in every country have also been achieved. Priority focus on deinstitutionalization is gaining ground (in several provinces of Argentina and Paraguay); mental health laws have been introduced or updated (in Paraguay); ministries of health have restructured to increase focus on mental health (in Bangladesh); mental, neurological and substance use disorders have been included in national insurance coverage (in Ghana); essential medicine lists now include essential psychotropic medicines (in Zimbabwe); health information systems have expanded to include common mental, neurological and substance use disorders (in Nepal); provincial, district or local government units are increasing allocations for community mental health services (in Nepal and the Philippines); services for child and adolescent mental health have expanded (in Jordan); and, in addition to meeting emergency mental health and psychosocial support needs, Ukraine has progressed in the re-structuring of services, including establishment of more than 65 community mental health teams.

All countries have implemented elements of the WHO Mental Health GAP Action Programme (mhGAP)[5] and WHO's QualityRights[6] training, to include rights-based person-centered mental health services at primary health care levels, with many additionally expanding secondary care services in district level hospitals.

Remarkably, all this work has evolved from relatively small financial investments. Total expenditures for the Initiative to date amount to US$ 25 million. For every US$ 1 million spent, over two million people have now access to newly available mental health services in their communities. Or, put another way, the cost per newly reached person is less than US$ 0.50[7]. The vital system level changes that have emerged so far are paving the way for improved access and service quality in the future. Even though financial support for this type of longer-term mental health programme has not been easy to obtain, all contributions are attaining an impressive return on investment.

The WHO Special Initiative for Mental Health is by no means a perfect programme. It has demanded a heavy time and personnel commitment from governments, with robust support from local WHO staff, who have been subsequently supported by WHO regional and headquarters colleagues. Challenging long-held beliefs and practices about mental health services is taking time, and monitoring results from the Initiative has proved onerous and challenging. Figures presented here represent only high-level results being recorded, and the routine assessment of service user outcomes remains elusive. Similarly, the quality of services being provided requires further emphasis and oversight.

Although not a research programme, the Special Initiative will undergo reviews, case study analyses and the documentation of learnings in the coming 12-24 months. Exploring service user outcomes is also planned. These various learnings will benefit other countries seeking to undertake mental health transformation work. They will additionally inform WHO's plans to expand the Initiative by the end of 2028 under a second iteration.

Notwithstanding its limitations, the WHO Special Initiative for Mental Health is demonstrating that ambitious targets or recommendations, such as those set out in the Comprehensive Mental Health Action Plan[2] and the World Mental Health Report[1], are fea-

sible. While there are many angles from which such targets and recommendations may be achieved (e.g., focusing on specific groups, interventions or policies), having functional mental health systems and services will always be non-negotiable, as will a foundation from which to build quality and competency over time.

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The WHO would like to thank the Norwegian Agency for Development Cooperation, the Swiss Agency for Development and Cooperation, and the US Agency for International Development for their financial support to the WHO Special Initiative for Mental Health.

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DOI:10.1002/wps.21286

Minimal clinically important difference in obsessive-compulsive disorder

Researchers and clinicians treating people with obsessive-compulsive disorder (OCD) may want to know the smallest improvement in symptom severity that can be considered clinically meaningful. The concept of minimal clinically important difference (MCID) is gaining traction in psychiatry and is defined as the smallest change in an outcome that a patient or care provider deems beneficial or worthwhile[1,2].

To our knowledge, the MCID has not been calculated for OCD. Any MCID calculation should take into account the initial symptom severity, as the amount of improvement likely depends on the starting point. To be clinically meaningful, the MCID should also be validated against other important outcomes such as self-reported symptoms, general functioning or quality of life. In other words, the concept of MCID will only be useful to clinicians if it captures changes that matter to patients.

In this study, we calculated the MCID in a large international sample of youth and adults meeting DSM-IV or DSM-5 diagnostic criteria for OCD and with data available at baseline and post-treatment (N=2,136). Participants were drawn from randomized controlled trials and open or cohort studies conducted in Sweden (72%), the US (20%) and Australia (8%). All individual studies were approved by the relevant ethical review boards, and all participants provided written informed consent or assent (depending on age) prior to participation. A majority of the participants were under 18 years old (57%) and female (58%).

We used the clinician-rated Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) to calculate the MCID value[3,4]. The Y-BOCS is used internationally in OCD research, and is applicable to children, adolescents and adults. Y-BOCS total scores range from 0 to 40, with higher scores indicating higher severity. A score of 14 or higher indicates clinical severity[5]. In this study, the mean Y-BOCS score at baseline was 23.63±4.83, indicating moderately severe OCD, while at post-treatment it was 13.14±6.88, indicating subclinical to mild OCD[5].

As an anchor measure of improvement, we used the Clinical Global Impression -Improvement (CGI-I)[6,7], a clinician-rated measure that considers all available information about a patient to rate the degree of improvement or worsening compared to a previous measurement point (in this case, the baseline assessment). The scoring of the CGI-I ranges from 1 to 7, with 1 indicating that a patient is very much improved and 7 indicating that he/she is very much worse.

To calculate the MCID scores, participants were categorized as being at least slightly improved (CGI-I score 3 or lower, N=1,886) or unchanged/worsened (CGI-I score 4 or higher, N=250) at post-treatment. Both the raw and the percentage Y-BOCS change score were used as MCID variables. To identify the optimal MCID values, we conducted receiver operating characteristic (ROC) analyses, and calculated the area under the curve (AUC). The Youden index was used to identify the optimal MCID value, as it maximizes sensitivity and specificity simultaneously and is less sensitive to imbalanced groups.

The AUC for the raw Y-BOCS change score was excellent (0.92, 95% CI: 0.90-0.94). The optimal MCID value was a 6-point improvement on the Y-BOCS, yielding a sensitivity of 84%, a specificity of 86%, and an overall accuracy of 84%. The AUC for the percentage Y-BOCS change score was also excellent (0.93, 95% CI: 0.91-0.94), and the optimal MCID was a 25% improvement, yielding a sensitivity of 84%, a specificity of 90%, and an overall accuracy of 85%.

Next, we estimated MCID separately for those with mild (N=661), moderate (N=1,027) and severe (N=186) OCD at baseline, according to existing benchmarks[5]. Those with more severe OCD at baseline needed larger improvements to reach the MCID. This was evident for both the raw Y-BOCS change score (severe = 8 points, moderate = 6 points, mild = 4 points) and the percentage Y-BOCS change score (severe = 29%, moderate = 26%, mild = 18%).

Similar MCID values were obtained when analyzing separately

the subgroups of children and adults (6 vs. 6 points and 25% vs. 27%, respectively). Smaller MCID values emerged for Swedish vs. US/Australian participants (5 vs. 6 points and 20% vs. 26%, respectively), probably attributable to higher mean baseline severity in the US/Australian compared to Swedish participants (25.88±5.35 vs. 22.73±4.29, p<0.001, Cohen's d=0.69). Smaller MCID values also emerged for females compared to males (4 vs. 6 points and 20% vs. 25%, respectively), which was not explained by sex differences in baseline severity (24.00±4.80 vs. 23.68±4.81, p=0.15, Cohen's d=0.07).

Because MCID values differed across baseline severity groups, we used the percentage change of 25% for external validation. Participants reaching MCID showed more improvement than those not reaching MCID in self-reported OCD symptoms: the Cohen's d was 1.15 (MCID) vs. 0.25 (no MCID) among children (Obsessive-Compulsive Inventory-Child Version), and 1.31 vs. 0.72 among adults (Obsessive-Compulsive Inventory-Revised). The same applied to self-reported quality of life: the Cohen's d was 0.73 (MCID) vs. 0.22 (no MCID) among children (Child Health Utility, CHU9D), and 0.35 vs. 0.01 among adults (EuroQol-5D, EQ-5D). Similarly, for clinician-rated functioning, the Cohen's d was 1.25 (MCID) vs. 0.48 (no MCID) among children (Children's Global Assessment Scale), and 0.99 vs. 0.23 among adults (Global Assessment of Functioning).

The MCID will be useful to clinicians and researchers interested in knowing the smallest amount of symptom improvement on the Y-BOCS that corresponds to a clinically meaningful change. This measure is versatile, because it can be calculated either using raw Y-BOCS points or percentage Y-BOCS change scores, and is invariant across children and adults. However, the practical utility of the MCID may be somewhat limited by the fact that the value varies according to initial symptom severity and, for unclear reasons, also between sexes. It is important to specify that the MCID is not intended to substitute the more stringent constructs of treatment response and remission[8,9], which should always be the ultimate aim of any treatment for OCD.

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Supplementary information on this letter is available at https://osf.io/5awmz.

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DOI:10.1002/wps.21287

A new role for phenomenology in empowering patients based on quantitative evidence-based research

This piece illustrates the role of phenomenology in bringing a more nuanced understanding of the lived experience of patients' values (i.e., of what matters to them) within the remit of quantitative empirical medical research, thus contributing to patient empowerment. We first outline two exemplar studies – respectively, of mental illness and physical illness – and then discuss their wider significance for patient empowerment in evidence-based medical research underpinning the personalization agenda.

Our first exemplar study illustrates the power of phenomenology to illuminate the lived experience of people with eating disorders. Persons with anorexia nervosa may value thinness and fasting ahead of life itself. Rules concerning food are not merely about fasting and thinness as partial aspects of life, but about the way to make one's life *meaningful*. They are not merely the consequence of cognitive distortions. Food has a moral value – it is a sin and a temptation. Fatness is indicative of laziness, lack of self-care and self-control. Thinness, by contrast, is more important than health, because it means self-achievement and self-realization. Starvation is the unique salvation practice, since it serves to achieve a stable sense of identity.

In a series of publications, we found that these (to most people) incomprehensible values are readily interpreted through J.-P. Sartre's three-way phenomenology of the body. The essence of this interpretation is that the "visible" body, to which anorexic people attach so much value, takes on disproportionate importance because they only "feel" themselves through the gaze of others. This interpretation was validated using a phenomenological questionnaire[1]. We documented that feeling oneself through the gaze of the other is significantly more pronounced (effect size = 0.72) among patients with eating disorder (sample of 113 patients vs. 117 controls)[2]. Furthermore, a longitudinal observational study of 141 patients showed that higher levels of embodiment disorder predict diagnostic instability (odds ratio = 1.80), while its amelioration mediates the decrease in eating disorder-specific psycho-

pathology (indirect effect: 0.67)[3]. These findings have therapeutic potential when creating the relational premises for overcoming the symptoms[4].

This series of studies illustrates the power of phenomenological theory not only to provide insights into otherwise obscure values underlying psychopathology, but to do so in a way amenable to empirical validation, following the methodological demands of evidence-based medicine.

Understanding values is vital for the personalization agenda in mental health, because recovery is defined by reference to the values of the patient[5]. Clearly, there will be situations in which these values are irreconcilably at odds with those of other people (as in forensic psychiatry). However, in many other situations (as with eating disorders), understanding may be the first step toward reconciliation of values within recovery-oriented practice. The understanding provided by Sartre's phenomenology generates hypotheses about patients' values that – since they have been clinically tested through the resources of evidence-based medicine – provide a basis for recovery.

There are many other areas of phenomenological psychopathology capable in principle of generating hypotheses susceptible to evidence-based validation. Oxford philosopher K. Morris was early in the field with her use of Sartre's phenomenology to illuminate the experience of body dysmorphophobia.

Our second exemplar study illustrates similar results for bodily medicine achieved through a different aspect of phenomenology, i.e. its skills-based process. This focuses on the open observational stance instilled by training in phenomenology and captured in its concept of *epoché* (roughly, seeing clearly by stripping away preconceptions). The study illuminated lived experience, including patients' values, in women undergoing treatment for cancer, by drawing on the results of phenomenological research. Without an open phenomenological stance, the key finding – that women in this situation have increased awareness of and a deep need to speak about finitude[6] – would not have come to light.

The sequence of validation was broadly similar to our first exemplar study. A phenomenologically generated hypothesis[6] was validated with oncological patients in a quota representative sample of 440[7,8]. The research benefited directly from patient feedback in a consensual research design at both the qualitative and quantitative stages. The question regarding death had to be masked in the quantitative stage, which would not have been possible without direct feedback from patients on how to phrase it[7]. Indeed, without this feedback, the research would have been actively blocked by the local research ethics committee, on the (understandable but, as it turned out, misguided) grounds that such questions were too intrusive for women undergoing treatment for potentially terminal cancer.

Empowered, however, as the patients concerned were as partners, they pointed the research towards what would prove to be the clinically relevant finding on their awareness of finitude – increased among 66.8% of respondents regardless of cancer type and the length of treatment[7]. Following the patient-generated qualitative hypothesis, it was also found that chemotherapy had a very large effect (Cohen's d = 1.66) on changing the felt pace of time from flying to dragging, with impacts on care[8].

We turn now to the wider implications of our exemplar studies for patient empowerment. At the heart of both studies is a shift of focus from surface-level abnormal experiences to the exploration of deeper and more nuanced psychopathological aspects of lived experience, including patients' values. This shift in focus serves as a necessary foundation for identifying novel therapeutic targets defined (in part but crucially) by patients' values (i.e., by what matters or is important to them), amenable to empirical testing, and, consequently, enhancing outcomes for the individuals concerned. Evidence-based medicine, according to this model, thus both delivers on and is enhanced by engagement with the patient's voice in research.

In its contributions to such processes, phenomenology builds on secure foundations. We are, after all, not the first to emphasize the importance of the patient's voice in research: it is indeed some twenty years since the James Lind Alliance was established in Oxford with precisely this end in view (www.jla.nihr.ac.uk). Neither are we the first to build quantitative results on qualitative foundations: well-established social science methods support this move.

There remain, it is true, barriers to implementation: our second exemplar study illustrates one such barrier from (perhaps surprisingly) bioethics. These barriers are, of course, not unique to phenomenology. Indeed, as our second examplar study again illustrates, by carefully adjusting to the patients' usually hidden needs, phenomenology may have a role to play in overcoming them. This could be important for the wider problem of translation in the neurosciences: here, too, empowering the patient's voice in research could prove decisive[9].

To the extent that, as our exemplars suggest, phenomenology has a role to play in empowering the patient's voice in research, it holds a potentially key function across the board in advancing the personalization agenda of clinical care.

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DOI:10.1002/wps.21288

PSY-PGx: a new intervention for the implementation of pharmacogenetics in psychiatry

A recent Forum in this journal[1] highlighted the limited progress of pharmacotherapy in psychiatry, implying that new treatment strategies are urgently needed alongside the development of new drugs to improve patient care.

Individualizing treatment with established medications is one possible approach to significantly reduce the burden and health care costs per patient. Today, only about one third of patients attending psychiatric facilities respond fully to treatment with the available arsenal of medications[2,3]. The selection and dosing of these medications is based on a trial-and-error approach that relies primarily on the psychiatrist's experience and the patient's perception of the occurrence and intensity of side effects or clinical effects[2,3]. It can take weeks or even longer to find a medication that is sufficiently tolerable and effective for that patient[2,3].

Pharmacogenetic testing can improve this process by identifying individual-specific genetic variants that affect drug-metabolizing enzymes, drug transporters or drug targets[4-6]. In addition, genotype-dependent dosing guidelines for psychotropic drugs are available to physicians[5].

While an abundance of commercially available tests may suggest that pharmacogenetic approaches are a well-established tool in psychiatry, backed by a host of robust studies, this is not the case. The global psychiatric community still lacks an awareness and thorough understanding of the subject. Moreover, there is an urgent need for international, large-scale, independent clinical trials that can quantify and firmly establish the clinical benefits of the pharmacogenetic approach and subsequently enable further development in this area.

The European Union-funded and researcher-initiated PSY-PGx project was launched in 2021 (https://cordis.europa.eu/project/id/945151). It is the largest non-industry-funded project to implement pharmacogenetics in clinical psychiatry.

The project applies machine learning to data of already available biobanks, i.e. the Finnish hospital-based Auria Biobank (https://www.auria.fi/biopankki/sv/tutkijoille/fingenious.php) and the population-based UK Biobank (https://www.ukbiobank.ac.uk), aiming to assess the relationship between pharmacogenomics and clinical outcomes in patients with psychiatric disorders[6]. A medication prescription algorithm will be derived from these data.

Moreover, a clinical study is being conducted comparing individualized medication prescription based on pharmacogenetics to standard trial-and-error approaches. A comprehensive phenotyping and genotyping, utilizing a genome-wide microarray specifically designed with specialized pharmacogenetic content, is being performed[7]. Importantly, patients with mood, anxiety and psychotic disorders are being included. Phenotyping patients during the clinical trial aims to uncover additional genomic and environmental influences on individual medication response, incorporating passive behavioral monitoring through smartphones (https://www.behapp.com).

Patients from clinical sites across seven countries are being recruited and randomly assigned to either a pharmacogenetic group or a dosing-as-usual group, undergoing a 24-week treatment with four follow-up visits. The primary outcome focuses on personal recovery, assessed through the self-reported Recovery Assessment Scale (RAS-DS)[8]. Recent trends in psychiatric research highlight the importance of recognizing patients' personal experiences as essential outcomes and recovery indicators, complementing clinical recovery as assessed by clinicians using psychometric tools. While both dimensions are pertinent, personal recovery emphasizes the patient-centred perspective and the importance of having a good quality of life, which may be distinct from clinical improvement.

Secondary outcomes encompass measures related to treatment efficacy and tolerability, coupled with digital monitoring facilitated by the BeHapp application, which passively monitors proxies of patients' well-being and daily social functioning via their mobile phones, generating valuable longitudinal and quantitative real-world data[9]. Patient characteristics, including sex, age, comorbidity, comedication, and additional phenotypes, will be examined as covariates to assess their impact on treatment outcomes.

Furthermore, machine learning will be harnessed to scrutinize the collected data, identifying characteristics that influence medication responses. The aim is to optimize medication and dosage selection for individual patients. The collected data will be made available for re-use, facilitating further (pharmaco-)genomic research.

PSY-PGx stands as an initiative firmly grounded in rigorous adherence to good clinical and research practices. It leverages a diverse network of genomic researchers and health professionals across various disciplines. Our collaborative efforts are backed by important organizations such as the European College of Neuropsychopharmacology (ECNP), the International Society of Psychiatric Genetics (ISPG), the WPA (project participant), and the Global Alliance of Mental Illness Advocacy Networks Europe (GAMIAN, project participant).

Despite the huge potential of pharmacogenetic approaches, most countries have yet to incorporate them into routine clinical practices. Progress has been hindered by unwarranted optimism and overstated claims. Aligned with the genetic testing statement by the ISPG (https://ispg.net/genetic-testing-statement), PSY-PGx pioneers a novel model aimed at personalizing medication prescriptions. This approach involves the utilization of federated learning, also known as collaborative learning, to develop the algorithm. By employing a decentralized training method for machine learning models, the need for exchanging data across various servers is eliminated. Raw data on edge devices are thus locally utilized to train the model, ensuring enhanced data privacy.

The envisioned outcome of this initiative is a groundbreaking

pharmacogenetic algorithm that is anticipated to become an integral component of the treatment decision-making process in psychiatric practice. This algorithm has the potential to significantly enhance the effectiveness, tolerability and safety of pharmacological treatments in psychiatry. Consequently, it can enhance treatment adherence, improve overall quality of life, and contribute to the reduction of health care costs. The resulting medication prescription algorithm, coupled with a Creative Commons License model, will be made publicly available, ensuring maximum societal benefit.

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DOI:10.1002/wps.21289

Impact of displacement on mental health in war-exposed Ukrainian adolescents: a longitudinal study

The Russian invasion continues to put strain on Ukrainian people[1]. The burden on mental health of adolescents is particularly devastating[2]. Many people are being displaced: as of March 2024, 3.7 million of the Ukrainian population were estimated to be internally displaced and 6.5 million externally displaced[3].

Evidence on the associations between displacement and mental health is mixed and limited, especially for children and adolescents. Displacement can substantially increase the mental health burden of affected populations[4], but being displaced could help people avoid exposure to war, which has devastating mental health consequences[2]. Furthermore, people can be internally or externally displaced, which involves different experiences and health consequences[5].

It is imperative to better understand the relationship between war-induced displacement and mental health, especially in a large-scale conflict such as the Russian-Ukrainian war. Though this is challenging – given the possibility of reverse causality as well as time-varying confounding due to war exposure – longitudinal data, coupled with causal inference methods that account for time-varying confounding[6], may help overcome these challenges. We took advantage of the longitudinal design of the Adolescents of Ukraine During the Russian Invasion (AUDRI) Cohort to investigate the impact of displacement on the mental health of war-exposed Ukrainian adolescents.

We conducted a prospective, observational study using longitudinal data from the first (May-June 2023) and second (November-December 2023) waves of the AUDRI Cohort. We recruited youths attending any secondary school in Ukraine (in person or online) who were aged 15 years or older at the time of wave 1. The cohort also included youths residing abroad while attending Ukrainian secondary school online[2]. The study was approved by the Ethics Committees of the Institute of Psychiatry at the T. Shevchenko National University of Kyiv and of the University of Tokyo. Informed consent was obtained from all participants and their parents/legal guardians, and data were anonymized prior to analyses.

Students agreeing to participate were sent invitations via email in the follow-up waves. All questionnaires were self-administered and presented in Ukrainian on Qualtrics. Participants were asked about their displacement status: not displaced; displaced within Ukraine; displaced to another country; or displaced but returned back. We used well-validated tools to screen for post-traumatic stress disorder, PTSD (the Child and Adolescent Trauma Screen, CATS); depression (the Patient Health Questionnaire-9 for Adolescents, PHQ-A); anxiety (the Generalized Anxiety Disorder 7, GAD-7); substance use disorders (the Care, Relax, Alone, Forget, Friends, Trouble Test, CRAFFT 2.1); and eating disorders (the Sick, Control, One stone, Fat, and Food Questionnaire, SCOFF).

We performed causal inference on the associations of displace-

ment with a positive screen for each psychiatric condition using g-estimation of additive structural nested mean models[7], which seeks to minimize bias from time-varying confounding. We calculated the risk differences (RDs) by displacement status (current displacement vs. no displacement) at wave 1 of positive screens for psychiatric conditions at wave 2. Linear regression models were adjusted for demographic variables (age, gender, education level of parents, and region of residence in wave 1), as well as baseline developmental traits and difficulties (having had learning difficulties as a child, having attended special education classes as a child, diagnosis of autism spectrum disorder or attention-deficit hyperactivity disorder). War exposure was included in the models as a time-varying covariate. We also ran two sets of regressions similar to the main regressions as above, with internal displacement compared to no displacement, and external displacement compared to internal displacement.

Standard errors were computed using sandwich variance estimators and were clustered on region. Missing data were imputed using missForest[8]. Analyses were performed using R statistical software, version 4.1.1.

We sent invitations to 8,339 individuals who provided informed consent as well as valid email addresses in wave 1 of the AUDRI cohort. Of those, a total of 1,020 agreed to participate in wave 2, and were included in the analyses. Among these participants, 25.4% self-identified as male, 71.4% as female, and 0.8% as transgender, while 2.4% did not self-identify as belonging to any of those groups. At the time of wave 1, 38.6% were 15 years old, 33.4% were 16, 17.0% were 17, 3.8% were 18, 0.5% were 19, and 6.7% were 20 or older.

In wave 1, 60.4% reported having been exposed to war and 29.2% were displaced; in wave 2, 61.5% reported having been exposed to war and 27.3% were displaced. The proportion of adolescents screening positive for each psychiatric condition was higher among those who were displaced than those not displaced. In wave 1, 53.8% vs. 41.3% screened positive for clinically relevant psychological trauma (as a proxy for PTSD), 47.3% vs. 41.9% for depression, 29.7% vs. 23.9% for anxiety, 18.3% vs. 16.9% for substance use disorders, and 40.8% vs. 34.7% for eating disorders. In wave 2, 52.9% vs. 43.8% screened positive for clinically relevant psychological trauma, 53.8% vs. 47.5% for depression, 33.2% vs. 27.3% for anxiety, 25.8% vs. 18.2% for substance use disorders, and 39.4% vs. 38.5% for eating disorders.

Displacement in wave 1 was associated with a higher risk of a positive screen for clinically relevant psychological trauma (RD: 8.24 percentage points (pp); 95% CI: 0.22-16.26) and eating disorders (RD: 8.00 pp; 95% CI: 0.23-15.78) in wave 2. Individuals who experienced displacement in wave 1 were more likely to screen positive for anxiety (RD: 6.03 pp; 95% CI: –0.63 to 12.69) and less likely to screen positive for substance use disorders (RD: –4.38 pp; 95% CI: –10.78 to 2.01) in wave 2, though the estimates were imprecise, due to wide CIs. The association was close to null for depression (RD: 2.27 pp; 95% CI: –5.63 to 10.17).

Compared to no displacement, internal displacement in wave 1 was associated with greater risk of positive screens for clinically relevant psychological trauma (RD: 11.00 pp; 95% CI: 0.93-21.08) and anxiety (RD: 8.63 pp; 95% CI: 0.22-17.03) in wave 2. Individuals who experienced internal displacement in wave 1 were less likely to screen positive for substance use disorders in wave 2 (RD: –5.81 pp; 95% CI: –13.82 to 2.19), although the estimate was imprecise. Associations of internal displacement with eating disorders (RD: 2.69 pp; 95% CI: –6.95 to 12.34) and depression (RD: –0.86 pp; 95% CI: –10.76 to 9.03) were close to null.

Relative to internal displacement, individuals who experienced external displacement in wave 1 were less likely to screen positive for most psychiatric conditions (RD: –22.83 pp, 95% CI: –44.89 to 2.23 for clinically relevant psychological trauma; RD: –20.07 pp, 95% CI: –41.28 to 1.14 for substance use disorders; RD: –3.81 pp, 95% CI: –28.06 to 20.44 for depression; RD: –14.03 pp, 95% CI: –37.64 to 9.58 for eating disorders), but were more likely to screen positive for anxiety (RD: 10.09 pp; 95% CI: –12.02 to 32.20), though the estimates were imprecise, due to wide CIs.

Our findings indicate that displacement was modestly associated with greater risk of positive screens for psychiatric conditions six months later. However, at the population level, even modest effect sizes may result in a large mental health burden[9]. The differences between internal and external displacement also warrant attention: individuals who experienced internal displacement had a greater risk of positive screens for most psychiatric conditions, which may be due to factors such as the constant insecurity and the risks associated with continuing to live in a war-affected country, as well as the limited access to mental health support services due to consequences of the war.

The results of this study should be interpreted in the light of some limitations. First, some CIs in the RD estimates were wide, and larger samples may be necessary for more precise estimates. However, with a sample of over 1,000 individuals, this is among the largest longitudinal studies in adolescents ever conducted in a conflict setting. Second, there may have been unmeasured confounders biasing the results. Third, a relatively large proportion of those who participated in wave 1 were lost to follow-up.

A key contribution of this study is the use of rigorous causal inference methods on longitudinal data to control for time-varying confounding. Therefore, it adds significantly to the available research evidence on the impact of displacement on mental health in adolescents.

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The AUDRI Cohort receives funding from the Chernobyl-Fukushima Medical Fund and Japan Foundation for Pediatric Research (grant no. 22-001). The EQUAL Partnership, funded by the Norwegian Directorate for Higher Education and Skills (project #10049), played an important role in establishing the foundations of the AUDRI Cohort. The study is part of the All-Ukrainian Mental Health Program, initiated by the First Lady of Ukraine O. Zelenska. The authors thank the First Lady

and the Coordination Center for Mental Health under the Cabinet of Ministers of Ukraine for supporting their work. They also thank the adolescents and parents who participated in the study. R. Goto and I. Pinchuk contributed equally to this work.

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DOI:10.1002/wps.21290

Efficacy of psychological interventions for multiple-event-related PTSD in children and adolescents: a network meta-analysis

About a third of children and adolescents in the general population report the experience of one or multiple traumatic events[1]. A substantial minority of traumatized young people develop posttraumatic stress disorder (PTSD) in the aftermath[1], with an increased risk following multiple exposures[2]. Given the large individual and societal disease burden of pediatric PTSD[1], its effective treatment constitutes a public health priority.

Treatment guidelines for pediatric PTSD recommend psychological interventions, with trauma-focused cognitive behavior therapies (TF-CBTs) regarded as first-line treatment. Two previous network meta-analyses on psychological interventions for pediatric PTSD reported good treatment efficacy[3,4]. Yet, neither differentiated between single- and multiple-event-related PTSD. Consequently, the efficacy of psychological interventions for multiple-event-related pediatric PTSD remains unknown. Increased knowledge about treatment efficacy in this condition is crucial, since many clinicians working with it are reluctant to address trauma for fear of destabilizing patients[5]. Clinicians, patients and caregivers need to be well informed about the efficacy of psychological treatments for multiple-event-related pediatric PTSD to draw evidence-based treatment decisions.

The present work reports on the first network meta-analysis on the efficacy of psychological interventions for multiple-event-related pediatric PTSD. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2015 guidelines[6] were followed. All data were extracted independently by at least two authors, and discrepancies were discussed until consensus was reached. The main research question of interest was: in children and adolescents with full PTSD or PTSD symptoms, how do psychological interventions, compared to either passive or active control conditions, or with each other, perform in terms of reducing PTSD symptom severity in randomized controlled trials (RCTs) in which most participants (i.e., ≥50%) reported PTSD related to at least two traumatic events?

Inclusion criteria were as follows: a) RCT investigating psychological treatment for pediatric PTSD compared to a control condition; b) all participants presented with full or sub-threshold PTSD; c) sample mean age <19 years; d) outcome data reported for ≥10 participants per arm. We searched PsycINFO, MEDLINE, Web of Science and PTSDpubs from inception to April 18, 2023 with all-field searches by means of various terms for PTSD and treatment (see supplementary information). We also searched 71 qualitative and quantitative reviews on psychological treatment of pediatric PTSD (see supplementary information), the reference lists of included trials, Google Scholar, and ResearchGate.

Risk of bias was independently assessed by two reviewers using the eight quality criteria reported by Cuijpers et al[7]. We distinguished three assessment periods: short-term (i.e., treatment endpoint); mid-term (i.e., up to 5 months after treatment endpoint); and long-term (i.e., longest follow-up beyond 5 months after treatment endpoint). The primary outcome of interest was the standardized mean difference in PTSD symptom severity between two arms at a given timepoint as measured with Hedges' g.

Random effect network meta-analyses were performed in R (version 4.1.1) using the netmeta package[8]. Analyses were run only in the light of sufficient accumulated evidence (i.e., at least four direct comparisons per psychological intervention category). Hedges' g was interpreted as small (0.20), medium (0.50) or large (0.80) effect size. Various assumption checks[9] were performed. Inconsistency was checked with the net splitting procedure. Outliers were defined as effect sizes scoring at least 3.3 standard deviations above or below the pooled g, but no outliers were present in any of the analyses. Potential influence of small-study effects was checked with the Egger's test. Psychological interventions were ranked by efficacy using surface under the cumulative ranking (SUCRA) based on 50,000 resamples.

The systematic literature search yielded 67 eligible RCTs (N= 5,297 patients) (see supplementary information). Psychological interventions were subdivided into five categories: TF-CBTs, eye movement desensitization and reprocessing (EMDR), other trauma-focused psychological interventions (i.e., not based on TF-CBTs or EMDR), multi-disciplinary treatments (MDTs), and non-trauma-focused psychological interventions.

In total, 44 RCTs (66% of eligible RCTs) involved ≥50% participants with multiple-event-related PTSD, whereas 14 RCTs (21% of eligible RCTs) involved mainly single-event PTSD, and the other nine RCTs did not report sufficiently on the matter (see also supplementary information). The current analyses were conducted on the 44 RCTs having ≥50% participants with multiple-event-related PTSD.

TF-CBTs, MDTs and non-trauma-focused psychological interventions had a sufficient number of direct comparisons for syn-

thesis. TF-CBTs could be analyzed throughout (i.e., short-, mid- and long-term efficacy); MDTs for short- and mid-term efficacy; and non-trauma-focused psychological interventions for short- and long-term efficacy. EMDR and other trauma-focused psychological interventions did not have sufficient data and could not be included in any analysis.

At treatment endpoint, TF-CBTs (g=1.24, p<0.001), MDTs (g=1.00, p<0.001), and non-trauma-focused interventions (g=1.02, p<0.001) produced large short-term effects compared to passive control conditions. Compared to active control conditions, however, only TF-CBTs produced a significant (moderate-sized) treatment effect (g=0.56, p<0.001). No outliers and no inconsistencies were detected. Heterogeneity in outcomes was large (see supplementary information).

At mid-term (up to 5 months following treatment), compared to passive control conditions, TF-CBTs produced a large effect (g=0.84, p<0.001) and MDTs a moderate effect (g=0.67, p=0.027). Compared to active control conditions, only TF-CBTs yielded a significant (moderate-sized) effect (g=0.56, p<0.001). At long-term (6-24 months after treatment endpoint), relative to passive control conditions, both TF-CBTs (g=0.74, p=0.004) and non-TF interventions (g=0.71, p=0.019) produced a moderate-to-large treatment effect. Compared to active control conditions, however, only TF-CBTs (g=0.45, p=0.004) produced a significant effect. TF-CBTs were the highest-ranking psychological intervention across all assessment periods in SUCRA (see also supplementary information).

Thus, TF-CBTs are currently the most extensively evaluated treatment for multiple-event-related PTSD in children and adolescents, with high efficacy found relative to passive controls and moderate efficacy relative to active controls in the short-, mid- and long-term. While several trials examined MDTs (short- and mid-term data) and non-trauma-focused psychological interventions (short- and long-term data), these treatments did not produce significant effects compared to active controls in any of the assessment periods. Insufficient data regarding multiple-event-related PTSD were available for EMDR and other trauma-focused interventions.

The finding that multiple-event-related PTSD responds well to TF-CBTs has important implications for the provision of treatments for pediatric PTSD, for therapist training, and for future research, and should guide decision-making in clinical practice.

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J. Mutz is funded by the National Institute for Health and Care Research (NIHR) Maudsley Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. R. Meiser-Stedman is funded by NIHR and the UK Medical Research Council. The views expressed here are those of the authors and not necessarily those of the funding institutions. Supplementary information on this study is available at https://osf.io/dx5ah/?view_only=e9d4ec7b1a154fa499d5eb4e1564d534.

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DOI:10.1002/wps.21291

How common is secondary psychosis? Estimates from a systematic review and meta-analysis

The estimated lifetime risk of developing a psychotic disorder is approximately 3%[1]. In most cases, psychosis arises in the context of a primary ("non-organic") psychiatric disorder, such as schizophrenia. However, in a subset of cases, psychotic symptoms are secondary to the effects of an underlying disease state[2] or an exogenous agent (e.g., a recreational drug)[3]. Identifying secondary psychosis is critical to providing patients with appropriate care, which may include treatment for the underlying cause[4]. Whilst it is recognized that psychosis can have a secondary basis, the proportion of patients with a secondary cause is unknown.

We searched electronic databases (Medline, PsycINFO and Global Health) up to August 2022, alongside references of included articles and reviews. We selected studies that: a) included patients presenting with psychosis; b) assessed for a secondary cause; and c) assigned a primary or secondary diagnosis for each patient. We did not select studies that: a) excluded patients with a suspected or confirmed secondary psychosis, or b) provided insufficient data to calculate the proportion of patients with a secondary cause. We also excluded studies in which psychotic symptoms were not the main presenting problem (e.g., studies reporting the prevalence of psychotic symptoms in patients presenting with memory impairment). Where two or more studies shared the same sample, the larger was included. There were no age or language restrictions.

Using meta-analytic methods, we estimated the proportion of patients with psychosis due to a secondary cause, defined as psychosis "probably" or "definitely" arising as the result of an underlying (not primary psychiatric) condition, or an exogenous agent (e.g., illicit substance, prescribed medication). MOOSE guidelines were followed, and the protocol was prospectively registered (CRD42023427237) (see also supplementary information).

Based on 33 independent studies (N=26,534), 11% (95% CI:

7-16) of patients with psychosis had a secondary cause, after exclusion of a statistical outlier, with marked between-study heterogeneity (I^2=98%). The estimated proportion of 11% corresponds to an average number needed to assess in order to detect one case of secondary psychosis of approximately 10.

The most common psychosis with a secondary cause was drug-induced psychosis (12%; 95% CI: 6-19). The proportion of psychosis due to any underlying medical cause was 5% (95% CI: 3-9), with the most common medical causes being infection (1%; 95% CI: 0-4) and autoimmune disease (1%; 95% CI: 0-2) (see also supplementary information).

Subgroup analysis found a significant effect of clinical context (p=0.04), with patients in a general hospital setting more likely to have a secondary cause (38%; 95% CI: 35-41; n=5) than patients seen in a psychiatric setting (7%; 95% CI: 6-8; n=20). There was also an effect of geographical area (p=0.003), with patients in Africa most likely to have a secondary cause. Meta-regression found no association with publication year, sample size or mean age.

Restricting studies to those which included patients presenting with a first-episode psychosis resulted in a slightly increased estimate of 14% (95% CI: 8-22; n=18), whilst restricting studies to those with a mean sample age under 35 years resulted in an increased estimate of 23% (95% CI: 10-39; n=13). Studies that assessed for multiple causes of secondary psychosis resulted in an almost unchanged estimate of 13% (95% CI: 7-21; n=20). When urine analysis was routinely performed, estimates for secondary psychosis increased to 23% (95% CI: 11-37; n=8). More modest changes were observed when electroencephalogram (8%; 95% CI: 0-27, n=3), cerebrospinal fluid analysis (5%; 95% CI: 2-9; n=5), blood tests (5%; 95% CI: 0.1-13; n=11), and magnetic resonance imaging (MRI) (4%; 95% CI: 1-7; n=2) were routinely performed. Funnel plot inspection and Egger's test (p=0.15) did not indicate publication bias (see also supplementary information).

There are several important limitations to acknowledge in interpreting these estimates. The attribution of causality in secondary psychosis is challenging. For example, traumatic head injury[5] and psychoactive substances[6] are recognized causes of secondary psychosis, but are also risk factors for the onset of a primary psychotic disorder, such as schizophrenia. Additionally, most studies did not employ a standardized approach to assessment, possibly leading to under-detection of secondary causes. On the other hand, some studies might be enriched for certain secondary causes, leading to ascertainment bias. Furthermore, some causes of secondary psychosis have been discovered only relatively recently, such as anti-NMDA receptor encephalitis[7], and therefore would not have been detected in earlier studies.

Our finding that a substantial minority of patients with psychosis have a secondary cause has important implications for clinical practice. Clinicians should be mindful of the need to exclude a secondary cause, particularly in patients presenting with psychosis for the first time. In particular, our findings suggest that clinicians working in a general hospital setting should have a particularly high index of suspicion that a patient with psychosis has a secondary cause.

In clinical practice, it is often unfeasible to undertake extensive investigations in all patients with psychosis to exclude every potential secondary cause. However, our findings seem to suggest that it may be advisable to carry out investigations for common secondary causes (such as a urine screen for illicit substances and blood tests for physical health disorders) in all patients presenting with a first episode of psychosis. A caveat to this is the need to consider other contextual factors, such as the net clinical benefit and economic constraints. For example, a urine drug screen can assist with the diagnosis of drug-induced psychosis, and has the benefit of being cheap, widely available, easy to interpret and presenting minimal risk to a patient, thus favoring its routine use.

There are no well-established "red flags" to indicate which individuals are at the highest risk of secondary psychosis. However, previous studies suggest that certain phenomenological characteristics, such as visual hallucinations, are more likely to be associated with secondary causes[8]. Prospective clinical studies, using standardized investigations and psychiatric assessments, are indicated to determine the demographic and clinical characteristics associated with secondary psychosis.

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DOI:10.1002/wps.21292

The WPA Global Study on Psychiatric Training

Recent and ongoing crises (income inequality, political instability, pandemics, armed conflicts and wars, increasing numbers of refugees, climate change) have raised even greater awareness of the importance of mental health and psychiatry in supporting general well-being and public health[1,2]. This situation has led to a growing need for accessible psychiatric care, including inpatient and community mental health services, simultaneously placing ever increasing demands on the already limited and overwhelmed service systems[1].

Due to their specialized medical training and extensive education in biological, psychological and social sciences, psychiatrists play a critical role in the provision of mental health services for patients and their families. However, there is a critical global shortage of psychiatrists to meet these growing needs, that is aggravated by a geographic maldistribution of these professionals.

Recruitment into psychiatry is a global challenge, more acute in some countries in which a significant number of psychiatrists are reaching the age of retirement[3]. Books such as *Where There Is No Psychiatrist*[4] or *Where There Is No Child Psychiatrist*[5] might now surge in popularity, not necessarily for the reasons they were initially intended.

Attracting medical students to psychiatry is crucial when planning tomorrow's mental health workforce. While some students enter medical school with the goal of becoming psychiatrists, many decide to specialize in psychiatry later, after their clinical and educational experiences in medical school. Having a positive experience of psychiatry through teaching, placement with clinical activities, exposure to psychotherapy during medical school, and/or additional exposure through clinical electives, can influence the choice of psychiatry[3]. However, many students find psychiatry interesting during their medical education, but ultimately decide to pursue another specialty. While successful recruitment into psychiatry is an essential goal, medical students who have high-quality psychiatry training can later be important members of the broader mental health workforce.

Psychiatric knowledge acquired in medical school is crucial, as this may be the only exposure to psychiatry for most future physicians. Irrespective of the medical specialty they choose, future doctors will be required to care for patients and family members who have mental health needs that are integral to their physical health. For these physicians, expertise in psychiatry can not only benefit their patients, but also facilitate the optimal timing and nature of referrals to psychiatrists.

The WPA has a well-documented track record of strengthening undergraduate psychiatry training worldwide. Beginning 25 years ago, it collaborated with the World Federation for Medical Education to define the Core Curriculum in Psychiatry, which provided a framework for equipping future doctors with the skills necessary to identify and treat mental disorders in a timely and non-stigmatizing way[6]. This Core Curriculum was subsequently revised to align with the principles of "new medicine", which recognizes that healing and treatment alone are not sufficient, and requires a growing emphasis on prevention of mental disorders and promotion of mental health.

More recently, the WPA Working Group on Medical Students has focused on attracting medical students to psychiatry by addressing stigma and providing educational resources[7]. This working group produced *Stigma*, a video with free online modules covering topics such as "well-being", "stigma in psychiatry", and "an introduction to psychiatry". The group has also organized several in-person and virtual events, including competitions and mentorship programs for medical students, that have garnered significant interest and attendance[7].

There are several studies initiated by WPA components that have been addressing the attitudes of undergraduate medical students toward psychiatry[7-10]. For example, a study conducted several years ago[8] asked medical students to clarify how they were taught psychiatry in their undergraduate courses, allowing the identification of differences across regions and countries. This study was performed by the WPA in collaboration with the International Federation of Medical Students. Psychiatry was reported to be included as a mandatory course in 81 out of 83 countries, and as an elective course in the other two[8].

While students' opinions on teaching of psychiatry are highly valuable, a recent global study on how psychiatry is taught to medical students from the psychiatrists' perspective is lacking. Such a study would have the potential to promote undergraduate psychiatry education and training worldwide, by identifying effective educational practices and practice gaps. Learning about effective strategies on how to attract future doctors to psychiatry and implementing these strategies can assist in addressing the global shortage of psychiatrists.

The WPA Committee on Education and Scientific Publications is going to launch a Global Study on Psychiatric Training, to explore the structure and quality of psychiatry teaching to medical students in many countries around the world, by examining the integration of and the emphasis on psychiatry within undergraduate medical curricula. This will include whether psychiatry is mandatory in the curriculum, the duration of clinical placements, and the range of subspecialties covered. Additionally, the study will evaluate current challenges and offer potential improvements in psychiatry training, including the availability of qualified trainers, examination formats, and opportunities for international collaboration and resource development.

The study will also address how the WPA can best help countries improve psychiatry training for medical students. Ultimately, it will help us all as we work to address global mental health needs and disparities by providing effective educational strategies that take regional contexts into account, while trying to reduce stigma and attract more medical students to psychiatry.

The WPA, through its Committee on Education and Scientific Publications, will contact the leadership of national psychiatric societies, inviting them to provide information via an online questionnaire. All societies will be invited to collaborate in the analysis

and dissemination of the results. The greater the participation, the greater the possibility for meaningful change.

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DOI:10.1002/wps.21293

Report from the WPA Section on Psychiatry and Sleep-Wakefulness Disorders

Insomnia, which is considered a psychiatric disorder itself, is the most common sleep-related complaint in the general population. Furthermore, complaints about sleep and wakefulness are among the most common and impairing symptoms in psychiatric patients. Disturbed sleep frequently precedes the onset of several mental disorders, exacerbates as mental disorders progress, and frequently presents as a residual and treatment-resistant symptom.

In recent years, remarkable progress has been made in sleep research and the treatment of sleep and wakefulness disorders in psychiatry, although many questions remain to be answered[1]. We still do not know exactly the causative link(s) between the various psychiatric disorders and sleep complaints, although it would be important to know, for instance, whether early treatment of sleep disturbances can prevent the development of depressive disorders. Moreover, the relationship between subjective complaints of insomnia patients and objective polysomnographic results remains elusive, and we do not know whether the health consequences of insomnia, for example on metabolic systems, are related to subjective or objective measures of sleep, or both.

Besides objective methods for assessing sleep and wakefulness – such as polysomnography (PSG), actigraphy, multiple sleep latency test, and maintenance of wakefulness test – there is now considerable literature on various biomarkers for sleep disorders.

For insomnia, the measures with the highest performance include PSG-derived cyclic alternating patterns, actigraphy, and brain-derived neurotrophic factor (BDNF) levels. These are followed by heart rate around sleep onset, deficient melatonin rhythm, and specific neuroimaging patterns, mainly reflecting the activity of the prefrontal cortex, hippocampus, and basal ganglia[2].

For central disorders of hypersomnolence, novel measures derived from quantitative electroencephalogram (qEEG), high-density EEG, cognitive testing, structural and functional neuroimaging, and pupillometry have been proposed[3]. Significant progress has also been made in the assessment of circadian rhythm sleep-wake disorders. In addition to established laboratory protocols, circadian rhythms can now be assessed through long-term ambulatory monitoring of activity, skin temperature, heart rate, and light exposure[4].

Significant progress has also been made in the treatment of insomnia, emphasizing not only the role of appropriate pharmacotherapy but, above all, non-pharmacological treatment options. Cognitive-behavioral therapy for insomnia (CBT-I) is currently recommended as the evidence-based psychotherapy for chronic insomnia, also in patients with comorbidities[5]. This treatment includes techniques such as sleep restriction, stimulus control, sleep education and hygiene, relaxation techniques, and cognitive restructuring. These techniques help strengthen the basic sleep-regulating mechanisms, including the homeostatic sleep drive and circadian rhythm, and reduce sleep-related anxiety and arousal[6].

The treatment of insomnia in psychiatry should be based on an integration of pharmacotherapy (including novel medications, such as orexin antagonists) and non-pharmacological interventions, to address psychological and behavioral factors that contribute to the development or persistence of insomnia. It is particularly important to emphasize the need to maintain a consistent sleep schedule, getting up at the same time every day, even after a night of poor sleep, and to exercise regularly. Additionally, creating a relaxing bedtime routine, and limiting naps and rest periods during the day are essential. To prevent insomnia, it is also important to limit screen time during the day and avoid screens (phones, tablets, TVs) at least one hour before bed.

Several new wakefulness-promoting agents have been introduced for the treatment of central disorders of hypersomnolence[7]. Moreover, it is now well recognized that effective treatment of obstructive sleep apnea in patients with mental disorders is critical for improving their response to treatment, quality of life, and overall health[7].

As the prevalence of sleep and wakefulness disorders has further increased during the COVID-19 pandemic, resulting in deterioration of mental health and increased alcohol and hypnotic use[8], it is evident that mental health professionals require effective training in diagnosing and treating disrupted sleep. People with

mental disorders can greatly benefit from mental health services that incorporate routine assessment and treatment of sleep and wakefulness disorders within standard care pathways.

Consequently, the main aim of the WPA Section on Psychiatry and Sleep-Wakefulness Disorders is to educate psychiatrists in recognizing and giving appropriate attention to sleep disturbances (such as insomnia and hypersomnolence) and in being able to provide guidance to their patients on the importance of basic sleep hygiene rules.

The education of psychiatrists should also include awareness on obstructive sleep apnea, which can manifest with psychiatric symptoms, including increased daytime sleepiness, fatigue or loss of energy, loss of interest or pleasure, irritability, mood swings, emotional instability, and cognitive dysfunction such as impaired memory, attention and executive functions. These psychiatric manifestations highlight the importance of diagnosing and treating sleep apnea promptly, as managing the sleep disorder can improve overall well-being and quality of life.

Moreover, since 30-40% of patients with chronic insomnia fulfill diagnostic criteria for obstructive sleep apnea, screening for this condition should be performed before initiating any hypnotic medication. This is crucial, because medications such as benzodiazepines are contraindicated in patients with untreated obstructive sleep apnea. Such screening can be performed with short questionnaires such as the STOP-BANG. This questionnaire consists of eight yes-or-no questions, focusing on snoring, tiredness, observed apneas, pressure (high blood pressure), body mass index, age, neck circumference, and gender (male). Each "yes" answer scores one point. A higher total score indicates a greater risk of obstructive sleep apnea[9].

Our WPA Section has been active for many years. Its activities have been focused on providing information about sleep and sleep-related disorders to clinical health professionals, as well as optimizing the diagnosis and therapy of sleep disturbances in patients with mental disorders. Since sleep is an interdisciplinary field, one of our main goals is to connect sleep specialists from around the world. We believe that our Section can mediate between basic researchers, clinicians, educational institutions, scientific professional societies, health care institutions, and governmental authorities, in order to improve the recognition and treatment of sleep disorders.

Our Section's action plan for 2023-2026 includes several goals. A primary one is advancing *research and knowledge* about disturbances of sleep and wakefulness in patients with mental disorders, by fostering collaboration between basic researchers, clinical scientists, and health care providers. Additionally, we will keep focusing on *education and training* on diagnosis and treatment of sleep disorders, by organizing workshops, webinars and scientific conferences with WPA involvement. Furthermore, we will be active in promoting *clinical practice guidelines*, to improve the quality and interdisciplinary nature of care in people with mental disorders suffering from disturbed sleep.

A major goal also pertains to engaging in *policy and advocacy*, by calling for pertinent actions in support of research and public health initiatives to improve access of patients with mental disorders to sleep medicine services. We will also be supporting the building up of *networking and collaboration*, by fostering relationships with scientific societies to promote interdisciplinary research and clinical care. To this end, our Section has already organized a highly successful symposium, "State of the Art in the Management of Insomnia", during the World Congress of Psychiatry in 2023.

Finally, we intend to develop *public sleep health campaigns* to educate the public on sleep hygiene, health consequences of poor sleep, and prevention of sleep disorders.

By implementing this action plan, our Section can play a pivotal role in advancing the field, improving patient care, and promoting the importance of sleep health in the broader mental health context.

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DOI:10.1002/wps.21294

Personality in the spotlight: activities of the WPA Section on Personality Disorders

The WPA Section on Personality Disorders has promoted greater understanding of personality dysfunction since 2003[1]. This subject is highly relevant to mental pathology. Personality disorders affect at least 10% of the general population[2], and their high levels of comorbidity with other mental disorders (Galenic syndromes)[3] means that many doctors in a variety of specialties are likely to come across these patients repeatedly in their everyday practice.

In the last fifteen years, much of the work of the Section has been devoted to the development of the new classification of personality disorder in the ICD-11. A radical revision was suggested that eliminated all the existing categories in the ICD-10 and replaced them with a single dimensional spectrum of severity[4]. In

other terms, it was proposed that, once the diagnosis of a personality disorder has been established, it should be described in terms of its level of severity: mild, moderate or severe personality disorder, or personality disorder of unspecified severity. Also described was "personality difficulty", not classified as a mental disorder but listed in the grouping of problems associated with interpersonal interactions. It was also proposed that personality disorder and personality difficulty could be further described using five trait domain specifiers: negative affectivity, detachment, dissociality, disinhibition, and anankastia.

Although this solution came under criticism as being too radical and apparently ignoring recent advances in the field, particularly in relationship to work on borderline personality disorder[5], the scientific justification for the change was a strong one[6] and has been embraced with increasing enthusiasm over time. There are now many studies suggesting that this classification is superior to that of the ICD-10 in terms of clinical utility, internal consistency and acceptability[7,8], and it has received international support by its full incorporation into the ICD-11 Clinical Descriptions and Diagnostic Requirements for Mental Disorders. Many studies are currently in progress to establish its psychometric properties and clinical value in selecting treatment.

Over the next few years, under initiatives developed by R. Mulder and Y.-R. Kim (current and future Chair of the Section), we hope to expand the knowledge base of the ICD-11 classification, facilitate its introduction in all countries covered by the WPA, and obtain research data that will guide clinical practice in an area where we currently have grossly lopsided empirical evidence. With these goals in mind, Section members are developing clinical measures of ICD-11 personality disorder severity and the five trait domain specifiers. Notably, B. Bach and M. Sellbom are working on a Diagnostic Interview for Personality Pathology in ICD-11 (DIPP-11).

One of the important roles of our Section is to promote the message that all psychiatrists (and physicians, for that matter) should be familiar with the concept of personality disorder and to realize that most of the patients they see will have some form of personality disturbance. This is not an academic extra; such knowledge will help them in choosing treatment, predicting outcomes, and planning care. We need to be rid of the notion that personality disorder is an outré subject only useful to specialists.

The Section will also be watching carefully and contributing to the current debate over the status of borderline personality disorder. The borderline option was included as a "pattern specifier" in the ICD-11 classification, following pressure from the large group who felt that this diagnosis was too valuable to be discarded[9]. But the pattern specifier is not a diagnosis; it is an option to be added to the appropriate severity diagnosis in the ICD-11, from personality difficulty to severe personality disorder.

If, as it seems possible, all the categorical diagnoses of personality disorder will be abandoned in future revisions of the DSM, the status of borderline personality disorder will become increasingly uncertain. As research into all aspects of borderline pathology is currently more active than research into all other areas of personality pathology, it is understandable that many would like to see the borderline group retained in some form. There is no reason why it cannot cohabit with the current ICD-11 approach in both clinical and research practice, but improvements are needed to achieve better harmonization.

We also hope that, by emphasizing that personality dysfunction is on a spectrum, and that most people in the population have some dysfunction, we can remove much of the stigma that surrounds the diagnosis. The stigma will also be reduced by showing that those with personality problems can get better, and that this can be achieved avoiding deceptively simple solutions such as changing their name.

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DOI:10.1002/wps.21295

The WPA Section on Preventive Psychiatry: report on 2014-2024 activities

Preventive psychiatry is a comprehensive field within psychiatry that encompasses the prevention of mental disorders and the promotion of mental health. Clinically, it applies across the lifespan, at any stage of illness, and across the bio-psycho-social framework. It transcends psychiatric subspecialties and is equally relevant to fields such as public health and health policy.

The significance of preventive psychiatry is profound: estimates based on the 2019 Global Burden of Disease study suggest that mental disorders account for up to 16% of global disability-adjusted life years (DALYs), with associated costs ranging from 4 to 8% of national gross domestic product, depending on the region. A considerable portion of this burden is potentially preventable, with secondary and tertiary preventive interventions capable of reducing clinical progression and disability, thereby also alleviating economic impact. Mental health promotion, arguably even more critical than prevention of mental disorders, addresses the entire population, focusing on enhancing quality of life rather than being nosocentric.

These considerations explain why preventive psychiatry is a central focus of the current WPA Action Plan[1], as it has been in all WPA Action Plans from 2014 to 2024. The WPA Section on Preventive Psychiatry seeks to increase the visibility of preventive psychiatry and promote its adoption in clinical practice, research, education and policy. Between 2014 and 2024, the Section has made significant progress toward these aims.

First, the Section has organized symposia at all World Congresses of Psychiatry since 2014, and contributed over 50 presentations at WPA co-sponsored and other international meetings. The themes addressed included "International issues in preventive psychiatry" (World Congress, Madrid 2014), "Preventive psychiatry, substance misuse, and early intervention" (WPA co-sponsored meeting, Athens 2015), "Disasters – mental health context and responses" (WPA co-sponsored meeting, Belgrade 2016), "Preventive psychiatry in the community" (World Congress, Berlin 2017), "Preventive psychiatry in primary care" (World Congress, Lisbon 2019), "Mental health in emerging adulthood: the facets of prevention" (World Congress, Bangkok 2021), "Diagnostics, treatment and prevention of eating disorders" (WPA co-sponsored meeting, Moscow 2022), "Prevention and early detection of psychosis" (WPA thematic conference, Athens 2022), "Preventive psychiatry in Alzheimer's disease", "Non-pharmacological strategies for maintaining mental health in older adults", and "Psychosis prevention: the latest updates of real-life practice" (World Congress, Vienna 2023).

The Section has also conducted research projects, such as the Education and Prevention Intersectional Project (EPIC), in collaboration with the WPA Section on Education, which reviewed the teaching curricula of medical schools worldwide. This project surveyed 530 medical schools, revealing that the vast majority did not include preventive psychiatry in their curricula, with less than 3% mentioning the subject at all. These findings, though not entirely surprising, underscored the urgent need to promote preventive psychiatry.

We then explored the potential of using preventive psychiatry as a conceptual foundation for medical school curricula. This perspective was elaborated in a book chapter in WPA's *Advances in Psychiatry, Vol. 4* (2019)[2], where it was argued that preventive psychiatry offers distinct educational advantages due to its relevance across psychiatry and medicine, its alignment with key educational outcomes (especially attitudes), and its inclusion of essential clinical skills such as communication, reflective capacity, and empathy. The integrative bio-psycho-social and anti-stigma potential of preventive psychiatry further reinforces its educational value.

Guideline development has also been a key focus for the Section. It contributed to the European Psychiatric Association (EPA) guidance on mental health and economic crises in Europe (2016)[3], which provided evidence-based recommendations on the mental health effects of financial crises; and to the international guidelines on the role of exercise in the prevention of dementia (2023)[4], a large consortium initiative that emphasized the necessity of mental health for effective dementia prevention. Guidelines on preventing psychosis in individuals at clinical high risk are currently under review.

We published over 20 journal papers and book chapters in the past decade, covering the interface of preventive psychiatry with other areas in psychiatry, including consultation-liaison psychiatry[5], psychosis and schizophrenia[6], substance misuse[7], financial crises[8], person-centered medicine[9], and child and adolescent psychiatry[10], among others. Finally, the Section participated in two consortia for European Union Horizon 2020 projects.

Overall, it has been a productive decade for the WPA Section on Preventive Psychiatry. Its active members and dedicated leadership are well equipped to continue advancing the clinical application of preventive psychiatry, supporting its integration into medical education and psychiatric training, and promoting its adoption by policy makers.

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DOI:10.1002/wps.21297

The role of the WPA Collaborating Centres in promoting mental health education and policy worldwide

The WPA Collaborating Centres compose a network of nine sites, located in eight different countries (Egypt, Hong Kong, India, Italy, Kenya, Qatar, South Africa and UK), which aim to strengthen psychiatric practice in their respective regions through building capacity for mental health at all levels[1], and to support WPA strategic policies through local and global initiatives in the arenas of education, research, policy and practice[2].

The Centres have a specific commitment to improve undergraduate and postgraduate education in psychiatry, including training in a range of psychiatric subspecialties and provision of additional postgraduate diplomas, masters, and doctoral degrees. A major focus is the process of detection, diagnostic formulation, and

development of individualized treatment plans[3,4].

Considering the different biological, social and psychological dimensions of psychiatry, mental health education should be considered as a continuously evolving process, where advances at scientific and clinical levels make educational updates essential for health care professionals, trainees and medical students[5]. Furthermore, the evidence available is continuously debated, and clear guidance and recommendations are accumulating whilst not always being implemented. Therefore, a significant effort is needed to update educational curricula and materials, to ensure that they reach all areas of the globe, and to support the implementation of best practice, taking account of local resources, cultural and political contexts. These are among the main objectives of the Centres.

The WPA Collaborating Centres are supporting the current WPA Action Plan, with a specific focus on prevention and public mental health. Almost 75% of the general population is at risk of developing a mental health condition over the life course, making targeted preventive strategies, educational activities and screening campaigns highly needed worldwide, focusing particularly on children, adolescents and their parents. At the same time, a great attention must be devoted to understanding the role of social determinants of mental health, including poverty, pollution, war, bullying, as well as lifestyle behaviors[6].

A specific focus of the current WPA Action Plan is the promotion of healthy lifestyles to protect and promote the mental health of people living with severe mental disorders. Thus, the Collaborating Centres are developing educational materials on healthy diet, quitting smoking, physical exercise, and regular sleep hygiene[7]. These materials will be translated into several languages and disseminated worldwide through the WPA Member Societies and the WPA website, which hosts a number of resources, including short videos providing advice as well as educational and research evidence.

The Collaborating Centres also have their own dedicated commitments. For example, the UK Centre, in partnership with the Royal College of Psychiatrists, has launched a new Public Mental Health Leadership course. The Chandigarh Centre in India has launched a "Chandigarh Charter on Public Mental Health" on the occasion of its Diamond Jubilee International Conference on Mental Health, which is hosted on the WPA website. Some Centres are actively collaborating with the WPA Committee on Education and Scientific Publications in the process of developing international policy papers and guidance documents, such as the WPA guideline on antipsychotic prescriptions in middle- and low-income countries.

Furthermore, the Centres are building on the WPA Action Plan by implementing a variety of local and global actions[8-10]. In fact, they are all working at the promotion and dissemination of educational activities focused on training in and implementation of the ICD-11 and related Clinical Descriptions and Diagnostic Requirements; on the management of physical comorbidities in people with severe mental disorders; and on the promotion of adolescent mental health. All these activities are being conducted in collaboration with other components of the Association[11-14].

The Collaborating Centres have a suite of activities supporting the WPA prevention mission. Just to give a few examples, the Centres in Hong Kong, Qatar, Kenya, South Africa and UK are investigating school-based and psychosocial determinants of poor health. The Qatar Centre has provided services to Afghani refugees, children and families from Gaza and Ukraine, by establishing appropriate child, adolescent and women's mental health services. The Centre in Egypt has worked in collaboration with the Ministry of Health to provide mental health services for women and children from Gaza on the border between Rafah and Gaza.

The Collaborating Centres are also partnering with various national and international organizations. In particular, they are constantly in contact with institutions and research networks active in the field of mental health and psychiatry, such as the World Health Organization, the Psychiatric Genetics Consortium, the Enhancing Neuroimaging and Genetic Meta-analysis Consortium, and the World Mental Health Surveys.

Scholarship opportunities have been provided by the Centres to early career psychiatrists and researchers to attend regional and global WPA meetings through trainee and medical student prize competitions. All Centres participate in setting the competition format, selecting the winners, and providing certificates. The WPA President usually presents the awards at the relevant regional or global meetings.

All the Centres are strongly involved with community engagement and advocacy for mental health, and they are all very active in supporting the leadership role of the WPA worldwide by participating in major national and international scientific meetings.

Opportunities and links for more interdisciplinary work across the Centres have been built in the last triennium, and we believe that this interdisciplinary network can further help the growth of the WPA in the near future.

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DOI:10.1002/wps.21298

Acknowledgement
This publication has been partially supported by
an unrestricted educational grant from
Rovi Biotech S.r.l., which is hereby gratefully acknowledged.