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World Psychiatry

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

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What is "evidence" in psychotherapies?

The concept of evidence-based medicine (EBM), which originated in the early 1990s at McMaster University (Canada) and spread to the UK and North America, heralded an effort to place medicine on firmer scientific footing. EBM's overarching goals were twofold: to establish hortatory ("thou shall") standards, guiding practitioners toward scientifically-supported interventions, and minatory ("thou shall not") standards, guiding them away from scientifically-unsupported interventions.

Soon, EBM found its way into the field of psychotherapies. Evidence-based psychotherapies are commonly conceptualized as a three-legged stool. One leg comprises the best available evidence bearing on the efficacy (beneficial effects in rigorously controlled conditions) and effectiveness (beneficial effects in real-world conditions); the other two comprise clinical expertise and patient preferences/values (see Cuijpers[1] in this issue of the journal).

Still, as EBM's influence has grown, a nagging question remains: how should we conceptualize evidence in psychotherapies? Although the concept of "evidence" may seem self-explanatory, interview data suggest that academicians across multiple disciplines, including social and natural sciences, often disagree sharply regarding how to define it[2,3].

Probably the most influential operationalization of the evidentiary prong of the above-mentioned stool was adopted in the mid-1990s by the American Psychological Association (APA). Initially termed empirically validated therapies and later empirically supported therapies (ESTs), this prong consists of psychotherapies, typically delivered via a manual, that have been demonstrated to work for a specific psychological condition.

Modeled largely after the US Food and Drug Administration guidelines for medications, the EST criteria regard a treatment as "well-established" if it has performed better than a placebo or alternative intervention or as well as an established intervention in at least two independently conducted (performed by different research teams) randomized controlled trials or in a series of systematic within-subject studies. A secondary EST category of "probably efficacious" interventions comprises, *inter alia*, treatments that outperform a waitlist control group or that meet the aforementioned "well-established" criteria without independent replication.

Other criteria for evidence-based psychotherapies, such as the recent APA practice guidelines for post-traumatic stress disorder, depression, and childhood obesity, and those of the UK National Institute for Health and Care Excellence (NICE), consider a wider range of outcome evidence than do the EST criteria.

These organizations' laudable efforts notwithstanding, there are increasing reasons to doubt whether the current operationalization of evidence-based psychotherapies has fulfilled its mission of stemming the tide of non-scientific interventions. For example, in 2016, the US Substance Abuse and Mental Health Services Administration added thought field therapy, which is premised on the scientifically dubious assumption that psychopathology can be treated by removing blockages in invisible and unmeasurable energy fields, to its evidence-based practice registry. In 2018, the NICE offered a "research recommendation" for a related energy therapy, emotional freedom techniques[4]. Numerous other scientifically doubtful methods, such as group drumming, equine-assisted therapy, acupuncture for depression, and music therapy for autism, have similarly claimed the evidence-based mantle. In fairness, most of these techniques might well satisfy the APA criteria for ESTs[5].

Although a useful first step, current evidence-based guidelines, including those for ESTs, omit several key evidentiary sources needed to adequately appraise a psychotherapy's scientific grounding. To address this oversight, EST guidelines must incorporate four additional lines of evidence.

First, the replication crisis in psychology and other fields reminds us that we should be skeptical of findings unless they have been extensively replicated by multiple independent teams, ideally with offsetting theoretical allegiances. When viewed in this light, the APA EST criteria are too lax: they accord empirical support to treatments that have yielded positive findings in only two studies, and even to treatments that have yielded multiple negative findings. To enhance evidentiary rigor, the EST criteria must accommodate the full body of treatment outcome data, both positive and negative, and published and unpublished. They also must account for the methodological quality of included studies, such as sources of potential experimental bias (e.g., differential group attrition, imperfect randomization to conditions). Finally, they need to adopt statistical procedures, such as Bayesian methods, p-curve techniques, and the r (replicability) index, for gauging evidentiary strength and estimating publication bias[6].

Second, evidence-based guidelines must move beyond reliance on measures of symptomatic improvement, emphasized in EST criteria, to incorporate objective and subjective criteria of everyday life functioning[1,7]. Some patients with major depression, for example, may display significant improvement in depressive signs and symptoms (e.g., anhedonia, guilt), yet remain impaired in work and interpersonal relationships.

Third, provisional but burgeoning data from experimental and quasi-experimental studies suggest that certain treatments, such as crisis debriefing following trauma, scared straight interventions for conduct disorder, and suggestive techniques to recover ostensible memories of sexual abuse, are iatrogenic for some patients. Nevertheless, most evidence-based guidelines, including those for ESTs, overlook the possibility of harm. One challenge to addressing this omission is that many psychotherapy studies rely on unipolar outcome measures, which range from no improvement to substantial improvement; they must instead administer bipolar outcome measures, which can detect patient deterioration during and after treatment[1,8].

Fourth, extant evidence-based guidelines focus exclusively on outcome evidence; none considers the scientific plausibility of the treatment rationale[5,9]. As a consequence, they open the door to all manner of pseudo-scientific interventions, many of which outperform waitlist or minimal treatment conditions. To be fair, the mode of action of many effective psychiatric interventions remains largely unknown. Yet, when interventions are premised on mechanisms that contradict well-established basic science, such as alterations in invisible energy fields, their scientific status should be suspect. Such procedures are unlikely to possess specific efficacy, that is, efficacy beyond placebo and other non-specific factors[9].

The analysis offered here leaves unresolved the knotty question of how these diverse sources of evidence should be synthesized and weighted when appraising interventions. Reasonable arguments can be advanced for a variety of alternative evidentiary frameworks. That said, for the discipline of psychotherapy to aspire to and attain more stringent scientific standards, it must embrace a multidimensional conceptualization of evidence, one that encompasses criteria for replicability and methodological rigor, goes beyond circumscribed indices of symptomatic improvement, accounts for potential harm, and considers all scientific evidence relevant to treatments, including basic science data bearing on treatment mechanisms.

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Migration, ethnicity and psychoses: evidence, models and future directions

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There is a large body of research reporting high rates of psychotic disorders among many migrant and minority ethnic groups, particularly in Northern Europe. In the context of increasing migration and consequent cultural diversity in many places worldwide, these findings are a major social and public health concern. In this paper, we take stock of the current state of the art, reviewing evidence on variations in rates of psychoses and putative explanations, including relevant theories and models. We discuss in particular: a) the wide variation in reported rates of psychotic disorders by ethnic group, and b) the evidence implicating social risks to explain this variation, at ecological and individual levels. We go on to set out our proposed socio-developmental model, that posits greater exposure to systemic social risks over the life course, particularly those involving threat, hostility and violence, to explain high rates of psychoses in some migrant and minority ethnic groups. Based on this analysis, the challenge of addressing this social and public health issue needs to be met at multiple levels, including social policy, community initiatives, and mental health service reform.

Key words: Migration, ethnicity, psychoses, socio-developmental model, structural violence, mental health services, social policies

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A defining feature of the modern world is large scale migration, both within and between countries, one consequence of which is increasing ethnic and cultural diversity in many places. In this context, repeated reports that some migrant and minority ethnic populations experience high rates of psychotic disorders are particularly concerning.

In this paper, we take stock of the current evidence and related debates, focusing on variations in incidence of psychoses and related explanations. We draw some, we hope, thought-provoking conclusions about the socio-developmental, and ultimately structural, roots of ethnic disparities and how these relate to other reports of poor clinical and social outcomes and more negative interactions with mental health services in these populations.

The pressing challenge is how to harness what we know about ethnic disparities to develop social policies, community initiatives, and mental health services to address this major public health issue.

VARIATIONS BY ETHNIC GROUP: INCIDENCE OF PSYCHOTIC DISORDERS

There is an extensive literature from the past sixty years reporting high rates of psychotic disorders among several minority ethnic populations in high-income countries. Several overlapping systematic reviews and meta-analyses have summarized these findings[1-9] (see Table 1). Overall, these reviews suggest that the incidence of psychotic disorders in all minority ethnic populations combined is around 1.5 to 3.0 times the incidence in majority populations.

However, these overall estimates can be misleading. The extent to which rates are elevated, relative to the majority population, varies considerably. For example, the highest reported rates are among Black minority groups (i.e., 4 to 6 times higher than in majority groups)[6]. This finding is driven in part by studies from the UK that report especially high rates for Black Caribbean and Black African populations[8]. The evidence for other minority ethnic groups in the UK suggests that rates are either not increased or only modestly so (e.g., around 1.5 times, at most, for White non-British and Asian populations)[9-11].

Variations are also evident in other countries. For example, in the Netherlands, rates are particularly high for Moroccan and Surinamese populations, but less so for Turkish[12,13].

These variations should not be surprising. These are populations with different migratory histories and cultural heritages, living in diverse social contexts, and occupying varying social positions. The place of migration may also matter. In the most recent review, for example, there was no strong evidence that rates of psychotic disorders were elevated in migrants to Canada or Israel[6].

Further, there may be variations in relative risks by gender. In a study in East London[11], evidence was found that rates of psychotic disorders may be specifically elevated among women from Pakistan (incidence rate ratio, IRR of 3.1) and Bangladesh (IRR of 2.3). In the Netherlands, there is strong evidence from several studies that the incidence of psychoses is substantially higher among men from minority ethnic groups compared with women, especially among those from the Maghreb (Morocco, Algeria, Lybia, Tunisia), with a ratio as high as 5:1[7].

More recent studies have reinforced the complexity of patterns of risk. For example, analyses of data from our study of psychoses in urban and rural sites in five European countries[14] found marked variations in the extent of elevated risk in minority ethnic populations depending upon setting. Further, a study using Swedish register data suggests that the incidence of psychotic disorders may be particularly high among refugees relative to other migrants (i.e., IRR of 2.9 for refugees vs. 1.7 for other migrants), a difference that was more pronounced among men[15].

Table 1 Summary of findings from meta-analyses, showing overall rate or risk ratio (RR) for all psychotic disorders, unless otherwise specified, in minority vs. majority ethnic groups

	Overall		First generation		Second generation		Men		Women	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Scope: International										
McGrath et al[1] (schizophrenia)										
Migrants, minorities (vs. majority)	4.6	1.0-12.9								
Cantor-Graae & Selton[2] (schizophrenia)										
Migrants, minorities (vs. majority)	2.9	2.5-3.4	2.7	2.3-3.2	4.5	1.5-13.1	2.5	2.0-3.2	2.4	1.8-3.1
From developed countries	2.3	1.7-3.1								
From developing countries	3.3	2.8-3.9								
From areas where majority population is White	2.3	1.8-3.0								
From areas where majority population is Black	4.8	3.7-6.2								
From areas where majority population is neither	2.2	1.6-3.0								
Bourque et al[3]										
Migrants, minorities (vs. majority)			2.3	2.0-2.7	2.1	1.8-2.5				
Men			2.1	1.7-2.6	2.5	1.8-3.4				
Women			2.4	1.9-2.9	3.0	2.1-4.2				
White			1.8	1.6-2.1	2.3	2.1-2.7				
Black Caribbean			3.9	3.4-4.6	5.8					
Black African			4.3	2.8-6.8	3.7	2.2-6.3				
Asian			1.7	1.3-2.3	1.3	0.8-2.1				
Middle Eastern			2.3	1.4-4.0	2.3	1.4-4.0				
Castillejos et al[4]										
Migrants, minorities (vs. majority)	3.1	2.7-3.5								
Schizophrenia	2.7	2.0-3.7								
Non-affective psychoses	3.1	2.6-3.6								
Affective psychoses	1.3	1.2-1.3								
Jongsma et al[5]										
Migrants, minorities (vs. majority)	1.8	1.5-2.0								
Schizophrenia	1.4	1.2-1.7								
Non-affective psychoses	1.7	1.4-2.1								
Selten et al[6]										
Migrants, minorities (vs. majority)	2.1	2.0-2.3								
From developed countries	1.7	1.5-1.8								
From developing countries	2.5	2.3-2.9								
White	1.7	1.5-1.9								
Black	4.2	3.4-5.1								
To UK	2.7	2.2-3.3								
To Scandinavia	1.9	1.8-2.0								
To Netherlands	3.0	2.4-3.7								
To Southern Europe	2.8	1.9-4.0								
To Canada	1.2	0.9-1.7								
To Israel	1.2	1.0-1.5								
To Australia	2.1	1.2-3.8								

Table 1 Summary of findings from meta-analyses, showing overall rate or risk ratio (RR) for all psychotic disorders, unless otherwise specified, in minority vs. majority ethnic groups (*continued*)

	Overall		First generation		Second generation		Men		Women	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Refugee	1.9	1.6-2.2								
Non-refugee	1.8	1.6-2.9								
Scope: Netherlands, Belgium, France, Italy										
van der Ven et al[7] (non-affective psychoses)										
Migrants, minorities (vs. majority)							2.9	2.7-3.2	2.6	2.2-3.1
From the Maghreb							2.9	2.0-4.1	1.4	0.7-2.6
From Asia							1.1	0.7-1.6	0.9	0.3-2.8
From Central and South America							3.0	1.7-5.3	3.2	2.1-4.8
From Western countries							1.3	0.9-1.9	1.4	0.9-2.3
From Sub-Saharan Africa							4.9	2.4-10.1	4.8	1.6-14.3
From Morocco							3.2	2.0-5.0	1.6	0.8-3.1
Scope: UK										
Tortelli et al[8] (schizophrenia)										
Black Caribbean vs. majority (White)	4.7	3.9-5.7								
Kirkbride et al[9] (schizophrenia)										
Black Caribbean vs. majority (White)	5.6	3.4-9.2								
Black African vs. majority (White)	4.7	3.3-6.8								
Asian vs. majority (White)	2.4	1.3-4.5								

Moreover, incidence rates may change over time. In our most recent study[16], in which we compared incidence rates in South London between 1997-1999 and 2010-2012, we found notable changes in incidence by ethnic group. For example, rates in the White British population increased from 20 per 100,000 in 1997-1999 to 39 per 100,000 in 2010-2012. By contrast, rates in the Black Caribbean population declined from 141 per 100,000 in 1997-1999 to 94 per 100,000 in 2010-2012. As a consequence, the relative risk for the Black Caribbean population decreased considerably (from 6.7 to 2.8).

These differences over time may, of course, be due to methodological inconsistencies in, for example, case detection. The main point, however, is that we should not assume that rates and rate ratios are constant over time. There is no single, universal, time-invariant migrant effect, as is often implied. Variation is the norm. This further implies that there is unlikely to be one simple explanatory factor that can account for such patterns. A multifaceted explanation is required.

A final note on the current epidemiological evidence. Most studies have been conducted in Northern Europe – in fact, in the UK and the Netherlands – with some studies in Southern Europe, the US, Canada and Israel. We do not know to what extent these findings generalize to other countries and contexts, in particular in the global South, where most migration occurs. Recent work on urbanicity and psychosis is a timely reminder that what we find in high-income settings does not necessarily extend to other contexts[17].

Moreover, we know very little about the effects of internal migration, which often involves movement over considerable distances and to very different social and cultural contexts. In a study in Northern Italy[18], incidence rates for psychotic disorders were similarly elevated for internal migrants (IRR=1.93, 95% CI: 1.19-3.13), predominantly from Southern Italy, and external migrants (IRR=1.79, 95% CI: 1.06-3.02).

Methodological artefacts

Since the earliest studies, the validity of reports of high rates of psychotic disorders, particularly in Black minority groups, has been the subject of much debate. There are several potential biases that could create spurious differences. These relate, for example, to selective migration, case identification, and under-enumeration of minority denominator data.

However, without entirely discounting these potential biases, it is unlikely that those noted can fully account for the observed patterns. For instance, various lines of reasoning suggest that selective migration is unlikely. In an intriguing thought experiment, Selten et al[19] re-calculated incidence rates for the Surinamese population in the Netherlands, assuming that the entire population of Suriname had migrated. After doing this, rates were still elevated relative to the Dutch majority.

Further, in more recent studies, methods for identifying cases have become more varied and comprehensive (e.g., use of case

registers, multiple sources), and denominator data for minority groups are more accurate, certainly in the UK. However, reports of disparities in incidence persist.

Misdiagnosis

More challenging is the suggestion that high rates result from systematic misdiagnosis of psychosis in minority ethnic groups[20,21]. This possibility merits careful consideration. In addressing this issue, it is worth stepping back to consider why these findings initially proved so controversial.

The earliest reports in the UK, where most studies initially originated, focused on schizophrenia. At that time, in the late 1970s and early 1980s, the prevailing consensus within psychiatry was that schizophrenia was primarily a genetic brain disorder. To link ethnicity or race with an increased risk of a heavily stigmatized disorder that was considered to be primarily genetic understandably provoked a reaction. It was uncomfortably close to racist ideologies of the genetic inferiority of Black people[20]. Considered from this perspective, the over-diagnosis of schizophrenia among Black people stemmed from wider stereotypes which, when refracted through the lens of psychiatry, led to the pathologization of culturally grounded beliefs, behaviours and expressions of distress as signs of psychosis.

For example, Littlewood and Lipsedge[21] argued that acute distress arising from difficult conditions and life experiences was systematically misdiagnosed as schizophrenia in the Black Caribbean population in the UK. Echoes of this history can be heard today, particularly outside of academia, in the framing of this issue as one of mis- or over-diagnosis.

To be sure, as recent evidence and trends re-highlight (see below), the nature of psychoses is clearly such that diagnosis is often challenging, especially across diverse cultural groups. Further, given that low-level psychotic experiences are common and frequently co-occur with symptoms of depression, anxiety and post-traumatic stress disorder[22,23], it is plausible that predominantly affective disorders may sometimes be misdiagnosed as psychotic disorders. What is more, there is some direct evidence that misdiagnosis does occur in relation to some minority populations (e.g., in the US)[24]. Certainly, this is an important clinical issue, with implications for management and treatment.

However, there are lines of reasoning and evidence that, on balance, suggest that variations in incidence by ethnic group are not simply an artefact of mis- or over-diagnosis. For example, there have been several attempts to assess the extent to which stereotyping and misdiagnosis occur and might explain reported variations in incidence rates. Two studies used vignettes to investigate racial stereotyping in diagnosis. Neither found strong evidence that psychiatrists are more likely to diagnose schizophrenia when the ethnicity of individuals described in case vignettes is Black[25,26].

Similarly, Hickling et al[27], in a study that compared diagnoses made by British and Jamaican psychiatrists in the same patients, found no differences in the percentage of Black patients diagnosed with schizophrenia. Further, recent studies focus on all psychotic disorders, not just schizophrenia, and tend to report high rates for all disorders. This is not, then, an issue of specifically mis- or over-diagnosing schizophrenia.

Finally, in the past 20 years, our understanding of the nature and aetiology of psychoses has changed considerably. It is now clear that schizophrenia and other psychotic disorders are shaped by a complex array of factors, including social conditions and experiences, that combine and interact over time to increase risk. High rates of psychoses in some migrant and minority ethnic groups does not, then, imply an excess of a genetic or purely biologically induced brain disorder.

VARIATIONS BY ETHNIC GROUP: PREVALENCE OF PSYCHOTIC EXPERIENCES

In parallel with research on psychotic disorders in migrant and minority ethnic groups, substantial evidence has emerged in recent years that low-level psychotic (or anomalous and unusual) experiences – such as fleeting and non-distressing hallucinations, suspiciousness, and magical thinking – are somewhat common in the general population[28,29].

This raises the possibility that psychotic experiences are continuously distributed, varying in frequency, severity and intensity, with disorder at the extreme end of this distribution. If this is so, in populations with high rates of disorder, we would also expect low-level psychotic experiences to be more common (see Figure 1). There are now several studies suggesting that this is indeed the case[30-32].

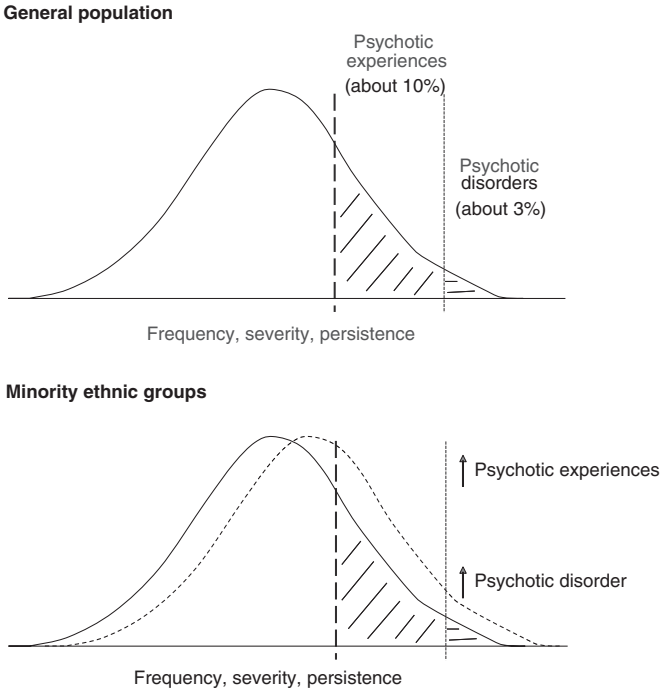

Figure 1 Hypothesized rightward shift in the continuum of psychosis in some minority ethnic groups

In a recent systematic review and meta-analysis, Tortelli et al[33] identified 19 studies of adults (age 16 or over) that have reported data on psychotic experiences in migrant or minority ethnic groups. The most consistent finding was that people from Black groups, compared with majority groups, more often reported psychotic experiences, both current (from 7 studies with 26 effect sizes: odds ratio, OR=1.8, 95% CI: 1.4-2.3) and lifetime (from 4 studies with 9 effect sizes: pooled OR=1.3, 95% CI: 1.1-1.6).

In line with this, in a survey we conducted in the same area of South London where many studies of ethnicity and psychotic disorder have been conducted[34], we found that, compared with White British, people from Black Caribbean and Black African populations were more likely to report psychotic experiences (see Figure 2).

AN EXPLANATORY FRAMEWORK

In considering why there are variations in the occurrence of psychotic disorders by ethnic group, it is useful to have in mind a framework for psychotic disorders in general.

Psychoses are highly heterogeneous – in their symptomatology, course and outcome – and our current diagnostic categories, at best, capture syndromes that may comprise multiple underlying disorders[35]. Moreover, these disorders, as noted above, may be the extreme, distressing end of a spectrum of beliefs and perceptual experiences that are somewhat common in populations.

As noted, the underpinning aetiological architecture of psychoses, across the spectrum, is complex. An array of factors, that are neither necessary nor sufficient alone to cause disorder, are associated with an increased risk, spanning genetic, neurobiological, substance use, psychological and social domains[36]. For example, several social factors have been implicated at area (urbanicity, social fragmentation, ethnic density) and individual (bullying, abuse, life events, discrimination) levels[37]. That none are sufficient or necessary means that multiple factors must co-participate over time – no doubt in various combinations – to push individuals along a developmental pathway to psychosis.

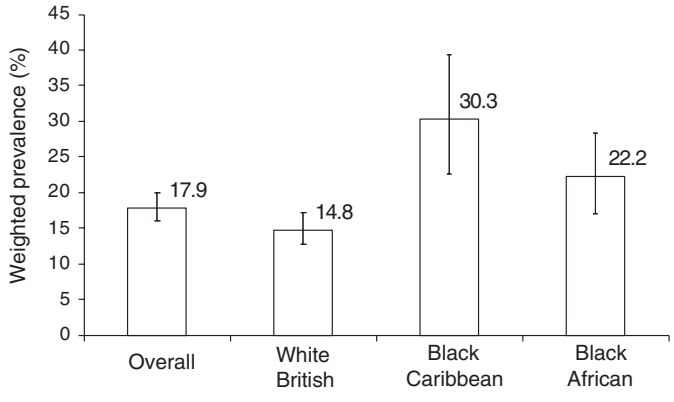

Figure 2 Prevalence of psychotic experiences by ethnic group in a community survey in South London

This may also explain the heterogeneity in the manifestations and outcomes of psychotic disorders. Particular clusters of causes may underpin different clusters of symptoms and subsequent trajectories. There is some evidence to support this. For example, childhood adversities are associated with more positive symptoms[38], while neurodevelopmental markers are associated with more negative symptoms[39]. Further, evidence is converging on interrelated psychological and biological mechanisms through which the array of factors increase risk, notably via effects on affective and cognitive processes and on physiological stress response and the dopamine system[40-43].

This evidence was synthesized by Howes and Murray[44], who drew from our socio-developmental model[45] to propose an integrated socio-developmental-cognitive model that is applicable to all psychoses. At the core of this model is the idea that psychoses emerge and fluctuate over the life course as a consequence of clusters of causal and protective factors operating at multiple levels, from the molecular to the social. It follows that variations across populations will arise where there are differences in the distribution and/or effects of clusters of causal, and protective, factors.

CANDIDATE CAUSES

Several previous reviews, including our own, have considered the evidence for a range of putative causal factors that may contribute to ethnic variations[45-47].

Population differences in genetic risk, obstetric complications or viral infections were proposed in early work on psychoses in minority populations[48], fuelling initial concerns about the links being drawn between race, ethnicity, biological deficits, and schizophrenia. However, there seems to be no evidence to suggest that variations in genetic or neurodevelopmental risk markers can explain the high rates of psychotic disorders in some populations. Rather, there is now a broad consensus that variations in incidence by migrant and minority group are most likely a consequence of external, environmental factors, in particular related to social conditions, position, and experience across the life course.

Substance use

There is strong evidence that the use of certain substances, particularly cannabis, is associated with an increased risk of psychosis. This applies especially to high-potency forms with high concentrations of tetrahydrocannabinol (e.g., skunk)[49,50]. This finding is particularly relevant here because cannabis use was one of the earliest and most controversial explanations proposed for the high rates of psychosis observed among the Black Caribbean population in the UK.

Previous work, however, has not provided any strong evidence to support this notion[45,51]. More recent work has been slow to emerge. However, it is likely that current interest in cannabis will produce samples that are sufficiently ethnically diverse to allow this question to be considered more fully.

Migration and acculturation

Migration is an unsettling, stressful experience that involves severe disruption to many aspects of individuals' lives. It is inevitably followed by a prolonged period of adaptation and acculturation, processes that may be more or less difficult depending on the reasons for migration (e.g., economic vs. forced), available economic and social resources, cultural distance from the new society (especially language), and levels of discrimination and hostility faced.

The recent findings that incidence of psychotic disorders is higher among refugees[15] hints at the potential importance of these processes and experiences. Asylum seekers and refugees are fleeing natural disaster, war, violence and persecution, and as such often arrive traumatized, with fewer resources and contacts, and face greater challenges in integrating with the host society. There is, however, surprisingly little research on the impact of experiences of migration and settlement on risk of psychosis.

In analyses of data from a small case-control study conducted in the mid-1990s, we found some evidence that cultural marginalization (i.e., distance from both culture of heritage and of majority society) distinguished Black Caribbean cases with a first-episode psychosis from Black Caribbean controls[52].

More recently, in analyses of data from the EU-GEI study, concerning 1,088 cases with a first-episode psychosis and 1,495 controls from sites in six countries, we found that adjusting for a measure of linguistic distance attenuated the association between migrant or minority group and case status[53]. Perhaps most intriguingly, the confounding effect of linguistic distance was stronger in first generation migrants, while social disadvantage was more important in second and subsequent generations. This hints at the possibility that the salient socio-cultural experiences are different for migrants and settled minority populations.

Still, migration and initial experiences of acculturation can at most provide a partial explanation for the high incidence rates of psychotic disorders in some groups. The time between migration and onset of psychosis is typically several years. Hollander et al[15], for example, found that the time from migration to first diagnosis was around three years for non-refugee migrants, which is in line with earlier reports. For refugees, the time was shorter, but still relatively long, at around 2 years[15].

Veling et al[54], in a study of incident cases in the Netherlands, found that earlier age of migration was associated with a greater risk. It may be that migration at an earlier age has a particularly pernicious impact on risk of psychosis, but earlier migration also means living longer, during formative years of childhood and adolescence, in the host society. Social conditions and experiences in host societies are then likely to be as, if not more, important.

Social contexts and experiences: ecologies of risk

Those from minority ethnic groups are more likely to live in densely populated and relatively disadvantaged and socially fragmented urban areas. Living in these types of places is – in general – associated with an increased risk of psychosis, at least in Northern Europe. However, it seems that these contextual characteristics of areas alone do not account for the variability in rates of psychotic disorders by ethnic group.

In an early study, Harrison et al[55] found no evidence that the area of residence could account for observed differences in rates of severe mental disorder between White British and Black Caribbean populations in Nottingham, UK, and our subsequent study in three UK centres (AESOP) found similarly elevated rates by ethnic groups in all centres, despite varying degrees of urbanicity (population density)[56]. Further, in a more recent study in the UK, Kirkbride et al[57] found that similar ethnic disparities were evident in rural and urban areas in a region in the east of England (i.e., 2- to 4-fold increased rates of psychotic disorders among Black Caribbean, Black African, and Pakistani populations, compared with White British).

This is not to say that context does not matter. One of the most striking and consistent findings in the literature is that rates of psychosis are higher among minority ethnic groups where they form a smaller proportion of the local population[58-60]. This ethnic density effect was reported as early as the 1930s in the US, in the seminal study by Faris and Dunham[61], and has been replicated in many studies since, including several recent reports[60,62-65].

Interpreting these findings, however, is difficult. When set alongside individual level data suggesting that repeated exposure to discrimination is important (see below), it is possible that living in areas of low ethnic density may increase risk because of exposure to more discrimination and hostility. Conversely, areas of high ethnic density may mitigate risk and promote resilience, possibly via access to more social supports.

Das Munshi et al[66], in analyses of data from a UK national survey, did find some evidence to support this: people living in areas of low own ethnic group density did report more experiences of racism and discrimination, and fewer social supports. However, no studies have directly investigated these possibilities in relation to psychotic disorder.

Further, the effects for psychosis may not be uniform. Schofield et al[67], in a study using Danish register data, found evidence of ethnic density effects for second, but not first, generation migrants, a finding again suggesting that different clusters of causes may underpin high rates of psychotic disorders in recent migrant vs. settled minority populations.

Social contexts and experiences: disadvantage, discrimination and hostility

At the level of individual experience, there is some evidence that more frequent exposure to social adversities over the life course, particularly discrimination, may be important. For example, family breakdown during childhood (indexed by separation from parents) is both associated with increased odds of psychosis and more common among some minority populations (e.g., Black Caribbean in the UK)[68]. The adversities indexed by separation (e.g., household discord, housing instability, and

financial difficulties) that are experienced more often by those from minority ethnic groups may, then, contribute to pushing more in these populations along pathways to psychoses.

There is similar evidence for markers of social and economic disadvantage and isolation in adulthood[69]. However, the indicators used in these studies are crude and they do not tell us anything about the more specific exposures they may index or the mechanisms through which they work. Further, in ecological studies, socio-economic status does not tend to explain much of the variance in rates of psychotic disorder by ethnic group.

Several studies have examined the potential role of discrimination and perceived disadvantage. Of particular note, Karlsen and Nazroo[70], in an analysis of data from the Fourth National Survey of Ethnic Minorities in the UK, found an association between the estimated annual prevalence of psychosis and reports of experienced racism (OR=1.6), verbal abuse (OR=2.9), and racial attacks (OR=4.8). It is notable that the strongest effect was for experiences involving physical threat and violence (racial attacks).

The limited relevant data from first-episode samples broadly supports these findings, albeit the approaches and measures used to capture discrimination and disadvantage vary. In the AESOP, we found that perceptions of disadvantage partly explained the high rates of psychosis in Black Caribbean and Black African groups[71]. Veling et al[72], in the Netherlands, reported that the highest incidence rates were among those populations known to have the highest levels of perceived discrimination (i.e., Moroccan: IRR=4.8).

In other analyses of case-sibling-control data on non-Western migrants, Veling et al[73] found that cases were more likely to have a negative ethnic identity, compared with their matched controls. These findings are reinforced by a recent review of 24 studies of perceived discrimination that found overall support for an association with psychoses[74]. Together, these findings point to discrimination and perceived disadvantage as potentially important factors among minority ethnic groups.

VARIATIONS IN SYMPTOMATIC PRESENTATION

Several studies have examined whether there are ethnic variations in the nature and presentation of psychoses. It is possible that, if a broad set of social factors underpin the higher rates, there would also be more positive and affective symptoms among those from minority ethnic groups. In other words, if there are different aetiological pathways to psychosis, we might expect that to be reflected in differences in the manifestations of symptoms.

A few studies have found some evidence that Black patients present with more positive (e.g., paranoid delusions, hallucinations) and affective symptoms and fewer negative symptoms. For example, in recent analyses of data from our Europe-wide incidence study, we found that migrant and minority patients presented with more positive (reality distortion) symptoms[75]. Veling et al[76], in a study in the Netherlands, also found evidence of similar ethnic variations, with Moroccan patients reporting more overall symptoms and more persecutory delusions, and both Moroccan and Turkish patients more often meeting criteria for a depressive disorder.

These findings fit with the hypothesis that minority patients will present with more positive and affective symptoms. However, as far as we are aware, no studies have directly linked these variations with hypothesized social factors, so a link remains conjectural. A recent study in Canada did not find any ethnic variations in symptoms at first presentation[77]. This again points to the possibility that patterns and associations vary across contexts and by ethnic group.

MECHANISMS

There are a small number of studies that have sought to investigate putative mechanisms that may link experience and psychosis in minority groups. For example, Gevonden et al[78] examined reactivity to daily stress in a sample of Moroccan and Dutch men, using experience sampling and an experimental exposure to social peer evaluations. They found no evidence that reactivity to stressors was more pronounced among Moroccan men. This is interesting, because it fits the epidemiological evidence. It is not that social factors have stronger effects in minority groups (i.e., that reactivity to stress is more pronounced); it is that they are more common.

Akdeniz et al[79], in a sample of 124 young men comprising Germans and second generation migrants, investigated the impact of migrant status on brain structure using structural magnetic resonance imaging. They found that grey matter volume was reduced among migrant men only, a finding they tentatively speculate may indicate effects of environmental stress (associated with migrant status) on brain development, providing a possible mechanistic link between social stressors among those from minority ethnic groups and psychoses.

SOCIAL DEFEAT

Selten et al[80-82] have hypothesized that the experience of social defeat is the common denominator explaining the high rates of psychoses in some minority ethnic groups. This model proposes that the long-term experience of being excluded from the majority group (i.e., social defeat) increases risk via effects on the mesolimbic dopamine system. This idea arose from analogy with animal studies showing that rodents subject to threatening and intimidating behaviour by other rodents become passive and submissive (i.e., defeated) and that this is associated with sensitization of the mesolimbic dopamine system[83], which has been implicated, in humans, in the underlying biology of psychoses[43]. This hypothesis has gained some traction and so merits careful consideration.

On the face of it, the hypothesis is plausible and has value in providing a catchy and memorable term that serves to highlight the centrality of social factors in generating variations in the inci-

dence of psychoses by migrant and minority ethnic group. However, when probed further, there are some issues that – for the hypothesis to have potential explanatory power – require further clarification and development. First, the hypothesis is largely tautological: it posits minority status (i.e., being excluded from a majority group) to account for high rates of disorder among those who occupy minority statuses. Second, it cannot be minority status alone that explains the observed patterns: psychoses are just too rare for that to be the case. At the very least, other factors must be involved. Third, in the animal studies that were the basis for the original formulation, social defeat is the outcome, not the exposure. It is prolonged intimidating and threatening behaviour (not outsider status) that produces the outcome – passivity and submission (social defeat)[83]. In other words, it is excessive and repeated threat that is associated with – or leads to – sensitization of the mesolimbic dopamine system in this model. Further, the end state of defeat that characterizes the rodents is reminiscent of a state of helplessness. This is why the social defeat paradigm is usually considered a model of depression[84].

In short, the social defeat hypothesis promises a single, elegant explanation – a characteristic that satisfies Ocam's razor. However, the high rates of psychoses in some minority groups are unlikely to be explained so simply[81]. The range of exposures involved and the mechanisms through which they impact on risk in minority groups are likely to be much more complex – and we need to embrace and seek to understand this complexity. As Einstein commented, "things should be made as simple as possible – but not simpler"[85]. In relation to mental health problems, Kendler has recently articulated this, noting the need to move beyond monocausal thinking[86].

A SOCIO-DEVELOPMENTAL PATHWAY TO PSYCHOSIS

In synthesizing the evidence around ten years ago, we proposed a socio-developmental pathway to account for the high rates of psychosis in many migrant and minority populations[45]. That is, we hypothesized a developmental pathway in which exposure to adversity and trauma (particularly in childhood and/or prior to and during migration) – in the absence of buffers and protective factors – interacts with underlying genetic risk and impacts on neurobiological development (in particular the stress response and dopamine systems) to create an enduring liability to psychosis (reflected in, for example, expression of low-level psychotic experiences). This liability becomes manifest (primarily as positive and affective symptoms) in the event of further cumulative stressors and/or prolonged substance use, especially high-potency cannabis. As noted, this proposal has been incorporated into broader models of psychosis.

Our purpose in highlighting a socio-developmental pathway is to draw attention to the possibility that there are some individuals for whom adverse social conditions and experiences are the primary factors in the development of psychoses: that is, in the absence of these exposures, psychotic disorders would not have developed. It further follows from this that, in populations where adverse social conditions and experiences are more common, rates of psychosis will be higher. Our hypothesis is that this explains the high rates in many migrant and minority populations.

The evidence that has accumulated in recent years – albeit fragmented and sporadic – both fits with this model and suggests refinements. Two lines of research are particularly noteworthy, and are described below.

Psychotic experiences during childhood and adolescence

Several studies have compared the prevalence of low-level psychotic, or anomalous, experiences in young people from diverse ethnic groups. For example, Laurens et al[32], in a study of 595 children aged 9 to 12 years in London, found that Black Caribbean children were around two times more likely to self-report psychotic experiences compared with White British (OR=1.92). There were, however, no differences between Black African and White British children (OR=0.96).

In a study of 1,545 children with a mean age of 13 years in the Netherlands, Adriaanse et al[31] found that Moroccan Dutch (OR=3.0) and Turkish Dutch (OR=2.2) children were more likely to report anomalous experiences with high impact, compared with Dutch children. In another Dutch sample, this time of young adults, Vanheusden et al[87] found that self-reported hallucinations were more common among most minority ethnic groups compared with Dutch participants (ORs ranging from 1.6 to 5.8). They further found interesting patterns by gender: for example, compared with Dutch participants, self-reported hallucinations were especially common among Turkish women (OR=13.5) and among Moroccan men (OR=8.4).

This raises the question of whether these patterns of low-level psychotic experiences in childhood, adolescence and young adulthood foreshadow the development of psychotic disorders later in life and, as such, represent opportunities both to understand the developmental origins of these later disparities and, more importantly, to intervene to prevent progression to more serious and intractable mental disorders.

Some studies have sought to investigate putative risk factors for psychotic experiences by ethnic group in young people, but this line of research is very much in its infancy. Adriaanse et al[88] extended their work on psychotic experiences in children to consider other problems and risk factors. They found that children from minority ethnic groups reported fewer internalizing but more externalizing problems than Dutch children, which was in part explained by indicators of social disadvantage. In a further set of analyses, they identified several risk and protective factors for mental health problems in general that were evident among minority ethnic children, including trauma, conflicts with parents, and perceived discrimination. These findings resonate with an earlier study of 3,426 children and adolescents in the UK, which found that a migratory history and family dysfunction were associated with around a four-fold increased risk of psychotic experiences[89].

Together, these findings are especially intriguing because they point to variations in mental health during childhood that mirror what is seen in adulthood, i.e. similar or lower levels of internalizing, emotional or common mental disorders and higher levels of psychoses. It is possible, then, that similar experiences of adversity – centred around family conflict and breakdown, and perceived disadvantage and discrimination – are expressed and manifest differently by ethnic group. This would also explain why greater social adversities over the life course are not reflected in higher levels of depression and anxiety in adulthood, that is, in disorders more commonly linked to difficult social conditions and experiences.

We are currently investigating these hypotheses in a newly established cohort study of around 4,000 young people aged 11 to 16 years, sampled from ethnically diverse and economically deprived neighbourhoods in South London (the REACH study, https://www.thereachstudy.com/).

Threat, hostility and violence

There is growing evidence in general that contexts and experiences involving high levels of interpersonal threat, hostility and violence specifically increase risk of psychoses. For example, using data from the E-Risk study, Arseneault et al[90] found that bullying and maltreatment, but not accidents, during childhood were associated with later psychotic (anomalous) experiences at age 12. Further, in analyses of data from our case-control study of adversity and psychoses, we found that the strongest effects were for childhood exposures and adult life events that involved severe threat, hostility and violence[91].

In relation to migrant and minority groups, these findings fit with the evidence of particularly high rates of psychosis among refugees (exposed, by definition, to extreme threat) and of effects for discrimination, especially involving violence, as detailed above. This points to a more specific formulation of the relevant social exposures: i.e., exposure – over the life course – to threat, hostility (including discrimination) and violence, especially in contexts of poverty, disadvantage and isolation (e.g., in areas of low ethnic density).

OUTCOMES

In some early reports, it was hypothesized that the course and outcome of psychosis among migrant and minority ethnic groups would be more benign and better[92]. There were two possible reasons to expect this. First, if misdiagnosis is a factor, then this should be reflected over time in fewer individuals experiencing the continuously symptomatic course that more often characterizes schizophrenia. Second, if the high rates are a consequence of social conditions, i.e., more reactive and less neurodevelopmental, with more positive and affective symptoms, this should again be reflected over time in fewer people experiencing negative and continuous symptoms.

There have been far fewer studies on course and outcome of psychoses among minority ethnic groups than on incidence, and the findings are mixed, perhaps partly because of methodological differences[93]. In brief, some suggest better outcomes, some suggest no difference, and some suggest worse outcomes.

This noted, our recent report on long-term course and outcome by ethnic group in the AESOP sample raises intriguing and troubling possibilities[94]. In what is the largest long-term follow-up of an ethnically diverse cohort of individuals with a first-episode psychosis, we found strong evidence that outcomes – clinical, social, and service use – were substantially worse for patients of Black Caribbean ethnicity, and worse or no different for patients of Black African ethnicity, compared with White British. Disparities, it seems, extend to outcomes.

Perhaps more intriguing, and relevant to this discussion, is that differences in clinical outcome were, at least in part, accounted for by differences in social disadvantage at baseline. That is, the poor clinical outcomes among Black Caribbean patients – in our data – were in part a function of high levels of social disadvantage at baseline. This raises the possibility that the effects of social disadvantage persist and further impact on course of disorder. It was clear, moreover, that these disadvantages persisted over the follow-up. For example, of those who were unemployed at baseline, only three (out of 54; 6%) Black Caribbean and one (out of 21; 5%) Black African patients were employed at follow-up.

STRUCTURAL VIOLENCE

A critical, but rarely made, point is that the social conditions and experiences considered in this paper are not randomly distributed in populations; they are socially structured. Higher levels of poverty, discrimination and threat in minority populations stem from long-term historical processes that, in predominantly White societies, have systematically marginalized and excluded those from minority groups, creating systematic barriers to education and economic opportunities, to wealth and upward mobility, to living in more prosperous areas, and to positions of power. In other words, entrenched social structures and practices, at root, determine the differential exposure of ethnic groups to the socio-developmental risks that, we argue, underpin the high rates of psychotic disorders – and subsequent poor outcomes – that have been repeatedly reported across diverse contexts over the past 60 years and more.

This is an example of what Galtung[95] termed structural violence – i.e., social structures and institutions harming the health of populations by creating barriers to resources that enable individuals to meet fundamental developmental needs. From this perspective, high rates of psychoses in some minority ethnic groups are, fundamentally, a political issue. As such, our analysis further underscores the importance of policies and community strategies to reduce ethnic inequalities across all domains (e.g., education, employment, income, physical health, mortality) and counter discrimination and racism, in all its forms.

IMPLICATIONS

The necessity of political action and community level initiatives noted, there are also important potential implications for the structure and delivery of mental health services. Alongside studies of rates of psychotic disorders in migrant and minority ethnic populations, there is a substantial body of research showing that individuals with a psychotic disorder from the populations with high rates experience more negative and coercive pathways to and through mental health services[96-98]. We found, for example, that higher rates of compulsory admission among Black Caribbean patients in the UK, compared with White British, persisted over a 10-year period following a first episode[94]. This is a deeply troubling picture: high rates of psychoses, poorer outcomes, worse and more coercive experiences of services.

There may be many reasons for differences in interactions with services, and they have been intensely and, at times, acrimoniously debated. This is a profoundly important issue.

Understanding is essential to responding effectively to reduce levels of coercion and to improve experiences of care. Our conclusion that more from minority ethnic groups develop psychoses against a background of poverty and disadvantage, with high levels of discrimination, threat and hostility, suggest one possible reason for – and consequent strategy to change – problematic interactions with services. In so far as mental health services are predicated on an illness model, in which responses and treatments are primarily focused on individuals and their symptoms, the social conditions and experiences that, for many, lie at the roots of their distress are marginal to the clinical exchange.

To be sure, many services, particularly early intervention services, do adopt more holistic approaches; but in practice attention to social circumstances and interventions to improve these are *ad hoc* and inconsistent. If we are right, that there is a predominantly socio-developmental pathway to psychosis, then by focusing primarily on symptom management, usually with antipsychotic medication, mental health services systematically fail to fully address the underlying problems that, in many, drove onset and that continue to impact on outcomes.

This will disproportionately be the case for minority groups, among which – again, if we are right – more individuals develop psychoses against this developmental background. Indeed, when asked, service users from minority ethnic groups point to multiple social stressors linked to social disadvantage to explain the reported high rates of psychosis[99]. Perhaps, then, a reorientation of services to ensure systematic attention to the social histories and worlds of those with a psychotic disorder, particularly from minority groups, will address what matters most to many patients, and from that facilitate engagement and reduce the necessity for coercion. This is not to dismiss medication or other interventions. It is, rather, to suggest comprehensive assessment of social needs and perhaps bespoke and enhanced packages of social interventions, where indicated.

CONCLUSIONS

It is now sixty years since the first reports in the UK of high rates of psychoses among migrants from the Caribbean. In the time since, there have been numerous studies that have replicated and extended these initial findings to other populations and other countries. There is considerable diversity in the incidence of psychotic disorders by minority ethnic group. The current evidence, albeit relatively thin, points to adverse social conditions and experiences, possibly particularly those that involve threat, hostility and violence, as the primary determinants of these variations. The specific clusters of social factors that are relevant may vary for first and subsequent generation migrants.

We have proposed a socio-developmental model, in which greater exposure to social risks across the life course accounts for the high rates of disorder in some groups, making the additional important point that these risks are socially structured. There is much research to be done to test and develop this model. But, most importantly, there is continued urgency to use what evidence we have to develop social policies, public health initiatives, and mental health services to tackle the interlinked problems of high rates of disorder, poor outcomes, and worse experiences of services among some of the most disadvantaged ethnic groups in our societies. Sadly, we are no further forward in meeting this challenge than we were twenty years ago.

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Post-traumatic stress disorder: a state-of-the-art review of evidence and challenges

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Post-traumatic stress disorder (PTSD) is arguably the most common psychiatric disorder to arise after exposure to a traumatic event. Since its formal introduction in the DSM-III in 1980, knowledge has grown significantly regarding its causes, maintaining mechanisms and treatments. Despite this increased understanding, however, the actual definition of the disorder remains controversial. The DSM-5 and ICD-11 define the disorder differently, reflecting disagreements in the field about whether the construct of PTSD should encompass a broad array of psychological manifestations that arise after trauma or should be focused more specifically on trauma memory phenomena. This controversy over clarifying the phenotype of PTSD has limited the capacity to identify biomarkers and specific mechanisms of traumatic stress. This review provides an up-to-date outline of the current definitions of PTSD, its known prevalence and risk factors, the main models to explain the disorder, and evidence-supported treatments. A major conclusion is that, although trauma-focused cognitive behavior therapy is the best-validated treatment for PTSD, it has stagnated over recent decades, and only two-thirds of PTSD patients respond adequately to this intervention. Moreover, most people with PTSD do not access evidence-based treatment, and this situation is much worse in low- and middle-income countries. Identifying processes that can overcome these major barriers to better management of people with PTSD remains an outstanding challenge.

Key words: Post-traumatic stress disorder, trauma, DSM-5, ICD-11, cognitive behavior therapy, definition, evidence-based treatment, access to treatment

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Although traumatic stress has been known for over 100 years by a number of terms, including "shell shock", "battle fatigue", or "soldier's heart"[1], it was only in the 1980s that persistent stress reactions were recognized in psychiatric nosology. In the wake of the mental health problems evident in many troops returning from deployment in Vietnam, the DSM-III introduced the diagnosis of post-traumatic stress disorder (PTSD).

Since that time, our knowledge about PTSD has grown significantly. However, in spite of this, the field of traumatic stress has often been dogged with controversy over the very definition of PTSD, its etiology, and optimal means for treatment. This situation has not changed today, since our conceptualization of psychological responses to trauma continues to be a matter of debate.

In this context, this review outlines our current understanding of PTSD, including diagnostic definitions, prevalence and risk factors, conceptual models, treatment approaches, and some of the major challenges currently facing the field.

DIAGNOSTIC DEFINITIONS

There are currently two major diagnostic definitions of PTSD.

The DSM-5 requires that a person experience or witness a major traumatic event (exposure to actual or threatened death, serious injury or sexual violence) (Criterion A). If one has experienced or witnessed such an event, there are four symptom clusters that he/she should manifest. First, one needs to have at least one of the following re-experiencing symptoms: intrusive distressing memories, recurrent distressing dreams, dissociative reactions (e.g., flashbacks), intense or prolonged psychological distress at exposure to reminders of the trauma, marked physiological reactions to internal or external cues symbolizing or resembling an aspect of the traumatic event (Criterion B). Second, one is required to have active avoidance of internal (e.g., thoughts, memories) and/or external (e.g., situations, conversations) reminders of the trauma (Criterion C). Third, at least two "alterations in cognitions and mood" symptoms are needed, including inability to remember an important aspect of the traumatic event, persistent and exaggerated negative thoughts about oneself or the world, persistent distorted cognitions about the cause or consequences of the event, pervasive negative emotions, markedly diminished interest, feeling detached or estranged from others, persistent inability to experience positive emotions (Criterion D). Finally, one has to present at least two of the following arousal symptoms: irritable behavior and angry outbursts, reckless or self-destructive behavior, hypervigilance, exaggerated startle response, problems with concentration, sleep disturbance (Criterion E). People are required to manifest these symptoms for more than one month after trauma exposure, in order to minimize pathologization of normal stress reactions.

It is worth noting that the DSM-5 definition has broadened the scope of PTSD from its traditional focus on fear responses to also include other emotional reactions to trauma. In fact, many PTSD patients, especially from military and first responder populations, present with non-fear emotional responses[2].

Many areas of the world operate on the World Health Organization's International Classification of Diseases (ICD) to guide psychiatric diagnoses, rather than the DSM-5. The ICD typically adopts a simpler approach to psychiatric diagnoses than the DSM, because of the need to impose less burden on diagnosticians in poorly resourced settings, who often cannot allocate lengthy assessments to each patient.

The recently approved ICD-11 diagnostic guidelines for PTSD strategically adopt a narrow focus on fear circuitry symptoms, comprising re-experiencing of the traumatic event, avoidance of reminders, and a perception of heightened current threat (reflected by various forms of arousal)[3]. Central to this definition is the proposition that a core component of PTSD is re-experiencing the memories of the traumatic event in the present.

In addition to PTSD, the DSM-5 also includes the diagnosis of acute stress disorder, which describes stress reactions occurring in the first month after trauma exposure. This diagnosis was initially introduced in the DSM-IV as a means for describing severely distressed people who could not be diagnosed with PTSD in the initial month, and also as a way to identify people who were at high risk for later PTSD. Subsequent longitudinal studies indicated that this diagnosis is only a modest predictor of PTSD: at least half of people who develop PTSD do not initially meet the criteria for acute stress disorder[4].

Initial conceptualizations of acute stress disorder placed much emphasis on dissociative responses immediately after trauma exposure (including depersonalization, derealization, reduced awareness of one's surroundings)[5], resulting in the DSM-IV requirement that dissociative symptoms be present to meet the criteria for the disorder. In contrast to this position, convergent findings indicated that, despite the relationship between peri-traumatic dissociation and later PTSD[6], many people who develop PTSD do not display dissociative responses in the acute phase after trauma[4]. As a result, in the DSM-5, the diagnosis of acute stress disorder does not require specific symptom clusters to be present, but, in recognition that people can experience acute stress in diverse ways, requires at least 9 of 14 potential acute stress reactions to occur in the initial month after trauma[7]. Importantly, this diagnosis is not intended to predict subsequent PTSD, but rather to describe people with elevated distress in the initial month who may benefit from mental health services[7].

A major reason for the inclusion of the category of acute stress disorder in the diagnostic system was that, in the US context, it is easier for many people to receive mental health care under local health insurance rules if they have a diagnosis. It was argued that the requirement that PTSD can only be diagnosed if the symptoms persist for more than one month after the trauma can result in many distressed individuals not receiving mental health care.

Another diagnostic construct that is worth noting is complex PTSD, which has been introduced in the ICD-11. To receive this diagnosis, one needs to present the core PTSD symptoms, and in addition experience disturbances in self-identity (e.g., negative self-concept), emotional dysregulation (e.g., emotional reactivity, violent outbursts), and persistent difficulties in relationships[3]. Although most commonly seen in the wake of prior prolonged childhood abuse, this disorder can also occur in survivors of other severe traumas, such as torture[8].

Complex PTSD has been the focus of many studies in recent years. A significant number of factor analytic studies tend to converge on the proposed factor structure of the disorder, with evidence of two overarching factors of PTSD symptoms and disturbances in self-organization[9-12]. Furthermore, latent class analyses have consistently documented that there is a class of individuals with high PTSD symptoms and high disturbances in self-organization, and another class with high PTSD symptoms and low disturbances in self-organization[12-16]. Importantly, there is also evidence that complex PTSD identifies a distinct class from borderline personality disorder[14]. Consistent with the proposal that complex PTSD emerges after prolonged childhood trauma, there are higher rates of childhood abuse in people with complex PTSD than in those with PTSD[13,14,17].

PREVALENCE

Although many people are exposed to traumatic events at some point in their lives, most of them rebound to enjoy pre-trauma levels of psychological functioning[18]. Epidemiological studies have reported lifetime PTSD prevalence rates of 13.0-20.4% for women and 6.2-8.2% for men[19,20]. The World Mental Health Surveys have observed higher 12-month prevalence rates in high-income (Northern Ireland: 3.8%; US: 2.5%; New Zealand: 2.1%) than in low- and middle-income countries (Colombia: 0.3%; Mexico: 0.3%)[21].

There is evidence that some features of a traumatic event are more likely to trigger PTSD. For example, there are markedly lower rates of PTSD following natural disasters (typically 5-10%) relative to sexual assault (>40%)[20,22]. Overall, interpersonal violence typically leads to higher rates of PTSD[23,24]. In fact, the World Mental Health Surveys found that organized, physical or sexual violence increased the risk for PTSD[25]. Adjusting for methodological factors, reported torture is the strongest factor associated with PTSD, followed by cumulative exposure to potentially traumatic events[26].

In studies that have focused on individual countries (which is methodologically sounder, because it allows greater consistency of potential contextual confounding influences), there is evidence that the prevalence of PTSD is higher in certain ethnic groups, such as Hispanics and African Americans in the US[27,28]. The finding that Hispanics are more at risk of PTSD has been confirmed in military samples[29]. Of course, these differences may be ascribed to differential access to health resources, ethnic discrimination, or socio-economic factors, so that their interpretation remains uncertain.

Epidemiological studies suggest that most people with PTSD have comorbid disorders, particularly depression, anxiety disorders, and substance use disorder[20,30,31]. These high rates of comorbidity may be explained by psychiatric disorders predisposing people to experience traumatic events[31], or by traumatic events or PTSD itself triggering the development of other psychiatric conditions. Indeed, depression may result from prolonged learned helplessness, and substance use disorder may be due to self-medication[32]. Greater exposure to traumatic events is likely to result in greater comorbidity[21].

COURSE

For many years it was believed that PTSD followed a linear course after trauma exposure, with a trend for symptoms to be highly prevalent in the days and weeks after exposure and to remit over the following months in most people. This view was supported by much evidence that rates of PTSD diminished by 6 months after trauma with respect to rates in the weeks after the event[33,34]. The exception to this trend was delayed-onset PTSD, which the DSM has traditionally defined as the onset of PTSD occurring at least 6 months after the traumatic event.

The understanding that PTSD follows a linear course has been challenged in recent years by evidence that the severity of the disorder fluctuates over time, that it can worsen or remit, and that this pattern can keep recurring, with the result that one's PTSD status is not static[35]. Recent studies have used latent growth mixture modelling to map the trajectories of the course of PTSD, reliably demonstrating a resilient class which consistently shows few PTSD symptoms, a recovery class with initial distress followed by gradual remission, a delayed reaction class with initial low symptom levels but increased symptoms over time, and a chronic distress class with consistently high PTSD levels[36-39].

Using network analysis, which considers the strength of relationships between symptoms, there is also evidence that the PTSD syndrome develops over time. In the acute phase after trauma, PTSD symptoms appear more loosely interconnected, while they become more closely related with the known factors (e.g., re-experiencing, active avoidance) as time progresses[40].

These convergent findings emphasize the challenges of predicting subsequent PTSD from acute reactions. Although there is evidence of an association between elevated symptoms in the acute phase and development of later PTSD[41-45], we do not have adequate cut-offs to reliably identify who will develop PTSD. One way of improving early detection comes from a consortium that recently pooled 2,473 trauma survivors from ten longitudinal studies using a likelihood estimate approach[46]. This study found that, in a patient with elevated early symptom severity, the concomitance of female gender, less than secondary level education, and exposure to past interpersonal trauma was associated with a 34% greater likelihood of developing PTSD.

RISK FACTORS

What predisposes only a small proportion of trauma survivors to develop PTSD? Many of the risk factors are in fact the same observed across several psychiatric disorders: female gender, low socio-demographic background, prior mental disorder, family history of mental disorders, and traumatic childhoods[47]. In terms of vulnerability factors more specific to PTSD, the disorder is more likely to occur after prolonged trauma or interpersonal traumatic events[47].

The subjective response to the trauma is also predictive, with acute dissociative reactions[48,49] and catastrophic appraisals[50-52] about the outcome of the event being strongly associated with later PTSD severity. The post-trauma environment is also important, with low social support and ongoing stressors contributing to risk for PTSD development[47].

MODELS OF PTSD

Neurobiological models

Most theories of PTSD invoke processes involving fear conditioning. This model posits that at the time of trauma the surge of stress hormones released in association with the fear experienced by the individual results in strong associative learning between cues present at the time of trauma and fear responses. The associated cues assume the property of predicting future threat, thereby resulting in a re-experiencing of fear when the individual is exposed to internal and external reminders of the trauma[53]. This model also posits that recovery from initial stress reactions usually involves extinction learning, in which one is repeatedly exposed to reminders of the trauma but on these occasions there is no adverse consequence; accordingly, there is new learning that the previously conditioned cues now signal safety[54].

There is evidence of neural changes in people with PTSD that are consistent with circuitry known to be implicated in fear conditioning: the amygdala, prefrontal cortex, and the hippocampus. Many studies indicate that PTSD is associated with a smaller size of the hippocampus, with meta-analyses reporting that this finding is observed bilaterally[55]. A recent consortium study including 1,868 participants (794 with PTSD) found an average smaller size of the hippocampus in those with the disorder[56]. The extent to which a smaller hippocampus is a consequence of PTSD or a risk factor has yet to be definitively addressed. One study compared monozygotic co-twins who either did or did not serve in Vietnam[57], and found that veterans with PTSD had smaller hippocampi than Vietnam veterans without PTSD, but the co-twins of those with PTSD who had not served in Vietnam had hippocampi that were just as small. There is also much evidence of reduced volume of prefrontal regions in PTSD[58], consistent with proposals that PTSD patients have problems with extinction learning.

Other studies have used fear provocation tasks to activate the threat network in PTSD patients. The most replicated finding is evidence of underactivation of medial prefrontal cortex regions, consistent with the notion of an impairment of the regulatory processes that promote extinction[59]. There is also evidence of dysfunctions in threat detection, executive functioning, emotion regulation, and contextual processing[60,61].

Noradrenergic dysregulation is well-documented in PTSD, and has been postulated to be key to the development of intrusive re-experiencing of trauma memories[62-65]. This notion is supported by evidence that prazosin (a noradrenergic receptor inhibitor) is efficacious in reducing nightmares and re-experiencing symptoms of PTSD[66,67]. Further support is from evidence

that administration of propranolol (a beta-adrenergic antagonist) in the hours after trauma exposure limits subsequent reactivity to reminders[68], although it does not prevent overall PTSD[69,70].

The PTSD field has also focused on the glucocorticoid system. Although increased cortisol levels are typically associated with chronic stress, PTSD is often linked with *lower* cortisol levels[71]. Further, lower cortisol levels shortly after trauma predict subsequent PTSD severity[72]. This paradoxical finding has been interpreted in terms of cortisol binding to the glucocorticoid receptors in a negative feedback loop that promotes homeostasis of the stress response[73]. This proposal posits that lower cortisol in PTSD may result in elevated ongoing activity of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in exaggerated catecholamine response and consequent over-consolidation of trauma memories. This idea has received some support from studies reporting that, in animal models, the administration of hydrocortisone shortly after stressor exposure results in reduced subsequent PTSD-like reactions[74]. There is pilot evidence that this procedure also limits subsequent PTSD symptoms following trauma in humans[75].

A consistent pattern in PTSD research is that females are twice as likely to develop PTSD as males[76]. Females have greater noradrenergic response to aversive stimuli[77,78], display greater context-potentiated startle magnitude[79], and show greater amygdala reactivity after threatening stimuli[80]. The menstrual phase (reflecting cycling levels of progesterone and estradiol) impacts PTSD phenomena, suggesting that sex hormones play an important role in this regard. Females with PTSD (relative to those without PTSD) show impaired extinction learning in the mid-luteal phase (when progesterone and estradiol levels are high)[81]. Indeed, females are more likely to experience flashback memories if they are exposed to traumatic events during the mid-luteal phase[82]. One reason why progesterone may facilitate emotional memories is that it binds to glucocorticoid receptors, thus affecting the release of endogenous glucocorticoids[83].

Supporting fear conditioning models is the robust finding of enhanced psychophysiological reactivity to reminders of the trauma in people with PTSD. Script-driven imagery paradigms direct participants to listen to pre-recorded accounts of their trauma, during which heart rate, skin conductance or facial electromyogram measurements are obtained; this typically results in greater reactivity in PTSD relative to non-PTSD participants[84]. Consistent with fear conditioning models is also the evidence of elevated resting heart rate in the days after trauma in those who subsequently develop PTSD[85], particularly in response to trauma reminders[86]. Further, people with PTSD display impaired extinction learning[87], and deficient capacity for extinction learning is a risk factor for PTSD[88-90].

Genetic factors

The well-documented fact that the vast majority of people who are exposed to trauma do not develop PTSD[40] highlights that there are key individual differences in propensity to manifest this disorder. Much evidence indicates that genetic factors play an important role, accounting for 30-72% of the vulnerability to develop PTSD[91,92].

Many studies have attempted to link PTSD with genetic candidates, and not surprisingly genes associated with PTSD are also linked with other common psychiatric disorders, including major depression, generalized anxiety disorder, panic disorder, and substance use[93]. For example, numerous studies have pointed to the functional polymorphism in the promoter region of the serotonin transporter gene (SLC6A4) across many disorders. The short allele (5-HTTLPR S), which reduces serotonergic expression and uptake by nearly 50%[94], has been linked with impaired extinction learning in both mice and humans[95]. Gene x environment association studies also show that a functional variant in FKBP5, a gene encoding a co-chaperone of the glucocorticoid receptor, increases risk for PTSD following trauma[96].

Over 50 gene variants have been linked with PTSD, involved in the function of HPA axis; noradrenergic, dopaminergic and serotonergic systems; and neurotrophins[97]. However, this field is characterized by poor replication of findings, and accordingly there is convergent agreement that the most promising avenue for understanding the genetic basis of PTSD is via polygenic approaches. The largest genome-wide study to date was conducted by the Psychiatric Genomics Consortium – Posttraumatic Stress Disorder Group, which recently reported an analysis of 20,730 people: no single nucleotide polymorphism was found to be significantly associated with PTSD, but the study did find a polygenic risk profile that overlapped with risk for schizophrenia[98].

The genetic vulnerability to PTSD appears to be moderated by contextual factors. Early life stress is particularly relevant, with evidence that childhood trauma modifies the genetic risk for PTSD[96]. Epigenetic studies in PTSD have typically focused on DNA methylation, with a primary focus on peripheral indicators of candidate genes[99], and epigenetic regulation of the HPA axis in particular[100]. Distinctive methylation in PTSD has been documented in a number of genes, including NR3C1, CRHR1 and FKBP5[97]. However, the evidence has relied to date on peripheral blood assessments, that may not reflect central mechanisms occurring in neural circuits.

Cognitive behavioral models

Although most cognitive behavioral models recognize the role of fear conditioning in the etiology of PTSD, they also place considerable emphasis on memory organization[101]. Cognitive models propose that trauma memories are encoded in a distinctive manner, as a result of the elevated arousal at the time of trauma. They tend to be encoded in predominantly sensory modalities, with a fragmented and disorganized sequencing, thereby reducing the likelihood that the memory is adequately embedded into one's autobiographical memory base[102]. There is some evidence that interfering with the visual memory sys-

tem during the consolidation phase after trauma exposure can limit subsequent PTSD symptoms[103].

Much emphasis is also placed on the extent to which people appraise the traumatic event, their responses to it, and their future likelihood of harm. It is postulated that excessively negative appraisals tend to exaggerate the individual's sense of threat, thereby maintaining PTSD[104,105]. As noted above, there is abundant evidence of the predictive role of catastrophic appraisals in the development and maintenance of PTSD, as well as of their decline after successful therapy[106]. These appraisals tend to result in strong avoidance of potential threats, which impairs emotional processing of trauma memories and extinction learning[107].

Implicit in most cognitive (and biological) models of PTSD is the attentional bias towards threat, as reflected in the inclusion of hypervigilance in the DSM-5/ICD-11 descriptions of PTSD. Using a range of experimental paradigms, PTSD has been found to be characterized by a strong bias towards potentially threatening stimuli[108-110]. Relatedly, PTSD patients have problems with disengagement from threat, response inhibition, and orienting[62]. The resulting intrusions and arousal can contribute to the well-documented deficits in neuropsychological functions such as concentration, sustained attention, executive control, and working memory[111].

PREVENTION

Defence organizations have sometimes tried to prepare their personnel for deployment to combat by targeting key mechanisms known to increase the risk for PTSD.

One example comes from an Israeli initiative that built on evidence regarding the attentional biases in PTSD. The disorder is characterized by both a bias towards threat[109,112] and a bias towards avoidance of the threat[113,114], resulting in greater attentional variability[115]. A computerized prevention program tested in Israeli soldiers involved training them to control their attentional biases by using a modified dot-probe task administered prior to deployment. The study found that soldiers receiving the program had fewer subsequent PTSD symptoms than those in a control condition, and this result was mediated by a reduction in attentional variability[116]. This program appears to be a promising preventive strategy, at least in military personnel, and has been found to reduce PTSD symptoms in treatment seeking combat veterans[117].

PSYCHOLOGICAL TREATMENTS

The treatment of choice for PTSD is trauma-focused cognitive behavior therapy (TF-CBT), as suggested by most treatment guidelines[118,119].

There are numerous variants of TF-CBT, including prolonged exposure, eye movement desensitization and reprocessing, cognitive therapy, cognitive processing therapy, and imagery rescripting therapy. Although these treatments are presented as distinctive, they all essentially comprise emotional processing of the traumatic memory and integration of new corrective information. This form of therapy has been shown to be effective in many populations, including victims of traumatic injury and assault, sexual assault, combat, terrorist attacks, displacement, and childhood sexual abuse[120-125].

The core component of this treatment typically involves exposure, i.e. the patient is directed to engage with the trauma memory for a prolonged period. This strategy is commonly conceptualized as a form of extinction learning, insofar as the person learns that the trauma reminder is no longer a signal of threat. Although this exposure was traditionally implemented for 40-60 min, later trials have shown that it can be effective with repeated sessions lasting 20 or even 10 min[126,127].

The introduction of the diagnosis of acute stress disorder triggered a series of early intervention studies targeting people who were regarded as being at high risk for PTSD development. These programs evaluated abridged versions of TF-CBT (usually 5-6 sessions), and typically found that they were more efficacious than control conditions[128-132]. Meta-analytic studies have supported the utility of early targeted intervention to limit later PTSD[133,134]. However, one large study found that, whereas early provision of TF-CBT facilitated recovery, all patients typically adapted in the long-term regardless of the type of intervention[135].

Although TF-CBT has been shown to be effective in PTSD, it is important to note that only two-thirds of patients respond adequately to this intervention[136]. This has led to attempts to augment treatment, mostly based on pharmacological or psychological strategies to increase extinction learning, building on animal neuroscience work[137,138]. These approaches have targeted the mechanisms of extinction by combining exposure therapy with device-based, pharmacological or behavioral techniques that promote neural processes to enhance associative learning.

Device-based techniques include repetitive transcranial magnetic stimulation (rTMS) focusing on the ventromedial and dorsolateral prefrontal cortex, areas that are relevant to extinction learning. Several studies suggest that rTMS is superior to sham in augmenting exposure therapy[139,140].

One of the earlier pharmacological attempts used D-cycloserine, an antibiotic that acts as an agonist of N-methyl-D-aspartate (NMDA) receptors and promotes extinction learning in animals. A series of trials tested this drug to augment exposure therapy for PTSD. One study found evidence of a faster rate of symptom reduction[141], while another reported a detrimental effect[142], and three further trials found no effect[143-145]. The conclusion was that this adjunctive treatment is not useful[146].

The other pharmacological adjunct that has received considerable recent attention is methylenedioxy-methamphetamine (MDMA). This drug enhances activity in the ventromedial prefrontal cortex, which is key for extinction. Furthermore, it increases cortisol release, which can promote emotional engagement and enhance extinction[147]. Several small trials suggest that MDMA-assisted psychotherapy does have a superior effect[148,149], and large multi-site studies are now underway[150].

Further attempts to augment PTSD treatment have combined

exposure with acute bouts of exercise, because this can promote extinction retention (possibly via increased release of brain-derived neurotrophic factor)[151]. One small pilot study did show that acute bouts of exercise after exposure can boost the effect of therapy[152].

Although some attempts to augment psychotherapy for PTSD appear to offer promise, we are not at the point of recommending any of them. Larger trials, more targeted augmentation strategies, and replication of findings are needed before we are in a position to integrate these approaches into clinical practice.

PHARMACOLOGICAL INTERVENTIONS

There is much less compelling evidence for pharmacological treatment of PTSD. In fact, psychotherapeutic approaches yield more robust effect sizes than pharmacological agents, and the potential for adverse side effects and relapse after discontinuation of medications supports the idea, endorsed by treatment guidelines, that psychotherapy should be the first line of treatment.

At present, two selective serotonin reuptake inhibitors (SSRIs), sertraline and paroxetine, are the only medications approved by the US Food and Drug Administration for treatment of PTSD, although their effect size in this disorder is small (0.23; 95% CI: 0.12-0.33)[153]. There is also some evidence for efficacy of the selective noradrenaline reuptake inhibitor (SNRI) venlafaxine. One common reason why these drugs are prescribed is that they are efficacious in treating major depressive disorder, which is highly comorbid with PTSD.

Other pharmacological agents have been used for specific PTSD symptoms: as noted above, multiple studies have found prazosin (an alpha1-adrenergic antagonist) to be effective in reducing nightmares and hyperarousal[154]. Benzodiazepines have often been prescribed in the context of PTSD, but they are generally contraindicated, because of limited efficacy and risk of abuse.

Over the past 20 years, there have been attempts to limit PTSD development by the early administration of agents that target key neurobiological processes occurring in the initial days after trauma exposure.

The proposition that PTSD is largely driven by a surge of noradrenergic release in the acute post-trauma period has led to attempts to reduce noradrenergic activity. These attempts have focused on administering propranolol (a beta-adrenergic antagonist) in the hours or days after trauma exposure, because of preclinical evidence that this drug blocks fear memory reconsolidation[155]. As noted above, the initial trial of propranolol found that it resulted in reduced subsequent reactivity to trauma reminders, even though it did not reduce the severity of PTSD[68]. Subsequent trials were negative, and one meta-analysis concluded that there was no evidence for the utility of propranolol in limiting PTSD development[156].

It is also worth noting that there is indirect evidence of a potentially protective role for morphine in the acute phase after trauma. The locus coeruleus, which produces noradrenaline, is inhibited by morphine, and animal work indicates that morphine injections into the amygdala impair memory for fear conditioning in rats[157]. It has been suggested that the administration of morphine in the initial days after trauma exposure may be associated with reduced PTSD at follow-up[158,159], but no randomized controlled trials are available.

The evidence that low levels of cortisol after trauma are predictive of subsequent PTSD[72,160] has led to attempts to limit later PTSD severity by increasing cortisol levels in the period shortly after trauma exposure. As noted above, animal studies reported that administering hydrocortisone to rats after exposure to a stressor results in less fear behavior compared to placebo[74]. Similarly, administering cortisol to humans immediately after exposure to a stressful event results in fewer memories of the event[161,162]. Indeed, a preliminary study found that the administration of cortisol within hours of trauma exposure is more efficacious that placebo in limiting subsequent PTSD[75].

MAJOR CHALLENGES FOR THE PTSD FIELD

The diagnostic conundrum

One of the main challenges in the PTSD field is the fact that we have two official definitions of the disorder that are somewhat different. As noted above, whereas the DSM-5 definition intentionally encompasses a broad range of trauma-related presentations, the ICD-11 adopts a much narrower approach focused on fear circuitry.

This situation is problematic, because multiple studies indicate that PTSD is diagnosed at higher rates using the DSM-5 criteria compared to the ICD-11 guidelines[163-165], although there are also some reports that rates are comparable[166]. Further concern comes from the evidence that the two diagnostic systems tend to identify different individuals, with one study showing that only 42% of trauma survivors were diagnosed as having PTSD using both definitions[163].

There has been considerable discussion about the relative merits of the two diagnostic definitions. On the one hand, it has been emphasized that the DSM-5 definition is applicable to a larger number of trauma survivors[164]. On the other, it has been argued that moving beyond the traditional focus on fear symptoms undermines much of the evidence base of exposure-based treatments for PTSD and may increase the rate of psychiatric comorbidities[167]. Actually, some studies suggest that the ICD-11 definition of PTSD is associated with less psychiatric comorbidity[166,168], while others indicate that there is not a marked difference in this respect between the DSM-5 and ICD-11 definitions[163,164]. A further argument is that, when using the DSM-5 definition of PTSD, there are 636,120 permutations of how the disorder may present[169], which may impair the identification of meaningful biomarkers.

Delayed-onset PTSD

Delayed-onset PTSD, traditionally defined as PTSD that develops at least 6 months after exposure to trauma, has been

described for many years, with cases of PTSD reportedly commencing decades after the trauma occurrence[170]. Systematic reviews indicate that, of those people who develop PTSD, approximately 25% may be delayed-onset cases[171,172].

Longitudinal studies suggest that most of these cases actually experience sub-syndromal levels of PTSD in the acute phase, and this reaction subsequently compounds to a more severe disorder, so that the diagnostic threshold for PTSD is surpassed[173-176]. Systematic reviews recognize, however, that some people do apparently have an initial period of minimal symptoms and subsequently develop PTSD[172]. This latter scenario has been particularly noted in military cohorts, where delayed-onset PTSD is markedly more common than in civilian trauma survivors[177]. It appears that many troops return from deployment with little indication of stress response, while on follow-up they display full PTSD symptoms.

Different theories have been put forward for delayed-onset PTSD. It is possible that, in the initial phase, denial and numbing inhibit PTSD responses and that, as time progresses and numbing abates, PTSD symptoms emerge[178] – however, no strong evidence supporting this hypothesis is available. A second possibility is that, immediately after the traumatic event, people are more preoccupied with immediate needs (such as pain, legal proceedings, post-deployment activities, or dislocation) that distract their attention from their stress reactions[179] – again, there is a paucity of evidence in favor of this explanation. The observation that many delayed PTSD cases experience significant acute stress responses that subsequently worsen has prompted the proposal that delayed PTSD may be caused by additional stressors in the post-trauma phase, compounded with diminished resources to deal with these demands[180] – indeed, there is evidence that delayed-onset PTSD is predicted by the severity of post-trauma stressors[135,173,181,182]. One further possibility is that relief from the immediate threat of danger may provide people with a temporary sense of safety, that subsequently gives way to ongoing perceptions of threat, leading to PTSD – this interpretation may be especially applicable to military cohorts, who may be relieved by abandoning the combat zone, but may then have difficulties to readjust to ordinary life[177].

PTSD in poorly resourced countries

The majority of people with PTSD do not access care. This situation is particularly stark in low- and middle-income countries, which are disproportionately affected by wars, natural disasters, and humanitarian crises that can facilitate the emergence of mental disorders such as PTSD[183]. A major challenge for the management of PTSD worldwide is the dissemination of evidence-based interventions that can be scaled up affordably in settings lacking adequate numbers of mental health specialists.

It is well documented that evidence-based programs can be implemented effectively in low- and middle-income countries[184,185]. However, they are rarely applied in ordinary conditions, because they typically involve many therapy sessions, require mental health specialists, and are predicated on a skilled diagnosis of PTSD. In response to this situation, there has been a concerted effort in recent years to engage in "task-shifting", which involves training non-specialists to deliver evidence-based programs to address a range of common mental disorders[186]. This approach has been used successfully in treating PTSD[187,188].

While some programs have been successful in addressing PTSD in low- and middle-income countries by adopting a transdiagnostic approach, that does not require sophisticated diagnostic skills but relies on targeting common problems that underpin anxiety and depression[189], others have used a modular approach that tailors key strategies to the primary problems that a person is experiencing[190,191]. Despite these promising developments, massive challenges remain in disseminating affordable evidence-based programs in low- and middle-income countries, because most of them lack the resources to implement and sustain mental health initiatives.

CONCLUSIONS

Since the introduction of the PTSD diagnosis 40 years ago, our understanding of traumatic stress conditions has grown significantly. However, despite this burgeoning knowledge, our capacity to facilitate recovery from PTSD appears to have stalled over recent decades. Although our treatments are reasonably efficacious, too many patients fail to respond optimally, and many more are not able to access them.

These problems remain a major challenge for the field. Considering the millions of people directly affected by trauma, the limited success in providing the majority of them with efficacious treatments is resulting in a major public health burden. Identifying novel mechanisms that can be translated into optimizing treatment outcomes, and overcoming the major barriers facing most health systems in delivering evidence-based treatments, should remain the top priorities for the field of traumatic stress in the years to come.

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Fidelity vs. flexibility in the implementation of psychotherapies: time to move on

In psychotherapy, treatment fidelity refers to the extent to which treatments are delivered as intended, and is considered to encompass adherence (the extent to which pre-specified interventions are used) and competence (the skill with which they are implemented).

Treatment fidelity is typically assumed to be positively related to outcome. This assumption rests on the drug metaphor – that there is a positive relationship between the "dose" of the "active ingredients" in any given treatment and the outcome. For instance, the extent to which therapists use specific theory-derived techniques and interventions, such as challenging automatic thoughts in cognitive-behavioural therapy or working with the transference in psychodynamic psychotherapy, should be directly related to better outcomes.

However, the most comprehensive meta-analysis to date suggests that fidelity may play very little, if any, role in explaining outcome across different treatment modalities[1]. In defence of the fidelity hypothesis, this meta-analysis also found considerable heterogeneity in studies of the relationship between fidelity and therapeutic outcome. More recent studies and meta-analyses are similarly inconclusive.

The unreliability of fidelity assessments and the limited range of fidelity scores, as therapists tend to be carefully selected, trained and supervised in clinical trials, caution against premature conclusions. Moreover, the therapeutic alliance and patient characteristics are known to be important moderators of the fidelity-outcome relationship[1]. Nevertheless, the lack of robust links between fidelity and outcome casts doubt on a core assumption of the dominant approach to the development of evidence-based psychotherapies, namely, that the use of specific techniques is vital to good outcome[2,3].

In response, more flexible, transdiagnostic and modular approaches have been developed, which may be at least as effective as "specialized" treatments focusing on a smaller number of problem-specific techniques and interventions[4,5]. Others have argued for a bottom-up approach in developing evidence-based psychotherapies by carefully studying psychotherapy as it is delivered, and emphasizing competencies in factors such as creating a therapeutic alliance and providing a convincing treatment rationale[3].

Yet, there are dramatic demonstrations of the importance of fidelity at the level of systemic implementation. The fidelity of programme delivery at the level of mental health care organizations (such as the UK's Improving Access to Psychological Therapies programme) has been shown to enhance efficacy and explain 11-42% of the variance in outcome[6]. Longer-term psychotherapy for borderline personality disorder has been shown to be three times less effective, when poorly implemented, than optimal treatment[7]. Such findings stress the importance of fidelity not only at the level of the therapist, but also at the levels of the therapeutic team, the management, and the broader sociocultural context[8].

The ambiguous results concerning fidelity to treatment protocols highlight important challenges for the scientific development of psychotherapies. A key problem with research on fidelity is that patients do not readily fit into the clinical categories for which evidence-based psychotherapies are designated. Comorbidity is the norm, and demands flexibility if specialized therapies are to be administered effectively.

In addition, most specialized treatments focus on only a limited number of mechanisms of change in the face of significant heterogeneity within diagnostic categories. There is growing evidence that a general psychopathology (or "p") factor may represent an as-yet-undefined facet of *all* mental disorders[8].

From these perspectives, transdiagnostic, modular and common-factor approaches probably have a major advantage compared with models that emphasize a limited number of specific factors. Recent studies indeed suggest that adherence flexibility (the capacity of the therapist to flexibly adapt treatment to the patient, which may involve using interventions from other treatment approaches and modalities) may be associated with superior outcomes[9].

By contrast, therapists using a specialized treatment may actually become more "adherent" to the specific treatment model with patients who are showing a poorer response. This may explain the negative relationship between fidelity and outcome reported in some studies, as these therapists may, by becoming more "adherent" to their treatment model, fail to address the specific problems of the patient simply because they are not targeted by that model[1].

In the absence of clear guidelines for adapting treatments to specific patient features, therapists tend to adapt treatment to their patients largely intuitively, using generic and specific therapeutic interventions "borrowed" from different treatment protocols. Such lack of specificity suggests the centrality of some common mechanisms in the action of therapies, which, after all, invariably rely on the possibility of change through social communication.

All effective treatments may incorporate elements which open up the individual to social learning that depends on trust in the person conveying information. The therapeutic alliance may be an important moderator of the fidelity-outcome relationship[1] because the therapist establishes epistemic trust that sets in motion a process of openness to adaptive learning in the treatment setting and beyond.

The current state of affairs reflects our lack of knowledge of how to shape treatment protocols to the particular social and psychological factors prominent in the history of any individual patient. Beyond this, the development of innovative psychosocial treatments awaits improved understanding of the

biopsychosocial mechanisms that underpin mental disorders. In marked contrast to physical illness, the overall prevalence of mental illness has not changed in the past 30-40 years. Therapies can reduce distress but they cannot cure, and there is a lack of established preventive interventions.

To conclude, the need to flexibly address particular underlying psychological mechanisms in a given patient may be a key factor explaining the loose coupling of fidelity and outcome in evidence-based psychotherapies. Such a flexible approach should ideally be embedded within a coherent, consistent and continuous organizational context.

More research is needed to identify transdiagnostic and transtheoretical mechanisms that are involved in the causation and maintenance of psychopathology. In addition, translational efforts are needed to develop treatments grounded in newly emerging knowledge of these mechanisms.

Finally, training of therapists should incorporate a greater focus on adherence flexibility and tailoring treatment to individual patient features. While this may make training more complex and lengthy, and thus more costly, it may improve effectiveness and reduce treatment costs.

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The Five Factor Model of personality structure: an update

The Five Factor Model (FFM) of general personality structure consists of the five broad domains of neuroticism (or emotional instability vs. stability), extraversion (vs. introversion), openness (or unconventionality), agreeableness (vs. antagonism), and conscientiousness (or constraint vs. disinhibition). Each of these domains includes more specific facets (e.g., gullible vs. cynical, meek vs. aggressive, soft-hearted vs. callous, and selfless vs. exploitative are within the domain of agreeableness vs. antagonism).

The FFM traces its roots to the lexical paradigm, which rests on the compelling premise that what is of most importance, interest or meaning to persons when describing themselves and others will be encoded within the language. Fundamental domains of personality emerge as persons develop more and more words to describe the gradations, variations and nuances of a respective domain. The natural, inherent structure of personality is provided by the empirical relationship among the trait terms, and the structure of the English language has converged well onto the "Big Five". The Big Five have also been replicated within the German, Czech, Dutch, Filipino, Hebrew, Hungarian, Italian, Korean, Polish, Russian, Spanish and Turkish languages, albeit the replication of neuroticism and openness is not as strong as the replication of the domains of agreeableness, extraversion and conscientiousness[1].

Empirical support for the FFM as a structural model of personality is substantial, including multivariate behavior genetics, childhood antecedents, temporal stability across the lifespan, cognitive neuroscience coordination, and cross-cultural replication[1]. The FFM has also been shown across a vast empirical literature to be useful in predicting a substantial number of important life outcomes, both positive and negative[2]. Cuijpers et al[3] compared the economic costs of FFM neuroticism (health service uptake in primary and secondary mental health care, out-of-pocket costs, and production losses) with the costs associated with common mental disorders (e.g., mood, anxiety, substance use, and somatic disorders). The economic costs of neuroticism were approximately 2.5 times higher than those of the common mental disorders.

Given that the Big Five account for virtually every trait term within the language, it is not surprising that the FFM accounts for every maladaptive personality trait, including those that define the personality disorder syndromes of the ICD and the DSM[1]. The dimensional trait models included within the DSM-5 Section III and the ICD-11 are aligned explicitly with the FFM. The FFM also provides the temperament base and personality foundation for the widely cited Hierarchical Taxonomy of Psychopathology[4], a dimensional structural model that covers much of all forms of psychopathology.

The ICD and DSM personality disorders are readily understood as maladaptive variants of the FFM, but this does not suggest that any measure of the FFM will fully account for every personality disorder. Most existing measures of the FFM do not assess for all of its maladaptive variants and therefore will not be able to account for all of the components and correlates of a respective personality disorder. For example, there are maladaptive variants for all ten poles of all five FFM domains, but existing measures typically fail to assess for the maladaptive variants of conscientiousness (e.g., compulsivity), openness (e.g., magical thinking), agreeableness (e.g., subservience), low neuroticism (e.g., fearlessness), and extraversion (e.g., dominance), thereby limiting the ability to cover traits central to the obsessive-compulsive, schizotypal, dependent, and psycho-

pathic personality disorders, respectively. The obsessive-compulsive personality disorder is defined largely by maladaptive conscientiousness (e.g., perfectionism, compulsivity, workaholism, and ruminative deliberation), but most measures of FFM conscientiousness do not assess for these maladaptive variants. Measures to assess maladaptive FFM traits, though, have been developed, including the Five Factor Model Personality Disorder scales[5], the Personality Inventory for DSM-5[6], and the Personality Inventory for ICD-11[7].

There are a number of advantages in conceptualizing the ICD and DSM personality disorders from the perspective of the FFM. Many of the ICD and DSM personality disorder syndromes have limited research interest and inadequate empirical support. The FFM brings to the personality disorders a substantial body of construct validation, including a resolution of such notable controversies as gender bias, excessive diagnostic overlap, and temporal instability. An understanding of the etiology, pathology and treatment of the personality disorders has been hindered substantially by the heterogeneity within and the overlap across the diagnostic categories. The American Psychiatric Association has been publishing treatment guidelines for every disorder within the DSM, but guidelines have been provided for only one of the ten personality disorders (i.e., borderline). The complex heterogeneity of the categorical syndromes complicates considerably the ability to develop an explicit, uniform treatment protocol. The domains of the FFM are considerably more homogeneous and distinct, lending themselves well for more distinct models of etiology, pathology and treatment[8]. Empirically validated treatment protocols have already been developed for FFM neuroticism[9].

A common concern regarding the FFM and any other dimensional trait model is that clinicians will be unfamiliar with this approach and will find it difficult to apply. However, the FFM organization is consistent with the manner in which persons naturally think of personality trait description. Persons who apply the FFM typically find it quite easy to use. There have in fact been a number of studies concerning the clinical utility of the FFM in comparison to the DSM syndromes. A few of these studies have favored the DSM syndromes but, when the methodological limitations of these particular studies were addressed in subsequent studies, the results consistently favored the FFM[8]. Experienced clinicians prefer the FFM and dimensional trait models for the conceptualization of personality disorders[8].

In sum, the FFM is the predominant model of general personality structure and offers the opportunity for a truly integrative understanding of personality structure across the fields of clinical psychiatry and basic personality science. The ICD and DSM models for the classification and diagnosis of personality disorder are shifting toward the FFM because of its empirical validation and clinical utility.

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The network approach to psychopathology: promise versus reality

The network approach to psychopathology has recently generated enthusiasm in the research community. This is likely due in large part to network methods being promoted with the promise of improving clinical prevention and intervention strategies by explicating the dynamic causal architecture of mental illness[1]. As a result, studies using network methods have proliferated with the aim of understanding causal interactions between psychiatric symptoms through empirical data.

As one example, there has been a substantial number of studies on the network structure of post-traumatic stress disorder (PTSD) wherein each network typically includes estimation of centrality indices for 16-20 symptoms, as well as the presence and weight of 120-190 edges. Few guidelines inform how to parse the multitudes of exploratory results in each symptom network. Confirmation bias is consequently hard to avoid, and the validity of a network is easily rationalized by the identification of intuitive findings[2]. By contrast, a variety of *post-hoc* explanations are available to dismiss unintuitive findings.

Estimated edges may represent a direct association between two symptoms (e.g., A→B or A←B), a reciprocal effect (A←→B), the common effect of an unmodelled variable (A←X→B), shared item content or method variance, or simply error (noise) in the data. Absent edges may represent conditional independence of two symptoms, or be the result of the specificity in the regularization method used. Central symptoms may cause other symptoms in the network and represent important targets for clinical intervention, or may be the consequence of those other symptoms and thus not useful targets for clinical intervention. Alternatively, as for estimated edges, high symptom centrality may summarize reciprocal relationships among symptoms, relationships with unmodelled variables, shared item content, method variance, or error. There are no methods for disentangling these different explanations of the focal parameters in cross-sectional symptom networks, which severely limits their utility. In other words, the results are equivocal.

The fundamental reason for this undermining ambiguity

is that, with few exceptions, the data used to investigate the network approach to psychopathology are ill-suited to do so. Network theory is alluring because it describes dynamic causal processes that play out within individuals. However, no statistical procedure can extract this information from the type of cross-sectional between-subject data that dominate the literature[3]. Indeed, networks estimated on these data are not expected to accurately reflect individuals' experiences or underlying causal processes, by network theorists' own arguments[4]. As such, the current state-of-the-art networks lack the capacity to provide the very insights they have been promoted to offer.

The unreliability of edges further complicates the interpretation of symptom networks, which change based on the specific set of symptoms in the network, the measures used to assess the symptoms, the use of a clinical or community sample, the sample size, and the type of network analysis adopted[5]. Remarkably, even when these characteristics are all held equal, key details of the model often do not replicate within or between samples[5,6]. This unreliability is predictable, given the intercorrelated nature of psychopathology symptoms, the limited reliability of single self- or clinician-report items, and a focus on the fully partialled relationship between each pair of symptoms (e.g., edge A–B represents what symptoms A and B share with each other, but not with any other symptoms in the network). Together, these common features of current network methods result in edges that are prone to substantial measurement error, leading to spurious associations and high sensitivity to minor variations in study methods and samples. It is therefore difficult to identify generalizable insights in the symptom network literature that advance our understanding of psychopathology.

In contrast, proponents of the network approach recently stated[7] that network structures replicate and generalize well, citing examples including "nearly identical" major depression and generalized anxiety disorder symptom networks, and a comparison of four PTSD networks. A closer look at these examples reveals, however, that almost a quarter (23%) of the total estimated edges were unreplicated between the two depression and anxiety networks[5], and that well over half (64%) of the edges were inconsistently estimated – as present or absent, or positive or negative – among the four PTSD networks[6].

The broader PTSD symptom network literature enables comparisons between additional studies that further highlight substantial inconsistencies[8]. Among eight of the studies in this literature that have used "state-of-the-art" network methods[9] in samples of people who have experienced trauma, the large majority (88%) of symptoms have been reported to have particularly high centrality – many in only a single paper, and none in a majority of the papers. Further, among these studies, all but three (98%) of the 120 possible edges among the PTSD symptoms in DSM-IV and DSM-5 have been estimated, and vary between studies in their presence, strength, sign, and hypothesized importance in the network.

There are not yet any methods that can indicate *a priori* whether or not a specific edge is likely to replicate. While it may be naive to expect exact replication, observed levels of inconsistency between networks seem particularly problematic in the context of a theory that emphasizes interpretation of the presence, absence, strength and sign of each individual edge and the corresponding centrality of individual symptoms. Importantly, optimistic perspectives on the reliability and replicability of symptom networks are often based on methods (e.g., bootnet, the omnibus NetworkComparisonTest, and correlations between lists of edges) that shift the focus away from these detailed features, and towards global network patterns that do not correspond with the basis of network theory or the insights that symptom networks have been promoted to provide[6]. The result is that these popular methods create an impression of reliability and replicability that fails to translate to the level at which networks are interpreted.

Our concerns surrounding the equivocal, stationary and ungeneralizable nature of current symptom network results contrast with the rhetoric in much of the network literature promising meaningful clinical insights from these methods. Alternative modeling methods and research designs – for example, collecting experimental data with reliable measurement of symptoms over time – are needed to make causal inferences about relationships between symptoms, and thus to achieve the aims of the network approach to psychopathology. Ultimately, it remains unclear what can be meaningfully concluded from the extant network literature with respect to the onset, maintenance or treatment of psychopathology.

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Cognitive remediation for severe mental illness: state of the field and future directions

After more than 20 years of studies examining the methods, efficacy and effectiveness of cognitive remediation for severe mental illness, this therapy is recognized as evidence-based for schizophrenia and is emerging in clinical practice.

As with all behavioral interventions, this period of development has not been without its criticisms, trial failures, and practical concerns about implementation. Recent innovations in cognitive remediation have focused on refining treatment techniques, broadening its application from schizophrenia to other severe mental illnesses, personalizing treatment, and increasing the likelihood of transfer to everyday functioning.

The Cognitive Remediation Expert Working Group defines cognitive remediation as a "behavioral training intervention targeting cognitive deficit (attention, memory, executive function, social cognition, or metacognition), using scientific principles of learning, with the ultimate goal of improving functional outcomes. Its effectiveness is enhanced when provided in a context (formal or informal) that provides support and opportunity for extending to everyday functioning".

There are several different approaches to cognitive remediation. Core features include using cognitive training techniques, typically computerized to enhance neuroplasticity; therapist-guided development and refinement of problem-solving strategies that can be used during cognitive training and in daily life; and facilitating the transfer of cognitive gains and new strategies to daily life.

Effect sizes have been reliably demonstrated to be medium for cognitive improvements[1]. When including therapists and a context for developing living skills (such as vocational rehabilitation or social skills training), effects on functioning are medium to large[1].

Allied approaches that are generally not considered cognitive remediation therapy are cognitive training (often using only independent computer-based training) and compensatory techniques that do not focus on enhancing cognition but instead modify the environment so that the persistent cognitive deficits produce less disability.

Although the evidence for cognitive remediation is clear, there are several factors within and across diagnoses that might help guide the continued development of this therapy. Transdiagnostic issues such as anhedonia, negative attributions about cognitive abilities, and reduced access to a cognitively enriching ecosystem, are likely to interfere with the efficacy and effectiveness of the therapy, yet are not often explicitly woven into treatment procedures.

These features also help us understand that cognitive remediation is not simply brain training delivered by a computer, but a therapy that will be most successful when therapists bring knowledge of neurocognitive dysfunction and skills from cognitive and behavioral treatment techniques.

Low motivation is a cardinal feature across severe mental illnesses and a robust predictor of engagement with psychotherapies[2]. Examination of recruitment and retention statistics in cognitive remediation studies reveals a pattern of difficulty with engagement that is similar to issues faced in other psychotherapies, with attrition rates as high as 50% and low adherence to homework. Addressing the effects of anhedonia will be critical to the successful implementation of cognitive remediation. Recent work has found that patient-determined scheduling[3] and motivational interviewing[4] can improve outcomes and engagement.

In addition to motivational issues, core negative beliefs about cognitive ability are likely to manifest within the cognitive remediation environment and may serve to suppress treatment effects. Those with severe mental illness tend to underestimate their cognitive and functional abilities, leading them to avoid cognitively challenging activities during treatment and in daily life. In the cognitive remediation treatment environment, a therapist is thus needed to play a key role in refocusing the patient on the goal of approaching cognitive challenges. Ongoing work is examining, in both experimental and treatment trial studies, the ideal techniques for addressing negative beliefs about cognitive abilities, attributions of how these abilities can be useful in daily life, and motivating patients to approach cognitive challenges.

The ultimate goal of having cognitive improvements transfer to daily life skills and outcomes is challenging for many people with mental illness who have lived for long periods of time in a cognitively understimulating ecosystem. This represents a measurement and treatment issue, since behavior change often lags behind more proximal treatment effects, and the patient's social, vocational and home environment might not present ideal opportunities for cognitive enrichment. It will thus be critical for cognitive remediation studies to measure change in functioning outcomes that is contextualized within the patient's environment and to continue to examine behavior change in the long term.

From a treatment perspective, future enhancements to cognitive remediation might examine how to bridge cognitive changes to daily life functioning. For patients with difficulties with memory and abstraction, it might be insufficient to rely only on discussion of how to bridge what is learned during treatment and recall it in a novel future environment.

Taken together, these findings point toward the potential of incorporating principles from more traditional cognitive-behavioral therapies into cognitive remediation. One such program, Action-Based Cognitive Remediation, uses goal setting, behavioral activation (with a focus on approaching cognitive challenges that the patient typically avoids), and role-plays to show how new cognitive strategies are used with real life tasks. Incorporating these techniques led to better retention and functioning outcomes[5].

In addition to adding to our treatment procedures, a critical area for more work in both research and clinical environments is to examine how supplemental, continued or intermittent treatment techniques affect the durability of effects. More than sustaining immediate effects, many recent cognitive remediation studies have reported a "sleeper effect", with larger improvements in everyday functioning in the months following treatment endpoint[5,6]. As is typical with clinical trials, however, these follow-up periods are relatively brief with respect to what we often view as lifelong issues with functioning in these disorders.

As the field continues to grow, with several treatment programs available, health care decision makers who wish to bring cognitive remediation to the clinic should be encouraged that, although this treatment requires training and staff time, the cost-benefit analysis is favorable. Studies of cognitive remediation have systematically reported on how this trade-off affects quality of life and financial burden associated with cognitive impairment, with evidence supporting higher rates of employment[7], reduced job stress[5], and lower institutional treatment demands[8,9].

The trade-off will be particularly important to examine as even brief, low-intensity cognitive remediation demonstrates positive effects on cognition and functioning[6], but most trials showing larger effects on functioning that are durable include a substantial role for therapists in a more treatment intensive environment[1,5].

The state of cognitive remediation has moved from "does it work" to "what works best for whom" across severe mental illnesses. Personalizing the treatment in everyday clinical use will continue to benefit from more experimental studies to explore the role of mechanisms mentioned herein as well as the analysis of larger datasets, including repositories of existing data and prospective multi-site projects, to examine mediating and moderating effects.

Uptake in clinical settings should be encouraged by the cost-benefit analysis of cognitive remediation, the only treatment in our armamentarium that reliably enhances the strongest predictor of functional disability – cognitive impairment.

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Targets and outcomes of psychotherapies for mental disorders: an overview

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It is not yet clear what mental disorders are and what are the causal pathways that lead to them. That makes it difficult to decide what the targets and outcomes of psychotherapies should be. In this paper, the main types of targets and outcomes of psychotherapies are described, and a brief overview is provided of some of the main results of research on these types. These include symptom reduction, personal targets and outcomes from the patient's perspective, improvement of quality of life, intermediate outcomes depending on the theoretical framework of the therapist, negative outcomes to be avoided, and economic outcomes. In line with the dominance of the DSM and ICD systems for diagnoses, most research has been focused on symptom reduction. This considerable body of research, with hundreds of randomized trials, has shown that for most mental disorders effective psychotherapies are available. There is also research showing that psychotherapies can result in improvement of quality of life in most mental disorders. However, relatively little research is available on patient-defined outcomes, intermediate outcomes, negative outcomes and economic outcomes. Patients, relatives, therapists, employers, health care providers and society at large each have their own perspectives on targets and outcomes of psychotherapies. The perspective of patients should have more priority in research, and a standardization of outcome measures across trials is much needed.

Key words: Psychotherapies, outcomes, targets, symptom reduction, quality of life, patient-defined outcomes, intermediate outcomes, cognitive behavior therapy

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Mental disorders are one of the most important public health challenges of this time[1,2]. With hundreds of millions people worldwide affected by them, these disorders are associated with severe personal suffering by patients and their relatives, considerable transgenerational transmission[3-5], huge economic costs[6], and increased levels of physical morbidity and mortality[7,8].

It is, however, still not clear what these disorders exactly are. There are no objective tests or measures to establish the presence of a mental disorder, nor are there clear thresholds for when a patient has a disorder and when not. The dominant systems for classifying and defining mental disorders in the past decades have been the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD). Although most research on mental disorders in the past decades has been using the different versions of these systems, they have been widely criticized.

For example, there is evidence that most mental disorders should not be considered as separate entities but rather as consisting of dimensions, on which some people score high and others score low[9-11]. Furthermore, high levels of comorbidity are more the rule than the exception[12]. Some argue that the diagnostic categories in the DSM and ICD have limited validity[13]. Treatments are also typically not effective in just one disorder, but across several different disorders, such as pharmacotherapies in mood and anxiety disorders, and cognitive behavior therapy (CBT) in most mental disorders[12].

So, if we do not yet really know what these disorders are and how they should be defined, what should be the targets of treatments and how can we measure their outcomes? The overall goal of treatments obviously is to make patients better or to help them cope with the problems they have. What this exactly means, however, and when it can be considered as accomplished, is not so clear. Not only because the nature and causes of the disorders are unclear, but also because it depends on whether one asks the patient, the clinician, patient's relatives, health insurance companies, or society at large to answer this question.

The focus of this paper is on the targets and outcomes of psychotherapies. We define the targets of a therapy as what should be tried to accomplish during the process. Outcomes are the results of a therapy. Because targets and outcomes are very much intertwined, we will consider them together in the discussion below, and often use the term "outcome" while we mean the broader concept that also includes targets.

We distinguish different types of outcomes: symptom reduction, which is the focus of most outcome research in psychotherapy; patient-defined outcomes; quality of life improvement; intermediate outcomes based on the theoretical framework and assumptions of the therapist; negative outcomes to be avoided; and economic outcomes. A summary of the types of outcomes, the research available on these outcomes, the results obtained, and the overall status of research is presented in Table 1.

SYMPTOM REDUCTION AS OUTCOME OF PSYCHOTHERAPIES

Symptom reduction can be seen as the core target and outcome of psychotherapies. Not only is symptom reduction by far the most common focus of outcome research, especially randomized trials, but qualitative studies also show that it is one of the most important outcomes from the viewpoint of patients (although certainly not the only one)[14]. Apart from researchers and patients, symptom reduction is

Table 1 Summary of the main targets and outcomes of psychotherapies for mental disorders

Type of target and outcome	Research	Results	Status of research
Symptom reduction	Examined in hundreds of randomized trials for many types of psychotherapy for all major mental disorders	Effective therapies exist for most mental disorders in the short term Effects are probably overestimated because of publication bias, low trial quality, lack of blinding Wide variety in measures	Most research on the effects of psychotherapy is focused on symptom reduction
Patient-defined targets and outcomes	Idiographic measures of the main problems as experienced by patients, such as the Target Complaints, the Simplified Personal Questionnaire, and the Youth Top Problems	These measures are mostly used in routine care	Limited systematic research available
	Qualitative research on the personal targets and outcomes of psychotherapies	Helpful impact of therapies: awareness, insight, self-understanding, behavioral change, solution of problems, empowerment, relief, better understanding of feelings	Limited systematic research available
Quality of life and related targets and outcomes	Studied as a (secondary) outcome in randomized trials	Significant effects of therapies on quality of life have been found for depression, eating disorders and anxiety disorders, but not schizophrenia	Relatively well-studied, but more research is clearly needed
Intermediate outcomes: mediators and working mechanisms	Each school of psychotherapy has its own theoretical framework to explain how therapy works	Mediators and working mechanisms have not been well established for any therapy, because of methodological problems	Limited systematic research available
Negative outcomes	Have become the focus of research only recently	Preliminary research suggests that deterioration in psychotherapies is lower than in control conditions Several types of negative effects have not been examined systematically Individual patient data meta-analyses are a promising approach	Limited systematic research available
Economic outcomes	Studies include cost-utility and cost-effectiveness analyses	For most mental disorders no more than one or two studies of psychotherapies are available Some more studies are available for cognitive behavior therapy in depression	Limited systematic research available

also a core outcome for other stakeholders, including therapists, although this depends on the model they adhere to.

The hundreds of randomized trials that have examined the effects of psychotherapies for mental disorders have mostly focused on symptom reduction as the primary outcome. In Table 2, the results are presented of some recent meta-analyses of psychotherapies (mostly CBT) compared to control conditions for the most important mental disorders. For each disorder, three of the largest meta-analyses published in the past five years are presented, and the type of intervention, the format of the intervention (individual, group, guided or unguided self-help), and the type of control group are summarized. We also report the number of studies included in each meta-analysis, the effect size (standardized mean difference), the level of heterogeneity in percentages (I^2), and whether it was a conventional or a network meta-analysis.

The effect sizes for depression, anxiety disorders (social anxiety disorder, panic disorder, generalized anxiety disorder), post-traumatic stress disorder and obsessive-compulsive disorder are moderate to large, with most effect sizes between 0.5 and 1.5. Effect sizes for psychotic and bipolar disorders are somewhat smaller, but that may also be related to the fact that control conditions typically consist of care-as-usual, which in these disorders means that most patients received intensive pharmacological treatment.

These findings clearly support the assumption that (at least some) psychotherapies have significant effects on most mental disorders when reduction of symptoms is taken as the primary outcome. However, these findings have been criticized as being too optimistic, because of publication bias[33-35], low quality and validity of many trials[15,36], and problems such as "researcher allegiance"[37], i.e. "the belief in superiority of an intervention and the superior validity of the theory of change that is associated with the treatment"[38]. Most research was also aimed at the short term, and longer-term effects are largely unknown. Furthermore, there are indications that one type of control condition, i.e. waiting list, may overestimate the effect of a therapy[39,40].

One major problem in examining the effects of psychotherapies on symptoms is that the instruments measuring change vary widely. For example, we identified

Table 2 Meta-analyses of randomized trials examining the effects of psychotherapies compared to control conditions

	Intervention	Format	Comparator	N studies	SMD	95% CI	I^2	Type
Depression								
Cuijpers et al[15]	Any therapy	Individual/group/ guided self-help	Any control	369	0.70	0.64-0.75	76	CMA
Mohr et al[16]	Any therapy	Individual/group/ guided self-help	Any control	188	0.54	0.45-0.64	82	CMA
Cuijpers et al[17]	CBT	Individual/group/ guided self-help	Any control	94	0.71	0.62-0.79	57	CMA
Social anxiety disorder								
Cuijpers et al[18]	CBT	Individual/group/ guided self-help	Waiting list, care-as-usual, pill placebo	48	0.88	0.74-1.03	64	CMA
Mayo-Wilson et al[19]	CBT	Group	Waiting list	28	0.92	0.51-1.33	NA	NMA
Barkowski et al[20]	CBT	Group	Waiting list	25	0.84	0.72-0.97	0	CMA
Panic disorder								
Cuijpers et al[18]	CBT	Individual/group/ guided self-help	Waiting list, care-as-usual, pill placebo	42	0.81	0.59-1.04	77	CMA
Pompoli et al[21]	CBT	Individual/group	Waiting list	17	1.14	0.87-1.41	61	NMA
Mayo-Wilson & Montgomery[22]	CBT	Guided/unguided self-help	No treatment	21	0.62	0.45-0.79	23	CMA
Generalized anxiety disorder								
Cuijpers et al[23]	Any therapy	Individual/group/ guided self-help	Any inactive control	38	0.84	0.71-0.97	33	CMA
Cuijpers et al[18]	CBT	Individual/group/ guided self-help	Waiting list, care-as-usual, pill placebo	31	0.80	0.67-0.93	33	CMA
Mayo-Wilson & Montgomery[22]	CBT	Guided/unguided self-help	No treatment	10	0.95	0.44-1.45	88	CMA
Post-traumatic stress disorder								
Bisson et al[24]	TF-CBT/Exposure	Individual	Waiting list, care-as-usual	28	1.62	1.21-2.03	89	CMA
Bisson et al[24]	TF-CBT/Exposure	Group	Waiting list, care-as-usual	16	1.20	0.69-1.70	71	CMA
Gerger et al[25]	CBT	Individual	Waiting list	16	1.10	0.85-1.36	NA	NMA
Obsessive-compulsive disorder								
Olatunji et al[26]	CBT	Individual/group	Waiting list, pill or psychological placebo	16	1.39	1.04-1.74	NA	CMA
Ost et al[27]	CBT	Individual/group	Waiting list	15	1.31	1.08-1.55	37	CMA
Ost et al[27]	CBT	Individual/group	Pill or psychological placebo	8	1.33	0.91-1.76	72	CMA
Psychotic disorders								
Velthorst et al[28]	CBT	Individual/group	Any control	28	0.09	–0.03 to 0.21	63	CMA
Burns et al[29]	CBT	Individual	Any control	12	0.52	0.35-0.70	0	CMA
Eichner & Berna[30]	Metacognitive training	Individual/group	Any control	11	0.34	0.15-0.53	3	CMA
Bipolar disorder								
Chatterton et al[31]	Psychoeducation + CBT	Individual/group	Care-as-usual	16	0.58	–1.25 to 2.41	NA	NMA
Chatterton et al[31]	Psychoeducation	Individual/group	Care-as-usual	12	0.14	–1.01 to 1.30	NA	NMA
Chiang et al[32]	CBT	Individual/group	Any control	13	0.49	0.03-0.96	90	CMA

CBT – cognitive behavior therapy, TF – trauma focused, SMD – standardized mean difference, CMA – conventional meta-analysis, NMA – network meta-analysis, NA – not available

310 randomized trials comparing psychotherapies with a control condition in people with depression[15]. Although the Beck Depression Inventory (BDI)[41] and the Hamilton Rating Scale for Depression (HAMD)[42] were the most used instruments, there were more than thirty other instruments measuring the impact of psychotherapies on depressive symptoms. As a comparison, in a recent meta-analysis of more than 500 randomized trials of pharmacotherapy for depression, 89% used the HAMD as the primary outcome measure[43].

Actually, the variety of instruments measuring an outcome was one of the main reasons why meta-analyses were introduced[44]. In a meta-analysis, the effect measured with one instrument is standardized into an "effect size", in order to pool it with the effects using other instruments. If all studies used the same outcome measure, this standardization would not be needed, because it would be possible to simply calculate the benefit of an intervention in terms of exact points on that measure.

Another issue is whether symptoms should be measured through self-report or clinician-rated instruments. It could be assumed that clinician-rated instruments provide a better estimate of the effects of an intervention, because they are applied by an independent observer (especially if the interviewer is blinded to the treatment condition). On the other hand, symptoms are experienced by patients, so one can also argue that patients themselves are the best raters of their problems. Furthermore, there are indications that outcomes rated by patients are more conservative than those rated by clinicians. We found in a meta-analysis that effect sizes of self-report measures were significantly smaller than clinician-rated measures from the same studies (differential effect size of g=0.20)[45].

There is no consensus about whether or not reduction of symptoms should be considered as the core outcome of psychotherapies. Therapists and researchers from the cognitive and behavioral tradition do support the notion that symptom change is the core outcome. However, therapists from the psychodynamic tradition consider personality and intrapsychic change as much more important[46], even if it cannot be measured very well. For them, symptoms are only the result of these personality and intrapsychic problems. They are assumed not to be the real core problem, and to improve when the personality and intrapsychic change is obtained. Therapists from the client-centered tradition would argue that self-actualization is the core outcome of therapy, and that symptoms are only one of the triggers for patients to find help.

In some cases, a worsening of symptoms can even be considered a positive outcome of therapy[46]. For example, it has been argued that the emergence of depression during existential psychotherapy could be a sign that the patient is being more in touch with reality, which in turn motivates urgency to reevaluate priorities[47].

The strong focus in research on the reduction of symptoms is in part related to the wide acceptance of the DSM and ICD, which have been dominating the field of mental health research in the past 50 years[48]. In recent years, however, the critique of these systems is strongly increasing. According to several authors[12,15,49], the progress in improving outcomes of treatments of mental disorders is not being satisfactory, and, in order to change that, new systems to understand mental disorders are needed.

One of the most important new projects that challenge the dominance of the DSM and ICD is the Research Domain Criteria (RDoC) initiative, launched by the US National Institute of Mental Health[50,51]. The RDoC is not based on the clinical descriptions of disorders, but considers these disorders from a translational point of view[12]. It starts with the fundamental, primary behavioral functions of the brain and the neural systems that are involved in the implementation of these functions. Examples are the circuits for fear and defense, for appetitive behavior such as learning to predict reward and moving toward reward, and for cognitive functions such as working memory[12]. The RDoC considers psychopathology as dysfunction in these systems. At this moment, it is too early to say whether this new approach will indeed result in new knowledge about if and how therapies work.

PATIENT-DEFINED TARGETS AND OUTCOMES OF PSYCHOTHERAPIES

A completely different type of targets and outcomes of psychotherapies are those that are defined by patients themselves. Patients typically do not only come to therapy to obtain relief from symptoms, but also to address other personal problems, which may include going back to work, solving intrapersonal issues, being a better parent, or stopping the fights with their partner or their boss. Addressing these problems of the patient can be regarded as one of the main goals of therapy[52,53].

Although these individual problems have not been examined as extensively as symptom reduction, there is a long tradition of research focusing on them, going back to the 1960s[54]. Several standardized measures have been developed to examine the targets and outcomes that are relevant from the perspective of the patient. In this context, the difference between nomothetic and idiographic outcome measures is relevant. Most outcome measures are nomothetic, which means that items of the measure are common to all people in varying degrees, and the measure is aimed at locating where a patient scores on that dimension[55]. Idiographic measures, on the other hand, rely on the unique features and views of the patient. For patient-defined targets and outcomes of therapies, idiographic measures are obviously more relevant.

The oldest of these approaches is probably the Target Complaints[54]. In this approach, the patient describes three target complaints in a clinical interview, and for each of these complaints both the therapist and the patient rate how significant the problem is. After the treatment, both the patient and the therapist are asked to indicate on a five-point scale how much each of these problems has improved.

Other patient-generated outcome measures include the Psychological Outcome

Profiles (PSYCHLOPS)[56], the Simplified Personal Questionnaire[57], and – in the field of child and adolescent mental health – the Youth Top Problems[58]. These instruments differ in terms of questions, possible answers and the point in time when they are rated. But the general idea is very much comparable with the Target Complaints, in the sense that the patient indicates which problems are important, to what extent he/she is affected by them, and the improvement during treatment. These measures differ from each other in terms of reliability and validity[55], but all have been found to be useful as a clinical tool.

The evaluation of these patient-defined targets and outcomes can be helpful in clinical practice in several ways[59], such as better specifying problems identified by standardized measures, focusing the attention of the therapist on these issues, and increasing patients' influence in the shaping of the agenda of therapy.

There is also some qualitative research examining the personal targets and outcomes of psychotherapies, although most of this research has been conducted in small and selective samples[46]. The studies included patients receiving different types of therapy, and do not point at clear, consistent types of targets and outcomes that can apply across patients. Much of this research suggests that what patients find important in therapy depends on what they need at that stage in their lives[59].

One study in a small group of patients used in-depth qualitative interviews[14], and found four categories of outcomes which were most important for patients: a) establishing new ways of relating to others; b) reduction in symptoms or change in patterns of behavior that used to bring suffering; c) better self-understanding and insight; and d) accepting and valuing oneself.

Another, more recent study was aimed at integrating the results of qualitative research on helpful impacts of psychotherapies[60,61]. Several categories of helpful impacts were identified, including awareness, insight and self-understanding, behavioral change and solution of problems, empowerment, relief, and better understanding of feelings.

QUALITY OF LIFE AND RELATED TARGETS AND OUTCOMES

There is a growing consensus that trials of psychotherapies and other treatments of mental disorders should not only focus on symptoms of disorders as targets and outcomes, but also consider the broader concept of quality of life[62]. What quality of life exactly means, however, is not so clear. It can be seen as a multidimensional construct encompassing physical, psychological and social dimensions of health[63]. It comprises a range of life domains, including social relationships, physical abilities, mental health functioning, role functioning and engagement in daily activities[64].

In most outcome studies of psychotherapies, quality of life is measured by self-report instruments. There is a considerable body of research on the effects of psychotherapies on self-reported quality of life for most mental disorders. The results of some of the most important meta-analyses are summarized in Table 3. Significant effects of psychotherapies on quality of life were found for depression, eating disorders and anxiety disorders, compared to control conditions. No significant effects were found for schizophrenia.

Quality of life also encompasses more concrete areas such as income level, employment and housing status. Many interventions are available for patients with mental disorders that are aimed, for example, at helping them to get employment, or supporting them with housing[69,70]. These interventions are, however, outside the scope of psychotherapy.

There is some research examining the effects of psychotherapies on broader areas of quality of life. For example, some meta-analyses found that psychotherapies for depression not only have a significant effect on depressive symptoms, but also on social support (g=0.38; 95% CI: 0.29-0.48)[71] and social functioning (g=0.46, 95% CI: 0.32-0.60)[72]. There are also indications from a small meta-analysis that psychotherapy for depressed mothers may result in improved parental functioning (g=0.67; 95% CI: 0.30-1.04), improved mother-child interactions (g=0.35; 95% CI: 0.17-0.52) and improved mental health of children (g=0.40; 95% CI: 0.22–0.59)[73]. In these meta-analyses, a strong association was usually found between the effects on psychopathology and on aspects of quality of life.

INTERMEDIATE OUTCOMES: MEDIATORS AND WORKING MECHANISMS

Although most research on psychotherapies has focused on symptoms of disorders as outcome, psychotherapists from

Table 3 Meta-analyses of randomized trials examining the effects of psychotherapies compared to control conditions on quality of life

Study	Disorder	Type of therapy	Comparator	N studies	SMD	95% CI	I^2
Linardon & Brennan[65]	Eating disorders	CBT	Any control	13	0.39	0.20-0.57	56
Laws et al[66]	Schizophrenia	CBT	Any control	10	0.04	–0.12 to 0.19	0
Hofmann et al[67]	Anxiety disorders	CBT	Any control	21	0.56	0.32-0.80	NA
Kolovos et al[64]	Depression	Any psychotherapy	Any control	31	0.33	0.24-0.42	21
Kamenov et al[68]	Depression	Psychotherapy	Pharmacotherapy	8	0.05	–0.19 to 0.29	NA
		Psychotherapy	Psychotherapy + pharmacotherapy	6	–0.36	–0.62 to –0.11	NA

CBT – cognitive behavior therapy, SMD – standardized mean difference, NA – not available

different schools have very diverse views on how these improvements are realized. Each type of therapy has its own theoretical model on how change is brought about in a patient. From a research perspective, CBT is dominating the field, with by far the majority of randomized trials focusing on this type of therapy.

CBT is focused on changing biases in thinking that are postulated to cause psychopathology, and CBT therapists assume that, when they succeed in changing these biases, the therapy is successful and the symptoms are taken away.

The evidence supporting the change in these biases as a mediator of CBT is, however, not very strong. Most research in this area has been conducted in depression. A meta-analysis of 26 randomized trials of CBT for depression found that dysfunctional thinking did indeed change as a result of that therapy[74]. However, it also changed with other therapies, that are not specifically aimed at dysfunctional thinking, and there was no clear difference between CBT and these other therapies. It is therefore possible that dysfunctional thinking can better be seen as a manifestation of depression, that improves when depression improves, and not as a mediator or core part of the working mechanism of CBT. As such, there is no evidence that changing biases in thinking should indeed be regarded as a target or outcome of an individual psychotherapy.

One important category of psychotherapies, the psychodynamic ones, assume that psychopathology is related to the quality of the person's early attachment relationships[75], and to significant childhood experiences that may have been accompanied by frustration, shame, loss, helplessness, loneliness, or guilt[76]. These experiences during developmental stages shape the personality and generate the vulnerability to psychopathology later in life. Symptoms of mental disorders are not seen as the core of the problem, but as a consequence of the broader personality problems. Therapies are therefore not aimed at symptoms but at solving the deeper intrapersonal problems. They are assumed to work via the reduction of unconscious conflicts[77].

There is some discussion about whether or not unconscious problems can be measured empirically[77,78]. Although there is no reason why they could not be examined as a mechanism of change of psychodynamic therapies, hardly any research on these mediators or mechanisms of change is available.

A third theoretical model for how psychotherapies work is the "common factors" one[53,79-81]. In this model, psychotherapies are assumed not to work through the specific techniques that are employed, but through factors that are common across all types of therapies. The relationship between patient and therapist is an important common factor, but also the hope and expectations that the problems will be solved (through the rationale given by the therapist on what the causes of the problems are and how they can be solved). So, according to this model, the development of an effective relationship with the patient is a necessary target of the therapy.

The main problem with intermediate targets and goals of psychotherapies is that randomized trials can show *that* a therapy works, but it is much more complicated to show *how* a therapy works[81-83]. Research on working mechanisms and mediators to date is always correlational: in order to establish that a mediator is indeed a causal factor in the recovery process, studies not only have to show that the outcome as well as the mediator improves, but also that these improvements are associated with each other. In addition to that, a temporal relationship has to be shown (change in the mediator comes before change in the outcome), a dose-response association has to be documented (stronger change in the mediator is associated with stronger change in the outcome), and evidence has to be provided that no third variable causes change in both the mediator and the outcome. And even if this is all demonstrated, supportive experimental research and a strong theoretical framework are needed to make a convincing case that a variable may indeed be a true mediator.

Currently, no (common or specific) factor meets these criteria and can thus be considered an empirically validated working mechanism. As Kazdin[83] argues, "after decades of psychotherapy research, we cannot provide an evidence-based explanation for how or why even our most well studied interventions produce change". This means that psychotherapies can have intermediate targets and outcomes, but there is no evidence that these targets and outcomes do indeed have an impact on mental health problems.

NEGATIVE OUTCOMES

"First do no harm" is an important injunction in all biomedical interventions[84]. Negative effects are a specific type of targets and outcomes, in the sense that they should be avoided instead of realized. Although the importance of negative effects of psychotherapies has been described for several decades[85,86], only recently this is emerging as one of the core issues to be prioritized in research[87-90]. At the moment, it can be said that there is a consensus in the field of psychotherapy research that negative effects should be better examined and that they have mostly been neglected in much of this research up to now[89,91].

It is not clear how negative outcomes of psychotherapies should be defined[91,92]. Important types of negative outcomes include an increased risk of deterioration during therapy[90] and serious adverse events[93]. However, there are many other types of negative outcomes that could be considered[94]. For example, non-response and drop-out can also be considered as negative outcomes.

There are several examples of so-called "fringe" or potentially harmful therapies, such as rebirthing, scared straight interventions, critical incidence stress debriefing, and recovered-memory techniques[87,95]. Such therapies are assumed to have overall negative effects, and should be avoided altogether. However, negative effects can also occur in evidence-based psychotherapies. Although the mean level of symptoms may improve with these therapies more than with control interventions, this does not mean that in some individuals the therapy cannot have negative effects.

Systematic research into negative effects of psychotherapies is mostly fairly recent. A conventional meta-analysis of controlled trials of psychotherapies for

depression found that only 6% of all trials reported deterioration rates[90]. The pooled risk ratio (RR) of deterioration in the 18 studies (23 comparisons) that did report these rates was 0.39 (95% CI: 0.27-0.57), meaning that patients in the psychotherapy groups had a 61% lower chance to deteriorate than patients in the control groups. Most studies defined deterioration according to the criteria proposed by Jacobson and Truax[96], which indicate that the patient's levels of psychopathology have become considerably worse and meet criteria for a severe disorder.

Individual patient data (IPD) meta-analyses are better suited to examine deterioration rates in psychotherapy trials. Randomized trials typically do not have sufficient statistical power to detect differences in deterioration rates between different conditions, because these rates are usually low. In IPD meta-analyses, the primary data from individual trials are collected and merged into one dataset. Because the resulting datasets are usually large, they have sufficient statistical power to examine relatively rare events, such as deterioration.

In one IPD meta-analysis, 16 trials with 1,700 depressed patients comparing CBT with antidepressant medication were included[97]. Five to 7% of patients showed any deterioration (an increased score on the HAMD or BDI of one point), 1% showed reliable deterioration (increase of more than 8 points on the HAMD, or more than 9 points on the BDI), and 4 to 5% showed extreme non-response (a post-treatment HAMD score of 21 or higher, or a BDI score of more than 31). No significant difference between CBT and antidepressant medication was found on any of these rates.

In two other IPD meta-analyses, deterioration rates in Internet-based guided self-help CBT for depression were examined. In one of them, data from 18 trials with 2,079 participants were included[98]. The rate of reliable deterioration was 3% in CBT and 8% in the control conditions (RR=0.47; 95% CI: 0.29-0.75). In the other meta-analysis, focusing on Internet-based CBT without any human support, 13 trials with 3,805 participants were included, and it was found that 6% in the CBT conditions deteriorated, compared to 9% in the control conditions (odds ratio, OR=0.62; 95% CI: 0.46-0.83)[99].

ECONOMIC OUTCOMES

In economic studies, the outcomes of therapies are often measured through cost-utility analyses (CUAs) or cost-effectiveness analyses (CEAs)[100].

For most mental disorders, no more than one or two CEAs or CUAs of psychotherapies are available. This is the case for bipolar disorder[101], obsessive-compulsive disorder[102], social anxiety disorder, panic disorder, post-traumatic stress disorder[100,103], and generalized anxiety disorder[100,104]. For depression, more studies are available[105]. However, most of these studies focus on CBT, while for other therapies there is hardly any research. Available evidence does suggest that CBT for depression is cost-effective compared to pharmacotherapy in the long term[105].

A growing number of CEAs and CUAs have focused on Internet-delivered interventions, with some evidence that they are more cost-effective as compared to waiting list, care-as-usual, group cognitive behavior therapy, attention control, or telephone counseling[106], although this is not confirmed in all studies[107].

DIFFERENT PERSPECTIVES FROM DIFFERENT STAKEHOLDERS

In this paper we described the main types of targets and outcomes of psychotherapies. But, what is the most important target or outcome? That depends very much on whom you ask this question. Most outcome research is focused on symptoms of a mental disorder. However, as we noticed, patients may not consider symptom reduction as the only or the most important outcome. Therapists also have their own perspectives on the targets and outcomes of therapies. They typically work in health systems where they are assumed to treat the mental disorder of the patient. So, one of their main targets is to reduce the symptoms of the disorder. But they also want to help the patient to solve his/her personal problems. Furthermore, they usually work within a theoretical framework, such as the cognitive-behavioral, the psychodynamic or the "common factor" model, each of which has important intermediate targets.

But there are further stakeholders. Health insurance companies also have their own views on what the targets and outcomes of therapies should be. They want the therapy to be effective, but to the lowest economic costs. Societies at large want therapies to help individual patients, but they also expect them to reduce the societal burden of mental disorders, in terms of economic costs, but also of problems caused in the public domain, for example by patients with an antisocial personality disorder. Relatives want the best outcomes for patients, but often also have their own targets and outcomes. Employers are particularly interested in getting patients with mental disorders back to work and as productive as they were before they developed the disorder.

So, the question of what is the most important target and outcome of a psychotherapy is very much dependent on the stakeholder considered. Currently, most research is focused on symptomatology of mental disorders, but it could easily be argued that patients should have a stronger voice in deciding what the most important outcomes are. Patients are the ones who suffer from mental disorders and, as long as we do not exactly know what these disorders are or what their causes may be, we should rely on the ones who suffer from them to decide what outcomes should have the priority.

CONCLUSIONS

It is not yet clear what mental disorders are and what are the causal pathways that lead to them. That makes it difficult to decide what the targets and outcomes of psychotherapies should be. In this paper, the different perspectives on this issue and the different types of outcomes were described.

The DSM and ICD systems have dominated the research field in the past decades and have led to a strong focus on core

symptoms of mental disorders as the main outcome of therapies. However, there is growing criticism of the DSM/ICD systems and, in line with this, the question is increasingly raised whether symptoms should be the core outcome of therapies. This paper highlighted that patients often have different perspectives concerning targets and outcomes of psychotherapies. Quality of life is one of the broader types of outcomes being examined in randomized trials. Therapists have other intermediate targets, and that depends heavily on the type of therapy they are implementing, while there is very little evidence that these intermediate goals are associated with outcomes. Economic outcomes are also important for patients, health care providers, and societies. Patients should ultimately have the strongest voice in deciding what targets and outcomes of psychotherapies should have priority.

It is also important that a consensus in the research field is achieved on what the core outcomes of randomized trials of psychotherapies should be. Because of this lack of consensus, many different outcomes and instruments are used across trials. Even if the instruments measure the same constructs, their heterogeneity may cause inconsistencies in reporting and difficulties in comparing and combining the findings in systematic reviews and meta-analyses[108-110]. Furthermore, the quality of outcome measures varies widely, and in many cases the most reliable and valid outcome measures are not selected[108]. Standardization of the selection of outcomes and their measures is therefore very much needed.

Several important types of outcomes have not been examined sufficiently in psychotherapy research, including outcomes from the patients' perspective, negative outcomes, mediators and intermediate targets and outcomes, as well as economic outcomes. It is important that more research is conducted on these outcomes.

The question of what the targets and outcomes of psychotherapies should be is not easy to answer and depends on which perspective one takes. Because of the huge burden of mental disorders, this is, however, an essential question, and answering it should be one of the priorities in the next decade.

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Reimagining outcomes requires reimagining mental health conditions

A striking observation in Cuijpers' review of the range of targets and outcomes for psychological therapies is the somewhat sobering statement that "it is still not clear what these [mental] disorders exactly are"[1].

Despite decades of research and billions of dollars spent, a major barrier to understanding the nature, and therefore treatment, of mental health conditions is the dominant approach to classification based on clinical phenotypes leading to binary categories. This approach, despite being the only pragmatic one devised to date, has "limited validity" and "although most research on mental disorders in the past decades has been using the different versions of these systems, they have been widely criticized"[1]. Thus, we are still unable to address the seemingly impossible-to-resolve question which has bedeviled psychiatry from its inception: what is a case?

The key reason for the limited validity of the binary classification approach is that "there is evidence that most mental disorders should not be considered as separate entities but rather as consisting of dimensions, on which some people score high and others score low"[1]. In short, binary models of mental disorder which classify people into "cases" and "non-cases" are not grounded in empirical observations. Indeed, the content of Cuijpers' paper could just as easily be applied to the full range of psychiatric therapies, including medications. The bottom line is that we need to develop a way of phenotyping mental health conditions using approaches which reflect their true pattern and distribution in the population.

The Lancet Commission on Global Mental Health and Sustainable Development[2] has endorsed the staging approach to bridge dimensional and binary frameworks to describing mental health conditions. Rather than being static, discrete and stable (implying distinct aetiologies and therapies), these conditions are syndromes which overlap and develop in stages. Our future classifications may well reduce the myriad diagnoses to a parsimonious number of dimensions, each of which might be mapped onto a specific brain network or circuit[3]. People experiencing mental health problems may then be characterized along these dimensions.

Implicit in the staging approach is the notion of a continuum from the complete absence of psychopathology to states where phenomena are mild and often undifferentiated, to states where clusters of phenomena begin to emerge, to an "end-stage" when they become severe and chronic. Across this continuum, there is a high degree of correlation with social functioning, with psychopathology and social functioning interacting in bi-directional pathways across the spectrum of severity.

Relatedly, a basic question is how "deep" should our phenotyping go beyond reported phenomena such as specific symptoms, to cognitive phenotypes such as impulsivity or attentional deficits, or what are the valid clusters of phenomena, and to what extent should these also capture social and somatic phenomena. The alignment of the staging approach with other frameworks, in particular Research Domain Criteria and network theories, is necessary to address these complex questions. As Cuijpers points out, these frameworks emphasize dysfunction of neural circuits as the mechanism for specific domains of psychopathology which can offer novel targets for interventions.

This approach is particularly suited to psychotherapies, as these can be calibrated according to the severity of the symptoms and social impairment[4]. From a clinical and public health perspective, the staging approach points to the opportunity to shift the care of those with mild, early-stage, problems to low-intensity interventions, such as digitally delivered guided self-care and community health worker delivered psychological and social interventions[5]. This is not only an efficient way to reserve expensive mental health specialist services for those individuals who are at the more severe end of the continuum, but it is simultaneously also more empowering to the large proportion of individuals with milder conditions who can recover and stay well without the need for a diagnosis through interventions which may be accessed via diverse affordable delivery platforms.

The dimensional approach also offers a mechanistic foundation for the growing body of evidence in support of single element psychotherapeutic interventions, for example behavioural activation for depressive symptoms or exposure for anxiety symptoms. These may be conceptualized as targeting the specific brain networks or circuits which are associated with these experiences (and which, as our ability to map and image the connectome improves, may offer novel targets for interventions). While some of these elements may themselves be transdiagnostic, reflecting how diverse brain regions influence one another through networks, multiple elements could be clubbed together into a single transdiagnostic protocol which can be tailored to target specific psychopathologies across a diverse range of mental health conditions.

What, then, might be the most appropriate outcome? Cuijpers argues: "if we do not yet really know what these disorders are and how they should be defined, what should be the targets of treatments and how can we measure their outcomes?"[1]. Indeed! While I completely agree that there need not be one outcome which is prioritized by all stakeholders, I believe that the distress experienced by the person receiving the mental health intervention must take precedence.

If that is the case, what then should this look like? Dimensional measures of general psychopathology which were once widely used (e.g., the General Health Questionnaire or the Self-Reporting Questionnaire) might return into vogue. Domain specific dimensional measures, such as the Patient Health Questionnaire - 9 (PHQ-9) for depressive symptoms, are already the most frequently reported outcomes. In essence, we do not need to define our "target" group on the basis of their baseline

"diagnosis" relying on current classification systems.

We still need to figure out what constitutes a meaningful change in scores and we might have to stick with relatively arbitrary clinical indices such as response (for example, the 50% reduction in scores often used in depression trials) which are also used for other dimensional health conditions (such as hypertension), or we could calibrate a meaningful change in scores against patient-defined global ratings to generate a "minimal clinically important difference"[6]. Outcomes may, in turn, vary across the severity dimension of the psychopathology; for example, the primary domain of concern may be symptom experience at one stage, but may shift to social functioning at another.

Another implication of adopting dimensional approaches is that new kinds of outcomes, amenable to remote monitoring, may become a reality, for example real-time passive assessment of digital behavioural markers. In this context, outcome assessments are not only useful as end-points to evaluate the effectiveness of psychotherapy, but also as dynamic decision points for guiding treatment choices which can allocate more intensive interventions as per patient trajectories, for example to distiguish early responders to low-intensity interventions from those who need more intensive treatments.

In short, reimagining outcomes and targets must require a reimagining of the nature of mental health conditions. We must invest in clinical research paradigms which adopt novel, dimensional, approaches to characterizing these conditions, offering new approaches to defining targets and outcomes. The current system which has been the foundation of psychiatric research, and which historically was envisioned to lead to an elucidation of etiology, mechanisms and therapeutics, has brought us to a dead-end.

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Therapeutic change processes link and clarify targets and outcomes

The dominance of the latent disease model of the DSM and ICD has led to an over-emphasis on symptom reduction as the primary target and outcome of psychotherapeutic interventions, as Cuijpers[1] points out.

Clients, employers, funders and the public at large did not demand the narrowing of focus that has accompanied psychiatric nosology. As Cuijpers[1] correctly notes, there are other targets and outcomes that might be far more important, such as improvement in quality of life or life functioning, or economic outcomes. To those we might add prosocial and physical health variables, such as reductions in interpersonal violence or lifestyle related physical diseases.

Cuijpers[1] concludes that the greatest weight should be given to patients when determining the priorities for the targets and outcomes of psychotherapies. We agree. But, if we are to consider a broader range of intervention outcomes, it will be all the more important to clarify how to move empirically from individual characteristics to individual goals by learning more about the "set of theory-based, dynamic, progressive, and multilevel changes that occur in predictable empirically established sequences oriented toward the desirable outcomes"[2]. In other words, we will need to understand therapeutic change processes and link them to effective intervention kernels.

The core question in modern intervention science is "What core biopsychosocial processes should be targeted with this client given this goal in this situation, and how can they most efficiently and effectively be changed?"[2]. In that context, we are concerned with Cuijpers' dismissal of processes of change and other theory-driven "intermediate outcomes". Without a process focus, broadening our outcome perspective could result in even more technological proliferation and confusion than we have now.

Based on studies of mediation, Cuijpers concludes that "there is no evidence" that it is helpful to target processes of change. We disagree. Mediation is only one approach, and the traditional approach to studying mediation is flawed in many ways. Processes of change are idiographic by their nature[3], and thus the statistical assumptions built into classical mediational analysis are universally violated.

Classical mediation focuses on a few processes, assumed to be related to outcomes linearly, unchanging across time, without any feedback loops or recursive processes. Such highly implausible assumptions form the basis of demands to prove that there have been no violations of temporality between mediators and outcomes, to show a dose-response effect, or to prove that no third variable can be involved. In some areas (e.g., third variables) there is no agreed upon way to meet these requirements, and in others (e.g., temporality) little can be recommended beyond guesswork.

Nevertheless, it is supposedly scientifically conservative to prohibit publication of mediational results unless these methodological requirements are met. The result is a domain of ignorance at the core of psychotherapy research that has been to some degree artificially produced. Psychotherapy is rarely – if ever – a paucivariate, linear, continuous and unidirectional event. Instead, psychotherapy typically changes many interconnected variables that form a dynamic system in a non-linear, bidirectional, dynamic and complex manner. This is best studied by adopting a dynamic systems and complex network approach[4]. Linear regression models of a few variables are simply inadequate.

Similarly, processes of change supposedly need to be treatment program specific. This idea emerges from a protocol focus – defending that a method engages unique processes of change – but it takes on a different hue when treatment is process-based[5,6]. If processes of change are central, why is it lethal if various technologies alter them? Treatment generality might in principle make change processes more important, not less.

Processes of change ultimately must be theory based and testable, but techniques under various banners and brand names may alter overlapping and broadly applicable processes of change. From the practitioners' point of view, so much the better. That fact empowers practitioners to broaden the range of methods they use in order to target an important change process.

Longitudinal evidence, basic research evidence, and component study evidence suggest that some processes of change are more important than others. For example, it would be strange if processes of change had no linkage to variation, selection, retention, and context sensitivity processes that are to be key to the evolution of complex systems in every other area of life[3].

Indeed, it is worth noting that some of the patient-supplied outcomes described by Cuijpers[1] – such as interpersonal effectiveness, social support, the capacity for problem solving, accepting and valuing oneself, awareness, or self-understanding – have been examined in other contexts under the rubric of processes of change. This suggests that patients themselves intuitively care about processes of change even when traditional intervention science has not focused effectively on them.

Departing from a nomothetic latent disease model and embracing the idiographic complexity of human suffering could free the field to pursue a more process-based approach. Focusing on therapeutic change processes should not be a side note but should take center-stage if we want clinical science to move forward.

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Moderation, mediation, and moderated mediation

P. Cuijpers[1] links a focus on symptom reduction in psychotherapy research to the omnipresence of diagnostic systems such as DSM and ICD that are based on symptom clusters. However, diagnostic systems come and go, usually in an upward spiral. I trained under DSM-II that was largely guided by dynamic theory. Symptoms represent a form of psychic distress or behavioral dysfunction that is worthy of change on its own merit, whether we lump them together under a unifying theory (DSM-II) or split them apart (DSM-III on).

The DSM-5 has at least made some effort to introduce the notion of dimensionality into the discussion, and the Research Domain Criteria (RDoC) project takes that a step further by focusing on the presumed underlying mechanisms that drive the various disorders, although perhaps from an overly reductionistic perspective, given that the vast majority of people suffer from diagnosable disorders with lower heritability than political preference. Kidneys do not learn, but brains evolved to interact with and be modified by the environment, and we ignore the influence of learning and culture at our peril.

I wholly endorse the call for broadening the targets of treatment. Patients often come to treatment looking for change in their capacity to function or their quality of life, and anything we can do to address those concerns is laudable. I remind my patients that "I work for you, you do not work for me" and I mean that literally. Nonetheless, we often work on multiple goals in treatment; not only was cognitive behavior therapy (CBT) as efficacious as antidepressant medication (ADM) in one of our earlier trials, but it also got more patients back to work[2]. CBT also cuts risk for relapse by more than half relative to ADM following treatment termination[3].

P. Cuijpers is in the vanguard of one of the most interesting developments in recent clinical science. What he has been doing is collecting individual patient data from controlled trials in the treatment of depression and using the aggregated data to test for moderation in samples that are exponentially larger than can be collected in any given trial. He has shown that severity does not moderate differential response to CBT versus ADM[4], despite the fact that ADMs separate from placebo only among patients who are more severe[5]. His individual patient data meta-analyses can inform the use of machine learning to generate treatment selection algorithms that identify the optimal treatment for a given patient[6]. This is the essence of precision medicine.

Nonspecific processes account for the lion's share of change in depression, and this is likely true to a lesser extent for most other nonpsychotic disorders. Cuijpers accurately points out that most of the supporting evidence is purely correlational in nature and thus a weak basis for drawing a causal inference, but he himself has provided some of the most compelling evidence for a causal role for such processes. What he did was to conduct a meta-analysis[7] in which he used within-group change in minimal treatment controls to establish the proportion of variance in change that could be attributed to spontaneous remission, and comparisons both within and between such controls to nonspecific and specific interventions to carve out the rest. He found that about one third of the change in depression was a consequence

of spontaneous remission, about half was due to nonspecific factors that would occur in any given treatment, and only about a sixth was due to the specific effects of presumably "active" treatments.

Because all of the studies that he included in his meta-analysis were randomized controlled trials, he could legitimately draw a causal inference with respect to the nonspecific factors. After decades of process research that sought to determine how treatments work, but could not answer the question as to whether they actually do work (have a causal effect), Cuijpers has provided a most compelling answer and a very clever roadmap for others to follow.

I do think, however, that it is premature for Cuijpers to conclude that there is no evidence that CBT works through cognitive change to produce change in depression. As he points out, the problem is that it is easier to detect an effect than it is to explain it, largely because we can use powerful experimental methods to test for causal effects of treatment on both the purported mediator and the outcome, but are left to rely on purely correlational methods to try to draw a causal inference regarding the link between mediator and outcome. That being said, I think he is wrong when he asserts that the absence of specificity denotes an absence of causal effect. If cognition did not change over the course of CBT then it could not be a mediator, but the fact that it shows comparable change in ADM does not rule such a causal process out.

The problem is that a given process can be both a cause and a consequence of change[8]. In an earlier trial we found that change in depression-relevant cognition predicted subsequent change in depressive symptoms with CBT but not with ADM, which likely worked through other causal mechanisms. The issue is one of moderated mediation in which the treatment affects the nature of the relation between the purported mechanisms and the outcome[9]. While CBT produces change in cognition that leads to (mediated) subsequent change in depression, ADM produces change in depression through other mechanisms that lead to subsequent change in cognition. Absolute change in cognition was comparable between the two treatment modalities, but the causal paths that led to that change were likely quite distinct.

Whereas moderated mediation as a consequence of differential treatment tends to obscure mediational effects that might be present, because it alters the apparent relation between the mediator and the outcome, moderated mediation as a function of individual differences among patients can be used to amplify that signal. As Kazdin[10] first pointed out, any instance of moderation suggests that different causal mechanisms may be at work in different patients. This means that tests of mediation can be made more precise (and therefore more powerful) if we include patient by treatment interactions in those analyses.

I agree with Cuijpers that mediation is difficult to detect, but a more sophisticated approach that takes moderated mediation into account may help to clarify the process.

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Building resilience through psychotherapy

In reviewing the main targets and outcomes of psychotherapy research, Cuijpers[1] notes emphasis upon symptom reduction, improvements in quality of life, and intermediate outcomes that depend upon theoretical framework. Critical unmet needs include little attention to patient-defined outcomes, negative outcomes (worsening of symptoms), and economic outcomes (cost-utility). Measuring symptom reduction over relatively short periods of time does not address illness course (incident episode, relapse and recurrence). Furthermore, little psychotherapy research has addressed outcomes grounded in an understanding of brain circuits and systems, or explored potential mechanisms of action through measurement of biomarkers. Cuijpers' emphasis on capturing and integrating different perspectives, from neurobiologists to payors, is critical to further advances in psychotherapy research and practice.

I would like to suggest that greater attention to the construct of resilience in psychotherapy research could be scientifically fruitful and clinically useful for addressing the unmet needs highlighted by Cuijpers.

What is meant by "resilience", and how can it be measured? Resilience is the ability to adapt, to thrive in the face of adversity, and to bounce back from life's challenges. One measurement widely used, the Connor-Davidson Resilience Scale (CD-RISC), has clinically relevant characteristics. For example, of specific relevance to unmet needs in psychotherapy research, Laird et al[2] recently reported an exploratory factor analysis of CD-RISC scores in depressed participants in clinical trials sponsored by the US National Institute of Mental Health at the University of California, Los Angeles. The authors found a four-factor solution, which they named "grit", "adaptive coping", "accommodative coping", and "spirituality".

Having a strong sense of purpose and not being easily discouraged were typical of items loading on "grit". Preference to take a lead in problem solving was charac-

teristic of "adaptive coping", while cognitive flexibility, cognitive reframing, a sense of humor, and acceptance in the face of uncontrollable stress loaded on "accommodative coping". Belief that "things happen for a reason" and that "sometimes fate or God can help me" characterized "spirituality". In a multivariate model, the greatest variance in total resilience scores was explained by less depression, less apathy, higher quality of life, non-White race, and – somewhat counterintuitively – greater medical comorbidity.

These data provide a rationale for a hypothesis that captures many of Cuijpers' under-investigated targets and outcomes: psychotherapeutic interventions designed to help patients build resilience (grit, active coping/problem-solving, accommodative coping, and spirituality) will prove effective in preventing and treating depression (and other common mental disorders). Behavioral activation may be a plausible mediator of depression prevention and treatment efficacy, because it is grounded conceptually in resilience and provides a patient-centered antidote to the antithesis of resilience – that is, learned helplessness.

What are the experimental data supporting the notion that interventions designed to enhance resilience effectively prevent and treat depression?

A meta-analysis from Cuijpers' group[3] estimated an incident rate reduction of 21% in the occurrence of major depressive episodes during 1-2 years, compared with care-as-usual or waitlist control, through the use of brief learning-based behavioral or depression-specific psychotherapies (such as cognitive behavioral therapy, interpersonal psychotherapy, and problem-solving therapy). The 38 randomized controlled trials (RCTs) in the meta-analysis were studies from high-income countries of either "indicated" depression prevention (enrolling participants with mild or subsyndromal symptoms), or "selective" depression prevention (enrolling participants with medical or neurological conditions such as stroke or age-dependent macular degeneration, placing them at risk for developing major depression).

Only one RCT of depression prevention has been conducted in a low- or middle-income country[4]. The "DIL" intervention (standing for "Depression in Later Life", and meaning "heart" in Hindi), delivered by lay counsellors to primary care patients in rural and urban Goa, India, was grounded in problem-solving therapy, but also included (as a result of extensive formative research to better capture patient-defined targets and outcomes) brief behavioral treatment for insomnia, education in better self-care for commonly comorbid medical disorders like diabetes, and assistance in accessing medical and social services. Over one year, we observed reduction in incident episodes of major depression in DIL compared to care-as-usual (4.4% vs. 14.4%; log rank p=0.04) and in the burden of depressive and anxiety symptoms (p<0.001).

Consistent with the hypothesis that building resilience may protect against, or reduce, depression, problem-solving psychotherapy teaches key facets, or tools, of resilience – active coping skills and enhanced engagement with life, combatting apathy and learned helplessness (the opposites of resilience). DIL participants reported engaging in pleasurable social and physical activities, a countermeasure to the paralyzing "tension" and worry that plagued their daily lives. They took a more active hand in managing their health, and came to feel less helpless and more in control of their lives. The DIL intervention built resilience in the form of active coping and behavioral activation, especially for dealing with health problems and their attendant threat of losing independence and degrading quality of life.

The efficacy of cognitive behavioral therapy and interpersonal psychotherapy both in preventing and treating depression[3] points to the importance of engaging in other resilience-building practices, such as accommodative coping (cognitive reframing and flexibility, humor), and social support. Common mental disorders like depression occur within an interpersonal context, and social connections support while loneliness destroys brain health. The Harvard Study of Adult Development[5] found that people who are well connected with family, friends and community are happier, physically more healthy, and live longer.

Social and interpersonal support fostered by psychotherapy nourishes the ability to adapt and to thrive in the face of adversity, while depression erodes adaptability. To this point, Jeste et al[6] showed that resilience counters the adverse effects of depression on self-rated health and successful aging. Further, regarding accommodative coping and spirituality, a psychotherapy for persistent impairing grief (rooted in both cognitive behavioral therapy and interpersonal psychotherapy) supports resilience and adaptation by strengthening both loss- and restoration-focused coping, and effectively resolves what ICD-11 now terms "prolonged grief disorder"[7].

It is time for neurobiology to inform psychotherapy development, targets, and outcomes[8]. Psychotherapy research needs data on biomarkers of risk and resilience to common mental disorders, such as major depression. Biomarkers may signal moderators of response, enabling the targeting of interventions to at-risk persons. They may also indicate mediators of response variability. Possible pathways through which psychotherapeutic interventions to enhance resilience might lower the risk for incident and recurrent episodes of depression include decreased inflammation, reduced oxidative stress, increased vascular and metabolic health, and increased neuroprotection. These represent fundamental hallmarks of aging at the molecular and cellular level, affected by depression, and expressed as senescence-associated secretory phenotypes[9].

Do psychotherapeutic interventions that enhance resilience affect these pathways and, thereby, reduce the risk for and burden of depression? Addressing the interplay between behavioral factors (resilience-promoting) and biological variables (associated with molecular signatures of brain and systemic health and with the reward and executive control circuits of the brain) may tell us how psychotherapies work. Attention to workforce issues and modes of delivery to streamline psychotherapy and to enhance scalability in the Research Domain Criteria era[8,9], with sensitivity to differing cultural milieus, may further serve to optimize cost-

utility.

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Toward a personalized approach to psychotherapy outcome and the study of therapeutic change

Cuijpers[1] highlights that, in spite of major progress in mental health research, there are still many important unanswered questions regarding psychotherapies. He emphasizes the significance of looking beyond symptomatic reduction and studying a range of treatment outcomes. He suggests (and we agree) that symptom reduction does not necessarily reflect many crucial and sustainable aspects of therapeutic change.

One of the reasons why change in symptoms is the most widely studied outcome is that researchers conducting randomized controlled trials (RCTs) are required to define their primary outcome *a priori*. Defining multiple primary outcomes results in an increase of the number of individuals to be included in a study to satisfy statistical power requirements. Thus, selecting a broader more representative range of outcomes becomes expensive, impractical and strategically problematic within the current major funding mechanisms. Additionally, reports of conflicting findings when similar research questions are examined using different measures make it difficult to determine which measures are to be prioritized conceptually and psychometrically.

It is indeed crucial to conceptualize and measure outcomes from the patient's perspective. Even patients who experience reductions in symptoms and meet remission criteria may still struggle in major domains such as navigating relationships, regulating emotions, maintaining consistent employment, and coping with stress. Other aspects of outcome, such as patients' capacity to cope with stressors and to use strategies learned in therapy in the face of adversity, should also be evaluated. Another understudied outcome is patients' gained subjective sense of freedom – one's ability to confront and resolve conflicting demands that arise from perceptions of the outer and inner worlds and make "choices" that are not determined by unconscious forces[2]. A patient-centered approach suggests that the treatment course should be guided by patients' specific needs, preferences, and perspectives on their own therapeutic change[3].

Many medical specialties are now shifting towards a "precision medicine" model – tailoring treatment to the individual patient. In psychotherapy, this model requires a comprehensive assessment of the individual patient's functioning across multiple domains in order to develop a personalized treatment plan[4]. Some progress has been made in the development of computerized algorithms, with preliminary evidence for efficacy of matching patients with the optimal treatment package[5]. However, implementing these algorithms requires the availability of skilled therapists who can deliver the selected "optimal" complex treatment modality. Treatment packages involve extensive clinical training and supervision, which limits their feasibility and applicability, especially for large populations of patients who reside in areas with limited access to experienced mental health professionals.

Thus, in addition to focusing on matching patients with treatment packages, researchers could focus on matching specific treatment components with specific patients' needs. One of the big unanswered questions is whether therapy should focus on the patients' strengths or remedy their deficits. For example, do patients who struggle with interpersonal relationships benefit more from treatments focusing on social and interpersonal skills? Similarly, will patients who struggle with avoidance or apathy benefit more from exposure to rewarding and meaningful activities? Alternatively, a personalized approach may focus on reinforcing existing strengths and resources[6]. For example, patients who are naturally aware of their thought processes may benefit from focusing on distorted cognitions (even if they do not receive a full manualized protocol of cognitive behavioural therapy). On the other hand, patients who have a strong social support system and connections with helpful significant others may benefit from behavioral activation focusing on social and interpersonal engagement. These are important research issues that have rarely been addressed.

One of the challenges in studying the benefits of particular treatment components (or mechanisms of change) is that researchers rarely include in their studies components that are not part of their declared treatment approach (although there are some exceptions[7]). This creates a gap between the relatively clean studies on treatment components associated with change and a clinical practice where most therapists flexibly integrate techniques from various approaches. Studies reflecting clinical practice could facilitate our understanding of which particular components of treatment are beneficial to patients with specific clinical presentations.

Another crucial challenge raised by Cuijpers is the high rates of non-response to treatment. Whereas meta-analyses provide valuable information regarding the

group-level rates of non-response, it is difficult to translate this information into meaningful clinical recommendations for individual patients. An important developing area of research is early detection of risk for non-response. Conventionally, non-response studies are conducted after the trial has closed and patients are no longer receiving treatment; i.e. treatment failure is studied retrospectively. We propose that efforts should be focused on detecting non-response or deterioration early on, after the first several sessions. Then, a stepwise treatment approach could be used in order to intervene (e.g., augment specific treatment components or shifting towards a different treatment focus)[4].

Data from RCTs are valuable as they provide opportunities to test various treatment components and outcomes over time within distinct controlled treatments. However, as funding for psychotherapy research rapidly declines in the US and around the world, researchers are faced with a significant crisis[8]. Some are shifting towards naturalistic studies through the development of practice research networks. Such networks are based on the premise that research thrives on true continuous communication between stakeholders and collaboration between clinicians in the community and researchers in academia. Studies developed are informed and guided by clinicians' observations and input, and findings are integrated in clinical settings[9]. These studies also promote greater diversity and representation of individuals from minority groups, who often do not have access to academic medical centers where RCTs are conducted. We anticipate that, in the future, more of our data will emerge from such studies.

Overall, future research should include combinations of rigorous methodologies and personalized approaches to psychotherapy. Studies should identify non-responders early on and develop protocols to address risk of non-response or deterioration before the trial ends. These studies should be done in collaboration between clinicians, researchers, policy makers and patients. Outcomes should include not only symptomatic changes but also a range of intermediate outcomes/mechanisms that may go beyond the researcher's theoretical orientation. Such collaboration can expand our understanding of the complex and nuanced aspects of "therapeutic change" and move us closer towards answering the question: "what makes psychotherapy work?".

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Putting the psychotherapy spotlight back on the self-reflecting actors who make it work

After decades of research, there is no general consensus on what the targets and outcomes of psychotherapy should be[1]. While this may seem a rather disappointing aftermath of much hard work, we should not despair. Psychotherapy research has come a long way and many effective therapies have been developed. The challenge now is to employ these therapies in such a way that the individual patients benefit from them optimally.

During the initial psychotherapy session, patient and therapist usually discuss the targets and outcomes of therapy and how they will go about achieving them. Subsequently, the patient is treated in accordance with the "treatment plan". For instance, in the case of depression, loss of interest and low mood are often formulated as the targets of therapy. This is not surprising, given the enormous success of academic psychology and psychiatry in presenting mental suffering and its treatment within the "specialist" diagnosis/evidence-based practice/symptom reduction/outcome monitoring model of mental health care[2]. As a result, treatments such as cognitive behaviour therapy are mostly oriented towards the specific target of symptom reduction.

Implicit in this approach is the assumption that the psychotherapeutic setting is a static environment, in which the problems present themselves as symptoms, and that a specific solution exists to remediate these: the theoretical protocol. The elephant in the psychotherapy room, however, is that the psychotherapeutic environment is infinitely more dynamic. Patient perspectives are likely to evolve over the course of therapy, along with the impact, burden, meaning and acceptance of symptoms, and the theoretical protocol almost by definition cannot accommodate all this. It cannot be predicted how the patient perspectives and wishes will dynamically and non-linearly evolve over time, but it seems unavoidable that they will. While the process of non-linear change is inherent to the practice of real-life psychotherapy, the theoretical framework underlying modern "evidence-based" psychotherapeutic approaches does not explicitly address this.

Routine process monitoring (RPM) may be required in psychotherapy to oversee the patient's satisfaction and desired direction, on a session by session basis[3], ideally combined with monitoring of contextual mental states in real life[4]. RPM

includes measures of daily functioning, patient's satisfaction and patient's and therapist's confidence in the therapeutic alliance. It is based on a process of collaborative self-reflection, and early results of the approach are promising[5]. Continuous patient feedback and collaborative self-reflection can prevent dropout and allow, when required, a speedy recovery of the therapeutic alliance.

The therapeutic alliance is the foundation on which patient and therapist can evaluate the psychotherapeutic process. It is crucial to establish a safe environment wherein the patient feels comfortable enough to disclose his/her own input on where the therapy is headed and should be headed, as well as his/her feelings about the therapist's influence on, and input in, the psychotherapeutic process. Simultaneously, the therapist should express his/her own views regarding the patient and the psychotherapeutic process. This practice of collaborative self-reflection is crucial in assisting the patient to reach his/her goals[5]. Indeed, evaluating the patient's dynamically evolving targets in each psychotherapeutic session has been shown effective in strengthening the therapeutic alliance and, in turn, in predicting self-reported symptom reduction[6].

The therapeutic alliance can be considered the basis of every mental health intervention. Extensive research shows that it is key in both psychotherapeutic and pharmacological approaches[7]. This is true for cognitive behavioural and interpersonal as well as for psychodynamic psychotherapies. Furthermore, the therapeutic alliance can interact with various elements of psychotherapeutic techniques, and this interaction can have a positive impact on outcome[8].

Measures of therapeutic relationship correlate more strongly with outcomes than specific technical ingredients of psychotherapy[9], and meta-analytic research shows that different techniques are equivalent in effect size for most mental disorders[2]. Furthermore, the *quality* of the therapeutic alliance may be the most robust predictor of outcome. Psychotherapy research should therefore re-evaluate its investment in technology and focus on developing ways to build stronger therapeutic alliances, and maintaining these over the course of therapy using RPM. While the body of research looking into alliance ruptures is steadily growing, there is little work on how to prevent such ruptures, which may effectively reduce patient dropout and facilitate the achievement of the desired outcomes.

There are now many psychotherapeutic interventions that for most disorders tend to show a similar efficacy at the group level. What we are currently faced with is the question of how the range of specific techniques can become effective agents of change, in the direction desired by the individual patients. A strong case can be made for an enhanced focus on the therapeutic alliance and on ways to use it to serve patient targets.

We will not know what the optimal targets and outcomes of psychotherapy are until we evaluate and re-evaluate them together, patient and therapist, in a process of collaborative self-reflection. By putting the lead actors back into the spotlight and empowering them with more focus and attention, we stand a good chance at achieving mutual goals.

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Outcomes help map out evidence in an uncertain terrain, but they are relative

It is a testament to P. Cuijpers' intellectual courage that he opens his paper[1] by stating that we do not really know what we mean by "mental disorder", and that we are not sure about what really constitutes a psychological treatment or underpins its effectiveness. He ends by pointing out that the outcomes of whatever we are treating with whatever means we have all depend upon the perspective we take, whether we are a patient, a clinician or anyone else. These are the uncertainties we are working with in psychotherapy, in mental health and, I suspect, in health more widely.

Although the goal of treatment is to make patients "better" (or to help them cope with their problems), precisely what "better" means, and when we can reliably claim we have achieved this, is definitely less clear. This is partly because the "nature and causes of [mental] disorders are unclear"[1]; and partly, I would add, because, like beauty, getting "better" is in the eye of the beholder.

Outcomes are very different when viewed by the patient, the clinician, the family, the public health doctor, the health insurance company, or the pharmaceutical company marketing department. While there may be overlap, there is unlikely to be full agreement. Indeed, there may be no overlap between the patient and the

pharmaceutical company marketing department, for example.

Most psychotherapy research has focused on symptom reduction as determined by clinicians. Moreover, most systematic reviews and meta-analyses of the majority of mental health interventions, and therefore guidelines, use reduction in symptoms or some similar clinician-measured variable (such as relapse reduction) as key outcomes. Cuijpers highlights the shortcomings of symptom reduction as an outcome deriving from the clinician's perspective rather than from that of the patient or family.

Nonetheless, it is important not to ignore how important symptoms are in the clinician-patient interaction. Symptoms are the clinician's interpretation and construction of the experiences that the patient describes to him. When the patient "gets better", from his perspective, the experiences that made him seek help have disappeared; from the clinician's perspective, the patient's symptoms have abated. Using the full set of experiences/symptoms relevant to the clinician and patient is not a bad way of understanding outcomes. In this context, "symptoms" are much broader than those defined in DSM and ICD[2].

It is, however, an entirely different matter when, in the reified world of network meta-analyses, a single symptom becomes the proxy outcome for the entire experience of the illness. This can lead to unexpected and possibly unreliable conclusions. For example, network meta-analyses of antidepressants suggest that they work for depressed people over 18 years[3] but not for people under 18 years[4]. For many reasons, it is likely that the "truth" is more complicated[5,6]. Reducing statistical evaluation to one or two outcomes may lead us to seeing a couple of trees and missing the wood entirely.

Nevertheless, in England, national mental health guidelines underpinned by the systematic review of outcomes, mainly based on symptom reduction, have highlighted the importance of psychological therapies within mental health. In recent years, the growth of services, such as early intervention in psychosis services and the Improving Access to Psychological Therapies (IAPT) programme (a primary care based treatment programme for common mental disorders), and of psychological treatments in children and young people's mental health services, has been based on the guidelines of the National Institute for Health and Care Excellence (NICE), which mainly use symptom reduction to demonstrate improved outcomes.

The use of symptoms-based outcome measures in routine clinical practice has become the cornerstone of the IAPT programme. Last year, IAPT services treated over a million people with common mental disorders. Although the use of symptom-based outcome measures has its flaws, having 95% paired outcome measures for a million or more patients per year makes this the most data-rich health programme in the world.

Being able to demonstrate effectiveness in routine practice has led to a further expansion of IAPT to also provide mental health care for people with long-term physical health problems, so that we can see 1.5 million people with common mental disorders per year, and new mental health services are now monitoring outcomes routinely.

In addition, economic outcomes are now of equivalent importance to clinical and patient-related outcomes. As Cuijpers alludes to, in the quality adjusted life years (QALYs), the economics of health care and quality of life are combined as a measure of cost utility/effectiveness. This approach, which tends towards the reification seen in network meta-analyses, has nevertheless allowed us to draw comparisons about the cost-benefit ratios between the treatment of depression using psychological approaches and the treatment of cancer with cytotoxic drugs and radiotherapy.

Cuijpers does not, however, deal with some further important outcomes. One fifth of people with anorexia nervosa die prematurely, an outcome which has led the National Health Service England to invest an extra £30 million per year into the treatment of eating disorders in children and young people (psychological treatments are the only proven treatments for these disorders). In addition, suicide, arguably the most devastating outcome for families in mental health, does not figure in Cuijpers' review. To the extent that death and suicide are outcomes of mental health problems, they are also possible outcomes of any mental health treatments.

Finally, it is worth spelling out how we can use outcomes in routine practice, not just to prove that patients are getting better, but also to add to the process of psychological therapies, at the level of the individual patients, the therapists, the teams and the organizations.

For the individual patients, outcome measurement provides a collectively agreed measure of "success" (recovery, improvement, less distress) for them to use. Outcome measures can give them a chance to recognize change and can instil a sense of hope. For the therapists, measuring outcomes allows them to compare their success rates to other therapists and to measure their own improvement over time, and can be an important guide in supervision.

Similarly, for the teams, outcome measurement can be used to benchmark their outcomes against others. It is a useful exercise for quality improvement and can help them recognize training needs and where to recruit in areas of weakness. At an organizational level, outcomes can underpin clinical and public health strategies and can be used to interrogate whether we are getting value for money.

All this applies to psychological treatments just as it applies to medical and other interventions. We need to choose the outcomes to suit the need.

In the end, the point of outcome measures in psychotherapy, or in any approach in mental health, and accounting for the different perspectives of the people involved, is that we can test out our theories about mental health, about psychotherapy and how each approach works, and our strategies for service delivery and change, and we can find out what the benefits are for particular groups of people.

Without measuring outcomes, we do not have evidence. And without evidence,

all we can do is jump to conclusions based on prejudice.

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Targets and outcomes of psychological interventions: implications for guidelines and policy

P. Cuijpers' review[1] on targets and outcomes of psychotherapies for mental disorders is pertinent to the World Health Organization (WHO)'s guidance on psychological interventions. The WHO adopted in 2007 a formal methodological approach to making guidelines. Since that time, it has produced a range of mental health guidelines, including those that cover psychological interventions[1-3].

As background, the WHO guidelines development process follows the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework[4]. The process starts with producing a protocol for guideline development that describes a proposed independent group of experts called the Guidelines Development Group (GDG). Group membership is only confirmed after declaration of interests are reviewed. Scoping questions – for example on the effectiveness of psychological interventions – are proposed to and reviewed by the GDG.

Questions are formulated using PICO format, where P stands for population, I for intervention, C for comparator, and O for outcome. Most PICO questions list multiple outcomes. Based on the scoping questions, systematic reviews are commissioned, except when a relevant recent review already exists. The evidence is synthesized – which typically involves meta-analysis – and then graded to communicate the certainty of the evidence, giving a transparent indication of how certain the reported effects likely are. Beyond evidence for the effectiveness of the interventions, there is systematic consideration for questions of balance of benefits versus harm, values and preferences, equity and human rights, acceptability, feasibility and resource implications. Informed by these considerations, the GDG then agrees on recommendations, which are subject to external review before finalization. The work is under the oversight of WHO's independent Guidelines Review Committee.

The above described process is not unique to WHO, and worldwide agencies and associations increasingly use similarly stringent and transparent processes of guidelines development involving answering PICO-formulated scoping questions, though WHO guidelines are likely unique in combining a global scope with independence from industry and other external pressures.

Cuijpers' review speaks to the outcome component of PICO questions in WHO guidelines. For example, in 2013, the WHO completed a guideline on the management of conditions specifically related to stress, which included the following scoping question with four outcomes: "For adults with post-traumatic stress disorder (P), do psychological interventions (I), when compared to treatment as usual, waiting list or no treatment (C), result in reduction of symptoms, improved functioning/quality of life, presence of disorder or adverse effects (O)?[3]. The GDG was asked to rank the listed outcomes according to importance using the GRADE levels (critical, important, not important). Both symptom reduction and improved functioning/quality of life were ranked as critical, while the other two outcomes were ranked as important.

In randomized controlled trials (RCTs), researchers target just one primary outcome, while, in start-of-the-art guidelines processes involving PICO scoping questions, there often are multiple critical outcomes. This makes the findings of Cuijpers' review pertinent to guidelines and policy development. Given that most trials in psychological interventions target symptoms as primary outcomes, it is not surprising that the vast majority of evidence is for that outcome. But what about other outcomes? Cuijpers' review shows that in psychological intervention research there is much less data on outcomes other than symptoms. He argues convincingly that there is specifically a need for more evidence on functioning and patient-defined outcomes, which in the context of psychological intervention research may be better referred to as *person-defined outcomes*.

Over the last ten years, the WHO has made at least ten recommendations on psychological interventions through its guidelines processes. For all these recommendations there was meta-analyzed evidence available on symptom reduction, but for none of these recommendations there was such evidence available on functioning. For functioning, the solution to this gap is straightforward: it would involve the routine adoption of functioning as an outcome in psychological intervention trials.

As crucially highlighted by Cuijpers, science will progress quickest if the same outcome measure is used across trials. Which outcome measure should that be for functioning? Ideally, a multidisciplinary group of stakeholders should propose what agreed scale should be consistently used to measure the functioning outcome across trials. I believe that they would propose the WHO Disability Assessment Schedule (WHODAS)[5] for this.

The WHODAS may be identified as routine outcome measure in psychological intervention outcome research among

adults, because it is the only measure of functioning that: a) has population norms and validation data across different countries; b) is well-understood both internationally and – through its inclusion in the DSM-5 – in the country that produces the most psychological treatment outcome data (i.e., the US); c) is already been used successfully in a range of major international studies[6-8]; d) provides data that can be easily analyzed for cost-effectiveness studies[6], including possible conversion into population-level outcomes such as quality adjusted life years (QALYs), which is important for policy making; and e) is used in research across different areas of health, making improvements in its scores interpretable by an audience beyond mental health experts.

Cuijpers also emphasizes the need to collect data on the perspectives of those who are meant to be helped by the intervention, the so-called patients, clients, service users, consumers, or people with lived experience. Though WHO guidelines take the perspectives of these and other key stakeholders into consideration, so far the WHO GDGs have not listed *person-defined outcomes* as outcomes in PICO questions, likely because of the absence of a strong research tradition to collect such data.

It is hoped that this may change in the future. Indeed, at the WHO we are promoting the use of person-defined outcomes through their routine inclusion in our own RCTs of psychological interventions among communities affected by adversity[8]. Again, the consistent use of the same outcome measure will be important. At the WHO we currently use the Psychological Outcome Profiles (PSYCHLOPS)[9] in many of our trials, and the experiences thus far are positive.

Showing effects on a person-defined outcome measure is helpful to convince skeptics of *etic* approaches[10], who in some countries may include local policy makers, that a suggested psychological intervention is locally meaningful.

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The author is a staff member of the WHO. He alone is responsible for the views expressed in this publication and they do not necessarily represent the decisions or policies of the WHO.

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The all-encompassing perspective of the mental health care patient

In his paper, Cuijpers[1] clearly describes the current state of the art of psychotherapeutic treatments for adults with a mental disorder. As he indicates, what the most important targets and outcomes are depends on whom you ask this question. Because of my personal experience of enduring severe depression, I tend to take the perspective of the patients when considering this issue.

When a depressive episode emerges, symptoms like rumination, indefinable anxiety and insomnia will manifest, and the patient's focus will be on feeling better and getting away from fatalistic thoughts. Obviously, patients want to spend energy on symptom reduction, because mental disorders are very disruptive.

In theory, I know that regaining mental well-being is not a goal in itself, since other life areas should receive some attention as well, such as the patient's family and relationships, occupation, social contacts and financial problems. Everything should be aimed at regaining a full-fledged and meaningful life. However, in ordinary practice, this integrated approach is hardly ever applied, despite the fact that, for example, stress about unemployment or financial issues can be extremely problematic and may very well interfere with the patient's recovery. It is also far from common to involve romantic partners, parents, or other loved ones in treatment, while they are often heavily burdened and very much in need of support and help to understand the situation.

In his paper, Cuijpers concludes that most research on the outcomes of psychotherapy focuses on symptom reduction. There is hardly any research on the preferred targets and outcomes that are defined by patients. Reference is made, however, to a study by Battle et al[2], in which they report on how patients and therapists each set specific targets for the outcome of treatment and afterwards evaluated the achievement of the targets they had set. This is, in my opinion, the core of psychotherapeutic treatments: setting goals together, defining outcomes, and regular evaluation of the goals and outcomes set.

In the Netherlands, Routine Outcome Measurement (ROM) is used to facilitate this. All patients in specialized mental health services are expected to fill in a questionnaire to assess their mental health problems and monitor their progress during treatment. There is an ongoing debate among clinicians about the usefulness of this system. Patients, however, often wish to implement this procedure, because it offers guidance in shared decision making and helps to structure the treatment. I myself, however, was never asked to fill in such a questionnaire before or during treatment, while I think my outcome could have benefitted from it. I think this indicates that Dutch mental

health care, and probably mental health care in many other parts of the world, can be improved considerably.

From a patient's perspective, it is daunting to read about the state of affairs with regard to the limited effect that psychotherapeutic treatment has on depression and other mental disorders. In addition, it is clear that the effects of antidepressants are also limited[3]. It is disheartening that the real causes of mental disorders are not yet well understood, and as a result the development of new medications has stagnated for years. Meanwhile, many patients continue to suffer from side effects of their medications. All this creates considerable confusion among patients: whom should they trust now? Are both psychotherapy and medications just not so good? Perhaps the individual attention by the therapist and the therapeutic relationship still yields some results, but apparently any improvement of the disease in the patient cannot be attributed to the therapeutic method itself. The current state of affairs in the treatment of mental disorders leads many patients to opt for interventions that have no demonstrable effect.

I am not a researcher, but as a patient I am interested in the developments in the field of treatment of mental disorders, and especially depression. Research evidently shows that a combination of two treatment methods (e.g., "drugs and talking") shows the greatest response and remission rates in depressed patients. This has been known for a long time, but still the effects are limited and it is necessary to develop new forms of combined treatment.

Cuijpers points out that progress towards improved outcomes is slow. And he thinks that new systems are needed to better understand mental illness. He refers to the US National Institute of Mental Health's Research Domain Criteria (RDoC) project. The points of reference there are the brain functions and the neural systems that are involved in behavioral functions (and dysfunctions). In line with this, I believe that many promising developments are to be expected in the area of neuropsychology. Personally I got involved in research on the effect of repetitive transcranial magnetic stimulation (rTMS). This treatment can be implemented in combination with psychotherapy. It could be an effective method in treating depression without side effects. rTMS is, in my opinion, a good example of a treatment that many patients are waiting for and that requires more research into its effects and potential to improve outcomes.

Overall, I agree with the conclusions drawn by Cuijpers. It does not appear to be easy to identify the best targets and outcomes of psychotherapy; the perspective you take to look at the issue matters quite a lot. As a patient I primarily care about symptom reduction. I think many patients will agree with me because we just want to get rid of those dark moods, sleep disorder, fears, suicidal thoughts, etc.. On the other hand, acting from an all-embracing perspective may eventually lead to a better quality of life. I have not, however, seen examples of such an approach. As patients we still have a lot to wish for.

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The effect of minority status and social context on the development of depression and anxiety: a longitudinal study of Puerto Rican descent youth

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Few longitudinal studies have explored to date whether minority status in disadvantaged neighborhoods conveys risk for negative mental health outcomes, and the mechanisms possibly leading to such risk. We investigated how minority status influences four developmental mental health outcomes in an ethnically homogeneous sample of Puerto Rican youth. We tested models of risk for major depressive disorder (MDD) and generalized anxiety disorder (GAD), depressive and anxiety symptoms (DAS), and psychological distress, as Puerto Rican youth (aged 5-13 years) transitioned to early adulthood (15-29 years) in two sites, one where they grew up as a majority (the island of Puerto Rico), and another where they were part of a minority group (South Bronx, New York). At baseline, a stratified sample of 2,491 Puerto Rican youth participated from the two sites. After baseline assessment (Wave 1), each youth participant and one caregiver were assessed annually for two years, for a total of three time points (Waves 1-3). From April 2013 to August 2017, participants were contacted for a Wave 4 interview, and a total of 2,004 young people aged 15 to 29 years participated in the assessment (response rate adjusted for eligibility = 82.8%). Using a quasi-experimental design, we assessed impacts of minority status on MDD, GAD, DAS and psychological distress. Via mediation analyses, we explored potential mechanisms underlying the observed relationships. Data from 1,863 Puerto Rican youth (after exclusion of those with MDD or GAD during Waves 1-3) indicated links between minority status and higher rates of lifetime and past-year GAD, DAS and past 30-day psychological distress at Wave 4, and a marginal trend for MDD, even after adjustments. Childhood social support and peer relationships partially explained the differences, as did intercultural conflict, neighborhood discrimination, and unfair treatment in young adulthood. The experience of growing up as a minority, as defined by context, seemingly elevates psychiatric risks, with differences in social relationships and increased social stress as mediators of this relationship. Our findings suggest that interventions at the neighborhood context rather than at the individual level might be important levers to reduce risks for the development of mood disorders in minority youth.

Key words: Minority status, social context, depression, anxiety, psychological distress, youth, social support, intercultural conflict, neighborhood discrimination, Boricua Youth Study

(World Psychiatry 2019;18:298–307)

Migration between regions, countries and continents has occurred at an unprecedented rate in the past century[1,2]. An important effect of migration processes is that ethnic minority groups are formed in regions that had previously been ethnically homogeneous. Sociologists, political scientists, economists, psychologists and health researchers have written extensively on the social, political, economic, psychological and health implications of being part of an ethnic minority group[3-5]. There is consensus that minority groups often endure discrimination and harassment, tend to be economically disadvantaged, and experience poorer health outcomes[6-10]. In addition, politicians and majority group leaders often propagate negative stereotypes of minority groups that increase maltreatment and dehumanization[11-13].

Any increase in risk for behavioral and mental disorders due to discrimination can become incorporated in the negative stereotypes of a minority group[14,15]. For example, persons who experience stress-related depression may miss work and be characterized as lazy. Stress-related anxiety may be manifested as irascibility or anger that is interpreted as threatening behavior[16]. Once established, these stereotypes create an essentialist explanation for why minority group members might not be thriving, allowing the majority to justify discrimination of those members.

The association between minority group status and mental health problems has been documented in epidemiological surveys[17-20]. For example, previous longitudinal studies have identified links between acculturative stress and both internalizing symptoms and reduced well-being among immigrant-origin youth[21,22]. However, these studies are limited in that they focus on heterogeneous race/ethnicity categories (i.e., Asian and/or Latino), include only school-based samples, do not measure outcomes in adulthood, and lack a majority-context comparison group. Further, the existing literature has often failed to identify the underlying mechanisms for observed relationships. These relationships are likely affected by selection effects (for example, in the case of immigrants, whether healthier individuals are more likely to migrate) or the links between minority status and other variables that may increase or decrease risk, such as poverty. To our knowledge, there are limited prospective studies that clarify the mechanisms behind the association between minority status and mental health risk.

In the present study, we examined whether and how being raised as an ethnic minority could convey differential risk for depression and anxiety as represented by four manifestations: a) presence or absence of major depressive disorder (MDD),

b) presence or absence of generalized anxiety disorder (GAD), c) counts of depressive and anxiety symptoms (DAS), and d) the severity of psychological distress. We focused on depression and anxiety because they are the most common mental disorders[23] and have been shown to be affected by stress[24,25].

We hypothesized that it is not being a member of a specific minority group *per se* (for example, being Latino), but the cognitive and affective experience of minority status[26,27] that could elevate the risk for psychiatric illness by impacting social interactions. Exposure to discrimination[4,28-30] and racism[31-34], and perception of low social position[35] are consequences of minority status that may lead to psychopathology. This is particularly true in the presence of cumulative exposure to violence (e.g., gangs, urban violence) and other stressors[27]. Elevated risks of mental disorders in the context of such negative experiences might stem from underlying physiological stress responses[36-38] and frequent uncertainty in social circumstances that create a sense of hypervigilance[39]. Minority status could transform one's social interactions and amplify stressors of social disadvantage[27,40-42] that negatively impact mental health[34,35].

By seeking to understand how growing up as part of a minority group can contribute to mental health disorders and symptoms, the present study fills existing research gaps in three respects. First, it represents one of the few longitudinal studies evaluating developmental trajectories of depression and anxiety in early adulthood in a homogeneous Latino subgroup (i.e., Puerto Ricans). Second, it includes two large population-based, rather than school-based, samples. Third, it compares the developmental trajectories of Puerto Rican youth in a minority context to those of Puerto Rican youth in a majority context.

Puerto Rico, a Caribbean island with 3.4 million inhabitants, has been a US territory since 1898, when it was transferred from Spain as war bounty[43]. Although Puerto Ricans obtained US citizenship in 1917, they primarily speak Spanish and do not enjoy all the rights and protections of the US Constitution[44] until they reside in the US[43]. Given high rates of poverty (43.5% of the island population is under the poverty level)[45,46] and lack of social mobility, emigration to the continental US has been common since the 1950s. New York City, and the South Bronx, became a common place of migration for Puerto Ricans in 1950s and 1960s, resulting in the largest population of Puerto Ricans outside of the island[47,48]. Since then, the South Bronx, like the island of Puerto Rico, has experienced high rates of poverty, unemployment, and exposure to violence. In 2010, the South Bronx was classified by the Census Bureau as the poorest district in the US, with 28.4% of the population living below the poverty line[49,50]. Forty percent of children in the Bronx were growing up in poverty in 2010[50], compared to 56.3% of children in Puerto Rico[51].

We studied Puerto Ricans for five main reasons. First, they are free to move between the island and the US mainland without immigration barriers, which minimizes the risk that this is a skewed subgroup of healthy migrants[52]. At the same time, they are treated like other Latino minorities when they migrate or are born in the mainland[2]. Second, our study design provides the opportunity to assess the effect of native and host environments on risk for a condition in a homogeneous ethnic subgroup[53]. For example, if the rate of a disorder in subsequent generations (i.e., in the South Bronx, where many youth are second generation or later) is elevated or lessened in the migrant group, this outcome would strongly suggest that environmental, socio-contextual and cultural factors interact with genetic vulnerability and are responsible for differences in disorder rates[54].

Third, each ethnic subgroup experiences migration and discrimination differently. The focus on one specific subgroup (Puerto Ricans) with a high risk of psychopathology[55] aims to avoid aggregating all Latinos and concealing important subgroup effects[56]. The fact that Puerto Ricans have the highest rates of mental disorders among Latino subgroups in the US[57], but low rates in the island of Puerto Rico[58], suggests that minority status might have a role in the risk for psychopathology. Fourth, in some studies, minority status is confounded with socio-economic status, while here both groups largely experience low status[59]. Fifth, since two-thirds of mental disorders develop between childhood and young adulthood[60], understanding this critical period can tell us about developmental psychopathology for youth growing up as members of minority groups, and help us identify mediators for these developmental pathways. Importantly, though we focus on Puerto Ricans in this study, key determinants and mechanisms of minority status risk could be similar for other minority groups.

To identify the mechanisms that could convey a causal effect of minority status on psychopathology risk, we relied on Garcia-Coll's integrative model in minority children[27], focusing on four classes of mechanisms: environmental and social context, cultural context and minority stress, parent and peer relations, and family/individual vulnerability factors. By "environmental and social context", we mean both the objective characteristics of a neighborhood which have been linked to depression and anxiety risk[61-70] and the subjective experience of living in a specific neighborhood. We also include the cultural context and the minority stress linked to youths' response to their neighborhood and its residents. Evidence suggests that experiences accompanying living as a minority group member in neighborhoods with low socio-economic status during childhood (for example, being perceived as dangerous by strangers) heighten physiological stress reactions and increase the likelihood for youth to perceive neutral interactions with others as hostile[71]. Our model also includes parent and peer social relations (e.g., support, parental warmth) and cultural factors that might impact social behaviors (e.g., intercultural conflict, ethnic identity) as potential mediators of the risk. We also examined social integration factors hypothesized to *protect* from the negative experiences of minority status by facilitating social integration, including positive youth-parent interaction[26], parental social support[72], and positive peer interaction[26,27]. The fourth set of factors posits that certain family/individual vulnerability factors, such as parental history of MDD and other mental disorders, in addition to early youth symptoms of depression and anxiety and exposure to adverse contexts, can exacerbate late

Table 1 Demographics and unadjusted and adjusted outcome differences between Puerto Rican (PR) and South Bronx (SB) youth (N=1,863)

	Total (N=1,863)	PR (N=1,015)	SB (N=848)	p
Wave 1 demographics				
Age				
5-9 years (%)	53.3	53.8	52.7	0.662
10+ years (%)	46.7	46.2	47.3	
Gender				
Male (%)	51.4	51.6	51.2	0.877
Female (%)	48.6	48.4	48.8	
Biological mother's age (years, mean)	34.4	34.7	34.1	0.166
Biological mother's education status				
Less than high school (%)	33.8	23.5	46.2	<0.001
High school diploma, vocational school, or more (%)	66.2	76.5	53.8	
Unadjusted prevalence rates at Wave 4				
Lifetime diagnosis of MDD (%)	13.8	11.8	16.2	0.017
Lifetime diagnosis of GAD (%)	4.1	2.6	5.9	<0.001
Diagnosis of MDD within last 12 months (%)	8.2	7.0	9.6	0.066
Diagnosis of GAD within last 12 months (%)	2.2	1.1	3.6	<0.001
Depressive and anxiety symptoms (mean)	4.8	4.1	5.7	0.002
K10 symptoms in last 30 days (mean)	15.0	14.2	15.9	<0.001
Adjusted prevalence rates at Wave 4				
Lifetime diagnosis of MDD (%)	13.9	11.9	16.2	0.059
Lifetime diagnosis of GAD (%)	4.0	2.4	5.9	<0.001
Diagnosis of MDD within last 12 months (%)	8.2	6.9	9.6	0.084
Diagnosis of GAD within last 12 months (%)	2.2	1.0	3.6	0.001
Depressive and anxiety symptoms (mean)	4.8	4.1	5.7	0.005
K10 symptoms in last 30 days (mean)	15.0	14.3	15.9	<0.001

The adjusted prevalence rates are based on propensity weighting estimates. MDD – major depressive disorder, GAD – generalized anxiety disorder, K-10 – Kessler-10 scale

adolescents' or young adults' risk of MDD and GAD, and psychological distress[37,38,73].

METHODS

Participants

We drew from the Boricua Youth Study, a longitudinal study with four waves of data from a random household sample of Puerto Rican participants (aged 5-13 years at Wave 1). The study was designed to be representative of the population of Puerto Rican youth in South Bronx (being raised as a minority) and in the San Juan Metropolitan Area of Puerto Rico (being raised as a majority), as defined by the US Census of the year 2000. Up to three children per household of Puerto Rican descent (i.e., having at least one primary caretaker who self-identified as Puerto Rican) were included[74-76], for a total of 2,491 participants (1,353 youth from Puerto Rico and 1,138 from South Bronx) at Wave 1.

After baseline assessment, each youth participant and one caregiver were re-assessed annually for two years, for a total of three time points (Waves 1-3; 2001-2004). From April 2013 to August 2017, participants were contacted for a Wave 4 interview, and a total of 2,004 young people aged 15 to 29 years participated in the assessment (response rate adjusted for eligibility = 82.8%).

Youth who were cognitively or neurologically impaired based on family report, deceased, or in prison during data collection were excluded from Wave 4 assessment (30 participants in South Bronx and 40 in Puerto Rico). The most common reason for exclusion was that the participant was deceased. Also excluded from analyses were participants with missing baseline data or a childhood diagnosis of MDD or GAD, as assessed during Waves 1-3 via the Diagnostic Interview Schedule for Children-IV (DISC-IV)[77] (N=68).

Table 2 Mediators of Wave 4 mental health outcomes suggested by a-path analyses (N=1,863)

Mediators	Differences between SB and PR, β (SE)
Baseline demographics	
Wave 1 parent-reported education: high school and above	–0.11 (0.03)***
Neighborhood context in childhood (area-level data)	
Proportion of female-headed households with child under 18	0.22 (0.01)***
Proportion of households moved within last 5 years	0.10 (0.01)***
Proportion of Latino residents	–0.33 (0.02)***
Murder rate of year 2002	–0.08 (0.02)***
Neighborhood context in childhood (participant-reported)	
Wave 3 parent report of neighborhood characteristics	4.59 (1.19)***
Wave 3 parent report of neighborhood monitoring	–1.71 (0.31)***
Wave 3 parent-reported parental monitoring	0.57 (0.15)***
Wave 3 youth report of exposure to violence	1.82 (0.24)***
Social context in childhood	
Wave 3 parent report of social support	–0.39 (0.04)***
Wave 3 youth report of social support	–0.17 (0.03)***
Wave 3 youth report of peer relationships	–0.59 (0.06)***
Cultural context and minority stress in childhood	
Wave 3 parent report of familism	–0.10 (0.04)**
Wave 3 parent-reported discrimination	0.55 (0.12)***
Wave 3 parent report of family cultural stress	0.63 (0.19)**
Wave 3 youth report of societal cultural stress	–0.93 (0.08)***
Wave 3 youth report of acculturation	1.88 (0.03)***
Cultural context and minority stress in young adulthood	
Wave 4 youth report of intercultural conflict	0.49 (0.11)***
Wave 4 youth report of neighborhood discrimination	4.38 (0.47)***
Wave 4 youth report of minority stress	2.35 (0.24)***
Wave 4 youth report of unfair treatment	0.49 (0.11)***
Wave 4 youth report of familism	–0.52 (0.24)*
Wave 4 youth report of ethnic identity	–1.15 (0.12)***

Only mediators significant at the p≤0.05 level are reported, SB – South Bronx, PR – Puerto Rico
*p<0.05, **p<0.01, ***p<0.001

Measures

Demographic data (i.e., participant age and gender, maternal age, parent education, family income) were collected via parent report at Wave 1.

Data from the 2000 Census and American Community Survey[78] were used to assess objective environmental context at Wave 3, i.e. to calculate, at the Census block group level, the proportion of individuals living below the poverty level, of female-headed households with a child under 18, of households having moved within the last five years, and of Latino residents. Precinct-level police crime data from 2002 were matched to Census block groups, and 2002 murder rates from each site were used as crime indicators. We used the murder rate as the only crime indicator for this study, as other indicators (e.g., rates of assault, burglary and rape) are subject to variations in reporting and definition between sites.

We characterized subjective environmental context at Wave 3 based on parent and youth report. We assessed four variables: parent-reported neighborhood characteristics, parent-reported assessment of neighborhood monitoring, youth-reported exposure to violence, and parent-reported parental monitoring. Neighborhood characteristics included the parent's perception of neighborhood problems such as vacant lots, crime and pollution. Neighborhood monitoring referred to the extent to which neighbors monitor and intervene in situations where there are safety concerns or problem behaviors that might impact children. Exposure to violence was a continuous measure derived from youth report of exposure to violent events (for each event, the participant was asked if he/she witnessed it directly, saw it happen to someone else or heard about it happening; a weighted sum, in which direct experience was given more weight, was used for the analyses). Parental monitoring referred to the extent to which the parent reported monitoring his/her own children (e.g., direct supervision and curfews).

We assessed cultural context at Wave 3 using two variables: youth-reported level of acculturation (e.g., language preference, ethnicity of close friends, ethnic pride), and parent-reported level of familism (cultural value placed on family cohesion and togetherness). We characterized minority stress at Wave 3 using a cultural stress module which assessed three variables: parent- and youth-reported discrimination in the neighborhood, parent-reported family cultural stress, and parent- and youth-reported societal cultural stress (e.g., having problems due to not speaking English well or to being Puerto Rican, feeling of not belonging in either Puerto Rico or the US).

We assessed youths' social context at Wave 3 using parent-reported maternal warmth/parent-child relationship quality, parent-reported level of social support, youth-reported level of social support, and youth-reported positive peer relationships.

We accounted for three additional psychological risk factors at Wave 3: parent-reported maternal depression (past-year diagnosis from parent report of symptoms), parent-reported overall parental psychopathology (depression, suicide attempts, and substance use), and youth-reported number of stressful life events (e.g., death of a loved one).

Several late adolescence/young adulthood cultural variables collected concurrently with outcome data at Wave 4 were also examined as potential mediators. These factors included two youth-reported measures of cultural context (familism, ethnic identity) and six youth-reported measures of stress (unfair

Table 3 Wave 3 mediators of the effect of minority status on Wave 4 mental health outcomes (N=1,863)

Outcome	Lifetime MDD	Past-year MDD	Lifetime GAD	Past-year GAD	DAS	K10
c (no mediator)	0.22	0.21	0.98***	1.28***	1.20*	1.39***
Wave 3 proportion of households moved within last five years						
Mediation effect	-	-	-	-	-	0.31 (0.03-0.63)
a	-	-	-	-	-	0.09***
b	-	-	-	-	-	3.45*
Wave 3 youth report of exposure to violence						
Mediation effect	-	-	-	-	-	0.14 (0.02-0.29)
a	-	-	-	-	-	1.63***
b	-	-	-	-	-	0.09*
Wave 3 youth-reported social support						
Mediation effect	-	0.08 (0.02-0.18)	-	-	0.18 (0.01-0.40)	-
a	-	–0.17***	-	-	–0.17***	-
b	-	–0.46*	-	-	–1.04*	-
Wave 3 youth-reported peer relationships						
Mediation effect	-	0.12 (0.01-0.26)	-	-	0.50 (0.17-0.83)	0.38 (0.20-0.58)
a	-	–0.59***	-	-	–0.59***	–0.59***
b	-	–0.18*	-	-	–0.74**	–0.64***

Unstandardized regression coefficients and 95% bias-corrected confidence intervals are reported. a – effect of the independent variable (minority status) on the mediator, b – effect of the mediator on the dependent variable when controlling for independent variable, c – effect of the independent variable on the dependent variable, MDD – major depressive disorder, GAD – generalized anxiety disorder, DAS – depressive and anxiety symptoms, K10 – Kessler-10 scale
*p<0.05, **p<0.01, ***p<0.001

treatment, cultural stress, intercultural conflict, minority stress, heightened vigilance, neighborhood discrimination).

As outcome variables at Wave 4, we examined lifetime and past-year diagnosis of MDD and GAD, lifetime DAS, and past 30-day psychological distress. MDD and GAD diagnoses were derived from the Composite International Diagnostic Interview (CIDI)[79]. Lifetime DAS was calculated as a composite score derived from questions included in the CIDI modules for depression and anxiety. Past 30-day psychological distress was measured by the K-10 symptom scale[80].

Statistical analyses

We assessed unadjusted prevalence rates for MDD, GAD, DAS and psychological distress in the South Bronx and Puerto Rican samples at Wave 4.

We then assessed adjusted differences in prevalence rates using rescaled Boricua Youth Study sampling weights, that were further adjusted using propensity score weights. The sampling weights accounted for the probability that households and individuals would be selected based on each site's sampling design; were post-stratified to represent the age and gender distribution of Puerto Rican youth in both sites at baseline using 2000 US Census data; and accommodated non-response and attrition rates at Wave 4. These sampling weights were then rescaled so that each sample was weighted proportionally to the nearly equal sample size at each site. The last adjustment used the predicted probability (or propensity score) of living in Puerto Rico or in the South Bronx using baseline youth age, gender, maternal age, and maternal education, to account for baseline differences. This approach mimics randomly assigning participants to live in one or the other location. To assess site differences, we regressed each outcome variable on site and baseline characteristics. We fit weighted linear models for continuous outcomes and logit models for binary outcomes and used heteroskedasticity-robust clustered standard errors to account for intra-neighborhood and intra-family correlation.

We evaluated potential pathways that could explain observed differences following Garcia Coll's integrative model[27]. As already mentioned, we focused on four potential mechanisms: environmental and social context (objective characteristics and

Table 4 Wave 4 mediators of the effect of minority status on Wave 4 mental health outcomes (N=1,863)

Outcome	Lifetime MDD	Past-year MDD	Lifetime GAD	Past-year GAD	DAS	K10
c (no mediator)	0.22	0.21	0.98***	1.28***	1.20*	1.39***
Wave 4 intercultural conflict						
Mediation effect	0.13 (0.07-0.22)	0.13 (0.06-0.24)	0.11 (0.04-0.25)	0.18 (0.06-0.39)	0.67 (0.37-1.06)	0.46 (0.26-0.72)
a	0.48***	0.48***	0.48***	0.48***	0.48***	0.48***
b	0.23***	0.21***	0.22***	0.29***	1.40***	0.96***
Wave 4 neighborhood discrimination						
Mediation effect	0.21 (0.11-0.32)	0.21 (0.09-0.34)	0.19 (0.05-0.34)	0.25 (0.06-0.45)	1.00 (0.63-1.42)	0.80 (0.55-1.07)
a	4.42***	4.42***	4.42***	4.42***	4.42***	4.42***
b	0.04***	0.04***	0.04**	0.04**	0.23***	0.18***
Wave 4 minority stress						
Mediation effect	0.11 (0.03-0.20)	0.16 (0.05-0.26)	-	0.17 (0.02-0.36)	0.49 (0.25-0.81)	0.61 (0.40-0.86)
a	1.26***	1.26***	-	1.26***	1.26***	1.26***
b	0.09*	0.13**	-	0.14*	0.38***	0.48***
Wave 4 ethnic identity						
Mediation effect	0.13 (0.02-0.24)	0.14 (0.02-0.26)	-	-	0.47 (0.09-0.84)	0.21 (0.01-0.43)
a	–1.23***	–1.23***	-	-	–1.23***	–1.23***
b	–0.10*	–0.11*	-	-	–0.38**	–0.17*
Wave 4 unfair treatment						
Mediation effect	-	-	-	-	0.47 (0.08-1.25)	0.27 (0.04-0.76)
a	-	-	-	-	0.42***	0.42***
b	-	-	-	-	1.10*	0.64*

Unstandardized regression coefficients and 95% bias-corrected confidence intervals are reported. a – effect of the independent variable (minority status) on the mediator, b – effect of the mediator on the dependent variable when controlling for independent variable, c – effect of the independent variable on the dependent variable, MDD – major depressive disorder, GAD – generalized anxiety disorder, DAS – depressive and anxiety symptoms, K10 – Kessler-10 scale
*p<0.05, **p<0.01, ***p<0.001

subjective experience of neighborhood), cultural context and minority stress factors (cultural stress, acculturation, experiences of discrimination), parent and peer social relationships (social support, parental warmth), and family/individual vulnerability factors (parental psychopathology, child exposure to adverse events)[37,38,73].

We used mediation analyses to investigate potential mechanisms underlying site differences, starting with a-path analysis (regressing each mediator on minority status) to narrow down possible mediators. We tested each candidate's mediated effect on each outcome and used the counterfactual framework approach[81,82] to estimate the remaining direct effect of minority status and the indirect/mediated effect. We bootstrapped the sample to account for stratification and resampling in the original study, and used non-imputed data to circumvent computational constraints imposed by simulation of both bootstrap and imputed samples. Further details on measures and analyses are available upon request.

RESULTS

In total, 2,004 youth participants (921 in South Bronx, 1,083 in Puerto Rico) and 1,180 caregivers (490 in South Bronx, 690 in Puerto Rico) completed Wave 4 interviews. Among eligible Wave 1 participants, 82.8% of young adults and 73.6% of caregivers participated. For this study, we removed 68 participants who met criteria for depression and/or anxiety disorders during Waves 1-3 and 73 participants with missing baseline information, resulting in a final sample of 1,863 youth.

As shown in Table 1, unadjusted rates of MDD, GAD, DAS and psychological distress were higher in South Bronx compared to Puerto Rican youth (five of six differences were statistically significant and one failed to reach statistical significance), despite MDD and GAD prevalence rates having been similar across sites during the first three waves (results available upon request). Risk ratios for anxiety and depressive disorders ranged from 3.3 (past-year GAD) to 1.4 (lifetime MDD). Table 1

shows that, across sites, participants were similar in baseline age, gender and mother's age, but differed in mother's education (lower in South Bronx youth).

After propensity score adjustments, results were largely similar, although lifetime MDD (p=0.059) and past-year MDD (p=0.084) failed to reach statistical significance. However, given a trend toward site differences in these outcomes, we still examined them in subsequent mediation analyses to avoid missing small effects[83].

To determine whether minority status explained increased depression and anxiety risk, we tested a series of mediation models[84], as described above. Table 2 shows the 23 variables that were significantly related to site, from 35 potential variables. South Bronx youth resided, during their late childhood and early adolescence, in neighborhoods associated with substantially more female-headed households and greater geographic mobility than their counterparts in Puerto Rico. Parents living in South Bronx reported poorer neighborhood characteristics and neighborhood monitoring, and engaged in higher parental monitoring. Consistent with parents' reports, youth in South Bronx reported experiencing more exposure to violence in their neighborhood. Regarding social context, both parents and youth living in South Bronx reported less social support. In addition, youth respondents in South Bronx reported having worse peer relationships. Parents living in South Bronx reported lower familism level, more discrimination and greater family cultural distress. In early adulthood, respondents recruited from South Bronx reported experiencing more intercultural conflicts, neighborhood discrimination, minority stress, and unfair treatment than those growing up in Puerto Rico. These respondents also reported having lower levels of familism and weaker ethnic identity as compared to their Puerto Rican counterparts.

Table 3 presents all significant Wave 3 mediators. The relationship between minority status and greater psychological distress reported at Wave 4 was partially mediated by greater residential mobility (mediation effect: 0.31, 95% CI: 0.03-0.63) and greater exposure to violence (mediation effect: 0.14, 95% CI: 0.02-0.29) in South Bronx. Less social support from family and friends among South Bronx youth mediated the relationship between minority status and both past-year MDD diagnosis and DAS at Wave 4. Finally, poor peer relationships at Wave 3 mediated the relationship between minority status and past-year MDD diagnosis, DAS and psychological distress reported at Wave 4.

We performed additional mediation analyses with data collected at Wave 4. As shown in Table 4, intercultural conflict (i.e., between Puerto Rican/Latino and American customs) mediated higher lifetime (mediation effect: 0.11, 95% CI: 0.04-0.25) and past-year GAD (mediation effect: 0.18, 95% CI: 0.06-0.39) among South Bronx respondents. In fact, greater intercultural conflict and youth-reported neighborhood discrimination helped explain differences between South Bronx and Puerto Rico youth for all Wave 4 outcome variables. Increased minority stress (perceiving neighbors' negative attitudes/treatment toward minorities), weaker ethnic identity, and more unfair treatment (perceiving neighbors' negative attitudes/treatment toward self) among South Bronx youth partially accounted for effects of minority status on some, but not all, of examined outcomes.

Lastly, we tested the joint effect of multiple Wave 4 mediators on the relationship between site and GAD, DAS and psychological distress. For lifetime GAD, 21% of the total site effect was mediated by the combined effect of intercultural conflict and neighborhood discrimination. For past-year GAD, 30% of the total site effect was mediated by the combined effect of intercultural conflict, minority stress, and neighborhood discrimination. For both lifetime and past-year GAD, neighborhood discrimination had the largest effect of all the mediators. For DAS and psychological distress, site differences disappeared after incorporating all five mediators, with neighborhood discrimination and intercultural conflict accounting for the greatest proportion of the mediated effect.

We also observed protective effects of growing up in South Bronx, suggesting that the effect of minority status on mental health outcomes could have otherwise been larger. For instance, youth-reported level of acculturation at Wave 3 protected against past-year major depressive disorder at Wave 4 ($b=-0.37$, $p<0.05$) and was positively correlated with minority status ($a=1.88$, $p<0.001$). The direct effect of minority status increased once we incorporated acculturation level as a mediator. Similar protective effects were observed for lower neighborhood murder rate and greater proportion of female-headed households in South Bronx youth. Further details on all analyses are available upon request.

DISCUSSION

To our knowledge, this is the only longitudinal study with four waves of data from an ethnically homogeneous sample of youth living in two contexts (one in which they are the majority and another in which they are a minority) that examines the potential impact of minority status and social context on the development of internalizing symptoms and disorders in early adulthood. It is also the first large longitudinal study that sought to better understand what leads to augmented psychiatric risks as minority youth transition from childhood to early adulthood.

We investigated not only if, but also how, experiences of minority status confer a risk for MDD, GAD, DAS and psychological distress. The study's importance lies in demonstrating that it is not individual risk, but rather the environmental and social context that plays a prominent role in the development of internalizing disorders. Results demonstrated that Puerto Rican youth growing up as minorities in South Bronx were more at risk for these challenges than similar youth growing up as part of the majority in Puerto Rico, even under similar conditions of poverty.

Findings are consistent with other work suggesting that social stress related to discrimination and low perceived social position may contribute to anxiety and depressive disorders and symptoms over time[85], moving the focus from individual youth

to the social context as a meaningful lever for intervention. As children confront a negative social mirror within the context of their minority status, with worse peer experiences and less social support, they become more at risk for internalizing disorders.

These findings might have implications for immigrant youth in their host environment and highlight the importance of positive social relations to ensure that youth flourish, even under conditions of poverty. Experiences of "othering" rather than integrating those whose culture, physical characteristics, language or accent may be different, or whose affiliation is linked to reduced political, economic or social power is to our societal detriment and might convey greater risk for future illness.

Our findings highlight the importance of childhood social relationships and supports, as these factors partly explain poorer outcomes linked to minority status. Consistent with previous research, peer rejection appears to contribute to internalizing symptoms, whereas positive family support may protect against this outcome[86,87]. Youth from minority backgrounds may face contexts in which it is unclear who they can trust; thus, they become more likely to judge social situations as threatening and react accordingly, diminishing their opportunities for positive peer relationships[88]. Despite observed benefits of cultural dynamics on Latino youth mental health, cultural resources may not always be adequate to protect against psychological effects of peer-based discrimination[89]. Poorer peer relationships reported in South Bronx may also reflect a lack of available social networks or increased isolation because of community violence[90].

Our findings also suggest that residential mobility and neighborhood violence mediate the effect of minority status on negative mental health outcomes. Community violence can create an environment where people are afraid to go outside and interact with others[91]. This might limit options to relate with peers and socially congregate. Importantly, South Bronx had a lower murder rate than Puerto Rico – our findings indicate that, if not for this difference, South Bronx youth would have experienced even stronger negative outcomes. Other neighborhood factors (e.g., neighborhood monitoring) may play protective roles at younger ages but appear less relevant to mental health outcomes in adulthood. As children grow older, they might have more independence, and parental monitoring might not be as effective in protecting youth from negative interactions.

Parent-adolescent intercultural conflict mediated the relationship between minority status and poor mental health, while acting as a strong longitudinal risk factor for internalizing symptoms[92]. As Latino youth grow older in an environment that might require integration to US norms, this might raise conflict with parents and other family members that want to maintain Puerto Rican norms and values. Acculturation can help youth navigate and adapt to norms and values of their social context, becoming an asset for social integration and mobility, but create tensions in the family environment. However, links between acculturation and mental health outcomes are difficult to establish across sites, because the construct of acculturation can mean different things in Puerto Rico versus the mainland US. More work is needed to better comprehend how youth acculturate within host and native environments and how this varies by developmental period.

Within our ecological perspective, perceived discrimination (neighborhood discrimination, minority stress, unfair treatment) and cultural factors (ethnic identity, intercultural conflict) reported at Wave 4 also explained site differences in the risk for depression and anxiety disorders. The link between discrimination and internalizing symptoms may be related to physiological changes in the body's natural stress response (e.g., hypothalamic-pituitary axis, elevated cortisol levels[40]) similar to that induced by depression and anxiety[93]. Although using concurrently collected mediator and outcome data may raise questions about the direction of the relationship between these variables – for example, youth with depression or anxiety at Wave 4 might also perceive more discrimination at Wave 4 – the fact that this pattern was observed among South Bronx youth but not as strongly among Puerto Rican ones seems to suggest otherwise. Thus, it appears that discrimination experiences in a minority context contribute to increased psychopathology risk.

Our results suggest the relevance of parental and peer supports as stress-buffering mechanisms that can ameliorate toxic experiences of discrimination and worries of rejection in a minority context[91,94]. They may facilitate a sense of belonging and fitting, counteracting the social mirror in other daily experiences. Cultural factors also require attention, as intercultural conflict with family can have deleterious effects in this context, where sources of assistance are limited. For Latino youth, families often serve as a source of connection, identity, and anchoring of cultural customs; thus, familial disruption could leave youth feeling marginalized and unattached[95-97].

We acknowledge study limitations. Chiefly, we cannot disentangle the effects of site from the effects of minority status – therefore, we seek replication of results in other sites. Though we adjusted for age in our analysis, the wide age range (15-29 years) among Wave 4 participants might obscure important age-minority status interactions – this possibility will be examined in future work. Finally, participants may have been affected by larger sociopolitical changes taking place during data collection. In Puerto Rico, this study coincided with a worsening financial crisis; in South Bronx, increasing cost of living and gentrification led to increased mobility. Of note, 90.9% of the Puerto Rico sample remained in the island at Wave 4, while 85.8% of the South Bronx sample remained within 100 miles of South Bronx.

Our findings suggest the importance of addressing toxic stress related to anticipating and experiencing discrimination as a minority adolescent[98]. Results highlight the importance of social support and strong peer relationships, indicating that community interventions might focus on social relations rather than individual youth to help combat the epidemic of depression and anxiety affecting young people[91,99]. Public health approaches that target social interactions rather than clinically based interventions may have a better opportunity to address the lack of inclusion and the "othering" that create a negative social mirror and jeopardize mental health.

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The efficacy and safety of nutrient supplements in the treatment of mental disorders: a meta-review of meta-analyses of randomized controlled trials

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The role of nutrition in mental health is becoming increasingly acknowledged. Along with dietary intake, nutrition can also be obtained from "nutrient supplements", such as polyunsaturated fatty acids (PUFAs), vitamins, minerals, antioxidants, amino acids and pre/probiotic supplements. Recently, a large number of meta-analyses have emerged examining nutrient supplements in the treatment of mental disorders. To produce a meta-review of this top-tier evidence, we identified, synthesized and appraised all meta-analyses of randomized controlled trials (RCTs) reporting on the efficacy and safety of nutrient supplements in common and severe mental disorders. Our systematic search identified 33 meta-analyses of placebo-controlled RCTs, with primary analyses including outcome data from 10,951 individuals. The strongest evidence was found for PUFAs (particularly as eicosapentaenoic acid) as an adjunctive treatment for depression. More nascent evidence suggested that PUFAs may also be beneficial for attention-deficit/hyperactivity disorder, whereas there was no evidence for schizophrenia. Folate-based supplements were widely researched as adjunctive treatments for depression and schizophrenia, with positive effects from RCTs of high-dose methylfolate in major depressive disorder. There was emergent evidence for N-acetylcysteine as a useful adjunctive treatment in mood disorders and schizophrenia. All nutrient supplements had good safety profiles, with no evidence of serious adverse effects or contraindications with psychiatric medications. In conclusion, clinicians should be informed of the nutrient supplements with established efficacy for certain conditions (such as eicosapentaenoic acid in depression), but also made aware of those currently lacking evidentiary support. Future research should aim to determine which individuals may benefit most from evidence-based supplements, to further elucidate the underlying mechanisms.

Key words: Nutrient supplements, polyunsaturated fatty acids, omega-3, eicosapentaenoic acid, methylfolate, vitamin D, N-acetylcysteine, depression, schizophrenia, attention-deficit/hyperactivity disorder, adjunctive treatment

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Abundant evidence now suggests that people with mental disorders typically have an excess consumption of high-fat and high-sugar foods, alongside inadequate intake of nutrient-dense foods, compared to the general population[1-5]. The relationship between poor diet and mental illness appears to persist even when controlling for other factors which could explain the association, such as social deprivation or obesity, and is not explained by reverse causation[1,6].

Furthermore, although the metabolic and hormonal side effects of psychotropic medications can affect food intake[7,8], inadequate nutrition appears to be present even prior to psychiatric diagnoses. For instance, in depression, it seems that poor diet precedes and acts as a risk factor for illness onset[6,9,10]. Similarly, in psychotic disorders, various nutritional deficits are evident even prior to antipsychotic treatment[11].

The importance of diet for maintaining physical health is widely accepted, due to the clear impact of dietary risk factors on cardiometabolic diseases, cancer and premature mortality[12,13]. In parallel, the potential impact of diet on mental disorders is increasingly acknowledged[14,15]. However, along with regular food intake, nutrients can also be consumed in supplement form[16]. Supplements are typically used in attempts to: a) complement an inadequate diet (or low measured plasma levels of a nutrient) to achieve recommended nutrient intakes/levels; b) administer specific nutrients at greater doses than those found in a typical diet, for putative physiological benefits; c) provide nutrients in more bioavailable forms for individuals with genetic differences, or relevant health issues, which may result in poor nutrient absorption. Supplements can be synthetically manufactured or directly food-derived, typically including substances such as vitamins (e.g., folic acid, vitamin D), dietary minerals (e.g., zinc, magnesium), pre/probiotics (from specific strains of gut bacteria), polyunsaturated fatty acids, PUFAs (typically as omega-3 fish oils), or amino acids (e.g., N-acetylcysteine, glycine).

Nutrient supplements are widely used across the population. For instance, in the US, over half of adults take some form of nutrient supplements[17]. There is a lack of evidence that this wide-scale usage reduces the incidence of diseases or premature mortality (indeed, many of the best quality trials – e.g., of vitamins D[18] and E[19,20] – were negative). However, some specific

nutrient supplements are linked to health benefits for specific populations or clinical conditions (for instance, women in pregnancy are advised to supplement with folic acid to reduce the risk of neural tube deficits in offspring[21]; individuals with pernicious anaemia are treated with vitamin B12[22]; oral supplementation with zinc is a first-line treatment for Wilson's disease[23]; and national medical associations have recommended omega-3 fatty acids for patients with myocardial infarction[24]).

Currently, there is an increased academic and clinical interest in the role of nutrient supplements for the treatment of various mental disorders[14-16]. This growth of research is partly attributable to our evolving understanding of the neurobiological underpinnings of mental illness, which implicates certain nutrients as a potential adjunctive treatment for a variety of reasons[25].

First, recent clinical research has found that many mental disorders are associated with heightened levels of central and peripheral markers of oxidative stress and inflammation[26-29], and an association has been reported between the efficacy of both pharmacological and lifestyle interventions for mental illness and changes in these biomarkers[30,31]. Thus, the antioxidant and anti-inflammatory properties of certain nutrient supplements (such as N-acetylcysteine[32] and omega-3 fish oils[33]) indicates that these could be beneficial in the treatment of psychiatric conditions caused or exacerbated by heightened inflammation and oxidative stress.

Second, there are now extensive data from large-scale studies showing that psychotic and mood disorders are associated with significantly reduced serum levels of essential nutrients, including zinc[34,35], folate[36,37] and vitamin D[38,39]. Since these deficits appear to be related to treatment response and clinical outcomes in these populations[11,34,40], there is a possibility that nutrient supplementation could improve outcomes.

Third, there is nascent (but growing) evidence that mental disorders may be linked to dysfunction of the gut microbiome[41,42]. As gut bacteria can be modified through micronutrients and pre/probiotics[43,44], this suggests that some pre/probiotic supplements may serve as potentially useful novel therapeutic options worthy of further investigation[45,46].

Alongside the theoretical potential for nutrient supplements to target certain aspects of mental disorders, there is also a vast amount of clinical trials and meta-analyses examining their use in psychiatric treatment, and some data in prevention[47,48]. However, there remains considerable contention around their role in clinical care. This likely stems from the lack of clear and up-to-date guidance for clinicians and researchers regarding their: a) relative effectiveness for improving clinical outcomes in people with mental illness, and b) safety for use, particularly in conjunction with psychiatric medications.

The aim of this meta-review is to aggregate and evaluate the top-tier evidence for the efficacy and safety of nutrient supplements in the treatment of mental disorders, and to explore the conditions under which they may be effective. To do this, we identified, synthesized and appraised all available data from meta-analyses of randomized controlled trials (RCTs) examining health outcomes and quality of evidence for all nutrient supplements across various mental disorders. Along with providing a clear overview of the efficacy of specific nutrient supplements across different disorders, we also aimed to explore which dosages and symptomatic targets are most appropriate, while additionally reporting on the safety and tolerability for all supplements examined.

METHODS

The search strategy and data synthesis were conducted in line with the PRISMA statement[49], and followed a pre-registered protocol (PROSPERO: CRD42018105880).

Systematic search

The title and keyword search algorithm is presented in Table 1. The systematic search was conducted using Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Health Technology Assessment Database, Allied and Complementary Medicine (AMED), PsycINFO and Ovid MEDLINE(R), from inception until February 1, 2019.

A search of Google Scholar was conducted using the same key words to identify any additional relevant articles. Reference lists of included articles were also searched.

Table 1 PICO (Participants, Interventions, Comparisons, Outcomes) systematic search strategy

Participants (any mental disorder)
Depression OR depressive OR mental illness* OR mental disorder* OR mood disorder* OR affective disorder* OR anxiety OR panic disorder OR obsessive compulsive OR ADHD OR attention deficit OR attentional deficit OR phobia OR bipolar type OR bipolar disorder* OR psychosis OR psychotic OR schizophr* OR antipsychotic* OR post traumatic* OR personality disorder* OR stress disorder* OR dissociative disorder*
Interventions (any nutrient or nutraceutical)
Vitamin* OR mineral* OR nutrient* OR food supplement* OR meal replacement* OR nutritional supplement* OR health supplement* OR multivitamin* OR omega 3 OR fish oil* OR alpha lipoic acid OR alpha linolenic acid OR alpha linoleic acid OR eicosapentaenoic OR docosahexaenoic OR fatty acid* OR amino acid* OR taurine OR S-adenosyl methionine OR creatine OR acetylcysteine OR cysteine OR probiotic* OR tryptophan OR tocopherol OR alphatocopherol OR carotene OR retinol OR thiamine OR riboflavin OR niacin OR niacinamide OR nicotinic acid OR pantothenic OR pyridox* OR biotin OR methylfolate OR 5-MTH* OR levomefolic acid OR folate OR folinic acid OR folic acid OR inositol OR cyanocobalamin OR methylcobalamin OR cobalamin OR ascorbic acid OR cholecalciferol OR iron OR ferrous OR tocopherols OR trace element OR calcium OR phosphorus OR magnesium OR potassium OR manganese OR zinc OR selenium OR boron OR chromium OR lycopene OR isoflav* OR flavonoid* OR bioflavonoid* OR micronutrient OR carnitine
Comparator (placebo controlled trials)
Random* OR placebo OR control* or adjunc* or clinical trial*
Outcomes (any from meta-analyses)
Meta-analy* OR metaanaly* OR meta reg* OR metareg* OR systematic review*

Eligibility criteria

Eligibility criteria were organized in accordance with the PICO (Participants, Interventions, Comparisons, Outcomes) reporting structure, as described below.

Participants

We included studies of individuals with common and severe mental disorders, i.e., depressive disorders, bipolar disorder (type I and II), schizophrenia and other psychotic disorders, anxiety and stress-related disorders, dissociative disorders, personality disorders, and attention-deficit/hyperactivity disorder (ADHD). Studies of individuals who met criteria for being at "ultra-high risk" or "clinical high risk" for developing a psychotic disorder were also included.

All studies of the above conditions were eligible provided that at least 75% of the sample had a confirmed mental illness or at-risk state, ascertained by either clinical diagnostic history or reaching established thresholds on validated screening measures. Studies examining mental health outcomes of nutrient supplementation in the general population were only included if data from a mental illness subgroup (with 75% of the sample meeting the above criteria) were available. Studies examining nutrient supplements only for ameliorating the malnutrition associated with eating disorders or substance abuse disorders were excluded. Studies examining neurodevelopmental disorders (e.g., autism, intellectual disability) or neurodegenerative disorders (e.g., dementia) were also not included.

Interventions

All nutrient supplements were considered for this meta-review, used either as adjunctive treatment or monotherapy. Nutrient supplements were defined as vitamins, minerals, macronutrients, fatty acids or amino acids (including oral supplement forms of precursors to these) commonly found in the human diet. Meta-analyses of dietary modification interventions and herbal supplements were not included.

Comparisons

As this study aimed to provide a meta-review of the top-tier evidence, only meta-analyses of RCTs were included.

Outcomes

All data on physical and/or mental health outcomes (including changes in clinical measures, response rates, and adverse effects) from meta-analyses of RCTs examining nutritional supplements for any eligible disorder were included in this meta-review. A meta-analysis was classified as eligible if: a) it had clearly stated inclusion, intervention and comparison criteria aligned with the participant, intervention and comparison criteria listed above; b) it reported a systematic search with a screening procedure; c) it had used systematic data extraction and reported pooled continuous or categorical outcome data from more than one study.

Where overlapping meta-analyses of a given nutritional supplement for a specific outcome/disorder existed, the most recently updated meta-analysis was used, as long as it captured more than 75% of the trials in the earlier version. Where older meta-analyses presented unique findings, through inclusion of a greater number of studies or use of particular subgroup analyses, these data were used as secondary analyses for our meta-review.

Quality assessment of included meta-analyses

The quality of eligible meta-analyses was assessed using "A Measurement Tool to Assess Systematic Reviews" Version 2 (AMSTAR-2)[50], an updated version of the original AMSTAR designed to better capture review quality and confidence in findings.

AMSTAR-2 assesses 16 constructs, which all indicate the quality of a systematic review/meta-analysis. Seven of these were identified as "critical domains", which can be used to determine the overall confidence in review findings[50]. For the purposes of our meta-review, the included meta-analyses were scored on all the 16 AMSTAR-2 items, but also received a separate score for the number of "critical domains" they adhered to.

Data extraction and analysis

Primary analyses focused on the effects of nutrient supplementation on measures of physical or mental health outcomes from eligible meta-analyses. For each nutritional supplement used for each disorder, we manually extracted effect size data as standardized mean differences (SMDs) with 95% confidence intervals (CIs) compared to placebo conditions, along with the reported probability of the compared effects being due to chance (p value). Data were initially extracted by five authors (KA, ST, WM, MS, DS), and then cross-checked for quality with duplicate data extraction by four independent authors (JF, BS, JC, FS).

In line with conventional interpretations, SMDs were classified as negligible (<0.2), small (0.2-0.4), moderate (0.4-0.8), or large (>0.8). In cases where meta-analyses had provided effect sizes corrected for publication bias, these were reported alongside the main effects observed, and interpreted as the primary findings from the analysis. In cases where continuous outcomes were reported as weighted mean differences or raw mean differences, these were recalculated into an SMD (Hedges' g) using Comprehensive Meta-Analysis 3.0. Where original meta-analyses had reported beneficial effects of nutrient supplementation as negative value effect sizes (to represent a reduction in symptoms), these were re-coded to positive – such that all effect sizes

presented here are positive values when indicating benefit from nutrient supplementation compared to placebo, or negative values when placebo was associated with better outcomes than nutrient supplementation. Where meta-analyses had applied fixed-effects models to calculate the effect sizes of nutritional supplementation compared to placebo, these were also recalculated using a random-effects model, such that SMDs across supplements/disorders could be meaningfully compared.

The results of secondary analyses, focusing on safety and tolerability, were typically reported as categorical outcomes (relative rates of adverse events or discontinuation in active vs. placebo conditions). These were extracted as either odds ratios (ORs) or risk ratios (RRs), in line with the originally reported outcomes.

For both primary and secondary analyses, we also extracted the number of participants (N), along with the number of trials/comparisons (n) from which the pooled effect size was derived. Additionally, heterogeneity was quantified using the I^2 statistic, and categorized as low (I^2<25%), moderate (I^2=25-50%) or high (I^2>50%).

Where reported, all relevant study characteristics were also extracted, specifically with regards to the nutritional supplement used (including type, dose and co-factors), the sample and the diagnostic details, and any relevant subgroup analyses implemented (e.g., separating high/low quality trials, specific patient subsamples, or dosage levels).

The potential impact of publication bias was assessed wherever there were sufficient data for appropriate analyses, and the adjusted effect sizes (when controlling for small study bias) are presented alongside the main findings.

RESULTS

Systematic search results

The search returned 1,194 results, which were reduced to 737 after duplicates were removed. One further potentially eligible article was retrieved from the additional search of Google Scholar. Title and abstract screening removed 597 articles, while 141 articles were retrieved and reviewed in full. Of these, 108 were ineligible. Thus, in total, eligible data from 33 independent meta-analyses of RCTs of nutrient supplementation in mental disorders were included for this meta-review (see Figure 1).

Meta-analyses examined RCTs of PUFAs, vitamins, minerals, amino acid supplements and pre/probiotics, with primary analyses including outcome data from a total of 10,951 individuals. All meta-analyses were based on nutrient supplementation administered in conjunction with "usual care" (without specifying treatment regimens) or as an adjunctive treatment to a specific class of psychotropics (e.g., selective serotonin reuptake inhibitors (SSRIs) in depression, or antipsychotics in schizophrenia). Only one of the meta-analyses reported on a nutrient supplement as monotherapy for a mental disorder (i.e., omega-3 fatty acids for depression[51]), whereas no others specifically excluded patients taking medications. No meta-analyses directly compared nutrient supplementation to psychotropic medications. All studies[51-82] were placebo-controlled.

Specific psychiatric conditions (and reported outcomes) considered in this meta-review included: schizophrenia (examining total symptoms along with positive, negative, general and depressive symptoms, and tardive dyskinesia)[52-59]; states at risk for psychosis (examining attenuated psychosis symptoms, negative symptoms, transition to psychosis, and functioning)[60-63]; depressive disorders (including any clinical depression, diagnosed major depressive disorder (MDD), depression in pregnancy, in old age, or as a comorbidity to chronic health conditions)[51,59,64-73]; anxiety and stress-related conditions (including generalized anxiety disorder, obsessive-compulsive disorder (OCD) and trichotillomania)[68,72,74]; bipolar disorder type I and II (examining overall symptoms, bipolar mania, bipolar depression, functional impairments, and quality of life)[56,68,72,75,76]; and ADHD (including composite symptoms, hyperactivity-impulsivity, inattention, behavioural comorbidities such as aggression, and cognitive functioning)[77-82].

Quality assessment of the included meta-analyses

The quality assessment of the meta-analyses is provided alongside the respective outcomes in Figures 2-7. Individual meta-analyses fulfilled between 4 and 16 of the AMSTAR-2 criteria (median: 12, mean: 12). The majority of the meta-analyses (25 out of 33) adhered to five or more of the seven "critical domains", but only five of them adhered to all the domains[52,58,64,78,80]. Twenty-six of the 33 included meta-analyses were published in 2016-2019.

Efficacy and safety of nutrient supplementation for mental disorders

Figures 2-7 show the efficacy of nutrient supplementation (as determined by meta-analyses) for all clinical outcomes reported across different psychiatric conditions, including depressive disorders (Figure 2), anxiety disorders (Figure 3), schizophrenia (Figure 4), states at risk for psychosis (Figure 5), bipolar disorder (Figure 6), and ADHD (Figure 7). The overall quality of meta-analyses is also displayed in these figures. Nutrient supplements with sufficient data (i.e., from meta-analyses with >400 participants) are highlighted in Table 2. For all nutrients assessed, the specifics of these findings, along with data on safety and tolerability, are detailed below.

Vitamins and minerals

Folate-based supplements

The most widely assessed vitamin supplement for mental disorders was vitamin B9, which is also referred to as "folate" when

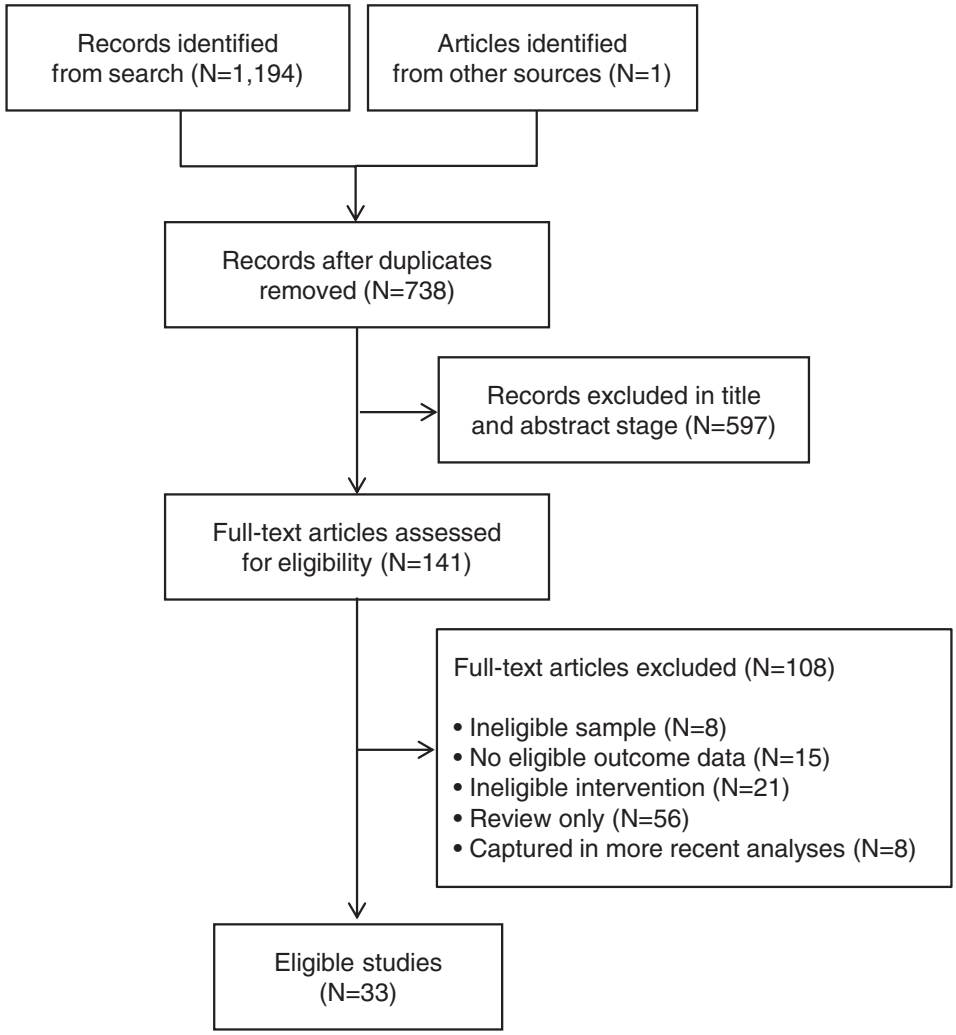

Figure 1 PRISMA flow chart

in dietary form. It can be administered in supplement form as folic acid, folinic acid or methylfolate (which is also known as l-methylfolate, levomefolic acid, or 5-methyltetrahydrofolate).

As an adjunctive to SSRIs in 904 individuals with unipolar depression (mostly MDD), folate-based supplements (including folic acid and methylfolate, administered at varying doses) were associated with significantly greater reductions in depressive symptoms compared to placebo, although there was large heterogeneity between trials (n=7, SMD=0.37, 95% CI: 0.01-0.72, p=0.04, I^2=79%)[67].

When administering vitamin B9 as folic acid (0.5-10 mg/day), no significant effects on depressive symptoms were observed (N=657, n=4, SMD=0.4, 95% CI: –0.08 to 0.88, p=0.1, I^2=83%). Significant effects were observed in the two trials using low dose (<5 mg/day) folic acid (N=190, SMD=0.57, 95% CI: 0.23-0.91, p<0.001, I^2=25%), while no significant benefits were observed from doses of ≥5 mg/day (N=467, n=2, SMD=0.24, 95% CI: –0.56 to 1.03, p=0.56, I^2=76%)[67].

Two RCTs examining a high dose (15 mg/day) of methylfolate (the most bioactive metabolite of folic acid) as an adjunctive treatment for MDD found moderate-to-large benefits for depressive symptoms (N=99, n=2, SMD=0.73, 95% CI: 0.28-1.19, p=0.002, I^2=3%)[67]. There was no evidence of adverse effects or statistical heterogeneity. However, when including the lower-dose trials of methylfolate (7.5 mg/day), no significant effects on depression were observed (N=249, n=3, SMD=0.34, 95% CI: –0.4 to 1.08, p=0.37, I^2=81%).

Seven RCTs (N=340) examined folate-based supplements as an adjunctive treatment for schizophrenia[54]. Vitamin B9 was administered as methylfolate (n=2) or folic acid (n=5), and also in combination with B6 and B12 (n=3). In overall analyses, the small effects of vitamin B9 on total symptoms were not statistically significant (SMD=0.20, 95% CI: –0.02 to 0.41, p=0.08, I^2=0), and subgroup analyses of high-quality studies confirmed the absence of overall effects (N=231, n=3, SMD=0.15, 95% CI: –0.11 to 0.42, p=0.26, I^2=0%). The folate-

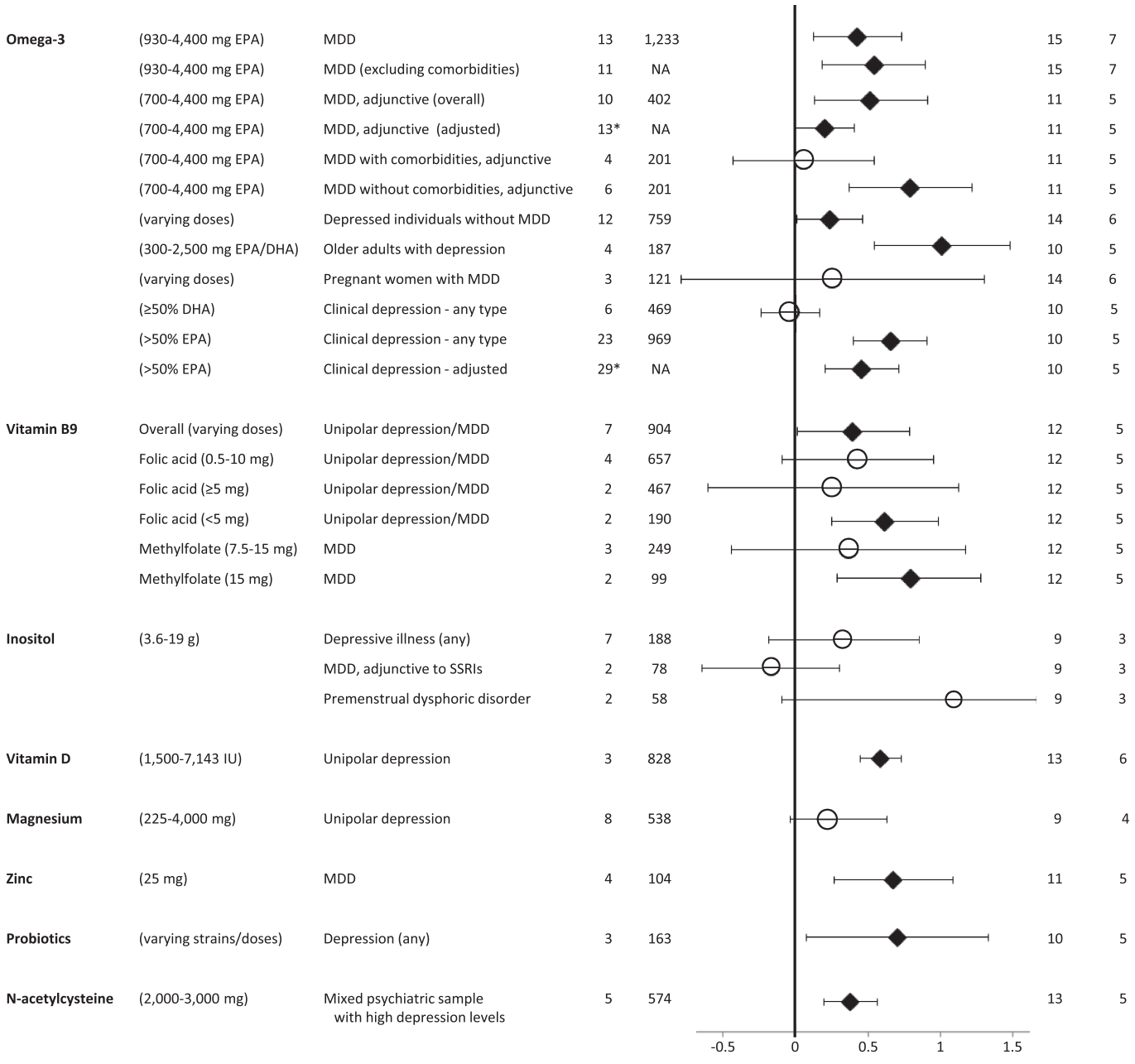

Figure 2 Effects of nutrient supplements in depressive disorders, shown as standardized mean difference with 95% CI. Circles represent no significant difference from placebo; diamonds represent p≤0.05 compared to placebo; * represents trim-and-fill estimate adjusted for publication bias. A2 – AMSTAR-2 total score, A2-CA – AMSTAR 2 "critical domains" adhered to, MDD – major depressive disorder, EPA – eicosapentaenoic acid, DHA – docosahexaenoic acid, SSRIs – selective serotonin reuptake inhibitors, NA – not available.

based supplements were ineffective on total symptom scores when administered as folic acid (N=268, n=5, SMD=0.13, 95% CI: –0.12 to 0.37, p=0.32, I^2=0%), even in combination with other homocysteine-reducing B vitamins (i.e., B6 and B12) (N=219, n=3, SMD=0.18, 95% CI: –0.13 to 0.5, p=0.24, I^2=16%). However, effects on total symptom scores in two trials of high-dose methylfolate (15 mg/day) approached statistical significance (N=72, n=2, SMD=0.45, 95% CI: 0.02-0.92, p=0.06, I^2=0%).

Folate-based supplements had no significant effects on positive symptoms, general psychopathology or depressive symptoms in patients with schizophrenia[54]. However, they reduced

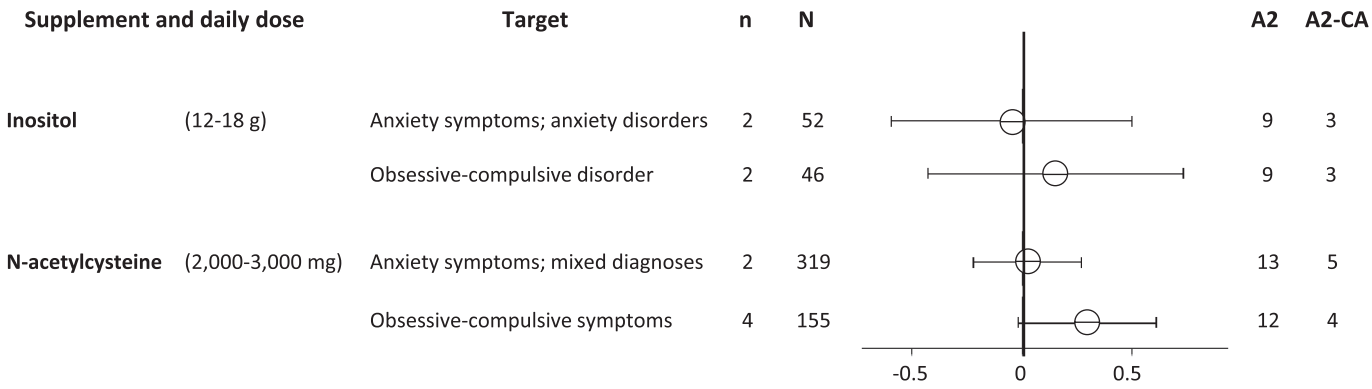

Figure 3 Effects of nutrient supplements in anxiety, shown as standardized mean difference with 95% CI. Circles represent no significant difference from placebo. A2 – AMSTAR-2 total score, A2-CA – AMSTAR 2 "critical domains" adhered to.

negative symptoms more than placebo (N=281, n=5, SMD=0.25, 95% CI: 0.01-0.49, p=0.04, I^2=0). The effect persisted in high-quality RCTs (N=190, n=2, SMD=0.30, 95% CI: 0.00-0.60, p=0.05, I^2=0), but became non-significant when excluding the RCT using 15 mg/day methylfolate (N=226, n=4, SMD=0.23, 95% CI: –0.04 to 0.50, p=0.10, I^2=0%)[54].

A significantly lower incidence of serious adverse events compared to placebo was observed over the trial periods in patients with schizophrenia (N=241, n=4, RR=0.32, 95% CI: 0.12-0.82, p=0.02, I^2=0%)[54].

Inositol

In an overall analysis of the effects of inositol (3.6-19 g/day, median: 12 g/day) on depressive symptoms across bipolar disorder, unipolar depression and premenstrual dysphoric disorder, no significant difference from placebo was found (N=188, n=7, SMD=0.35, 95% CI: –0.2 to 0.89, p=0.22, I^2=70%)[68]. Inositol was also ineffective when examined as adjunctive to SSRIs in MDD (N=78, n=2, SMD=–0.17, 95% CI: –0.66 to 0.33, p=0.50, I^2=0%) and for depressive symptoms in premenstrual dysphoric disorder (N=58, n=2, SMD=1.15, 95% CI: –0.08 to 2.39, p=0.07, I^2=78%)[68].

In schizophrenia, inositol supplementation (6-12 g/day) was not superior to placebo for total symptom scores (N=66, n=3, SMD=0.155, 95% CI: –0.35 to 0.58, p=0.63, I^2=87.2%)[53]. Among individuals with bipolar disorder, inositol (5.7-19 g/day) had no effect on depressive symptoms (N=42, n=2, SMD=–0.11, 95% CI: –0.75 to 0.52, p=0.72, I^2=0%) or response rates (RR=0.63, 95% CI: 0.35-1.12, p=0.12, I^2=22%)[68]. In anxiety disorders, inositol (12-18 g/day) had no effects on Hamilton Anxiety Rating Scale scores (N=52, n=2, SMD=0.04, 95% CI: –0.58 to 0.51, p=0.89) and symptom scores in OCD samples (N=46, n=2, SMD=0.15, 95% CI: – 0.43 to 0.73, p=0.60)[68].

Discontinuation did not differ between inositol and placebo groups[68]. However, inositol supplementation was associated with a trend towards a higher rate of gastrointestinal upset than placebo (N=183, n=6, SMD=3.26, 95% CI: 0.94-11.34, p=0.06, I^2=0%).

Other vitamins and minerals

Vitamin D was found to significantly reduce depressive symptoms in patients with clinical depression (N=948, n=4, SMD=0.58, 95% CI: 0.45-0.72, p<0.01, I^2=0%). This estimate included data from non-blinded trials using intramuscular injections[69]. Nevertheless, in our re-analysis of data using only double-blind RCTs of oral supplements, similar positive effects were observed at doses of 1,500-7,143 IU/day (N=828, n=3, SMD=0.57, 95% CI: 0.43-0.71, p<0.001, I^2=0%).

Eleven RCTs examined the efficacy of mineral supplementation for depression, using either zinc or magnesium. Zinc was administered at 25 mg/day (elemental) as an adjunctive treatment for MDD, and had moderate significant effects on depressive symptoms (N=104, n=4, SMD=0.66, 95% CI: 0.26-1.06, p=<0.01)[65]. Although there was no evidence of heterogeneity (I^2=0%), all included RCTs were identified as having high risk of attrition bias, due to lack of intent-to-treat analyses[65]. In individuals with depression identified using self-report measures, magnesium supplementation at 225-4,000 mg/day had no effects beyond placebo (N=538, n=8, SMD=0.22, 95% CI: –0.17 to 0.48, I^2=30.9%)[70]. No data on magnesium as an adjunctive treatment in diagnosed MDD are available.

No significant effects on total symptom scores in schizophrenia were observed from pooled analyses of antioxidant vitamins (vitamin C and vitamin E: N=340, n=6, SMD=0.296, 95% CI: –0.39 to 0.98, p=0.40, I^2=40.6%); mineral supplements (zinc and chromium: N=129, n=2, SMD=0.324, 95% CI: –0.48 to 1.13, p=0.43, I^2=0%); or vitamin B6 (N=75, n=3, SMD=0.682, 95% CI: –0.09 to 1.45, p=0.08, I^2=58.4%)[53].

As a therapeutic option for managing side effects of antipsychotics, vitamin E showed no difference from placebo on levels of improvement in tardive dyskinesia[52]. Nevertheless, it did significantly reduce the risk of tardive dyskinesia "worsening" over 1 year (N=85, n=5, RR=0.23, 95% CI: 0.07-0.76), although this result was based on low-quality trials[52].

All vitamin and mineral supplements appeared to have good safety profiles in schizophrenia, with none producing a greater number of adverse events than placebo control conditions[52,53].

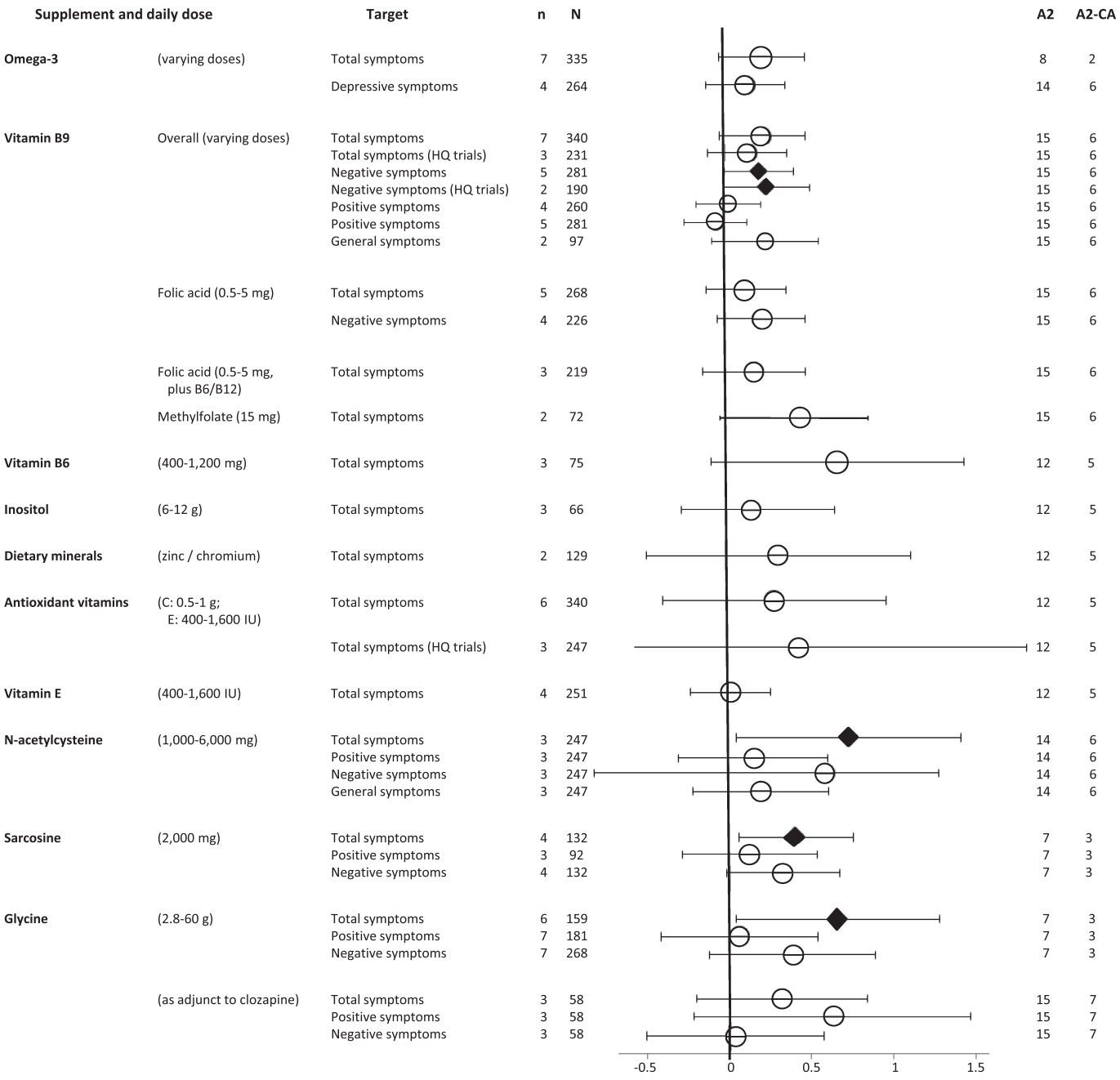

Figure 4 Effects of nutrient supplements in schizophrenia, shown as standardized mean difference with 95% CI. Circles represent no significant difference from placebo; diamonds represent p≤0.05 compared to placebo. A2 – AMSTAR-2 total score, A2-CA – AMSTAR 2 "critical domains" adhered to, HQ – high quality.

PUFAs

Depression and bipolar disorder

PUFAs have been the most widely assessed nutritional supplement across the various psychiatric conditions, administered as omega-3 fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and omega-6 fatty acids, such as linoleic acid (LA).

Across 13 independent RCTs in 1,233 people with MDD, omega-3 supplements (mean: 1,422 mg/day of EPA) reduced depressive symptoms (SMD=0.398, 95% CI: 0.114-0.682, p= 0.006, I^2 not available), with no evidence of publication bias[64]. When used specifically as an adjunctive to antidepressants in MDD, omega-3 supplements (930-4,400 mg/day of EPA) also produced moderate effects on depressive symptoms (N=448,

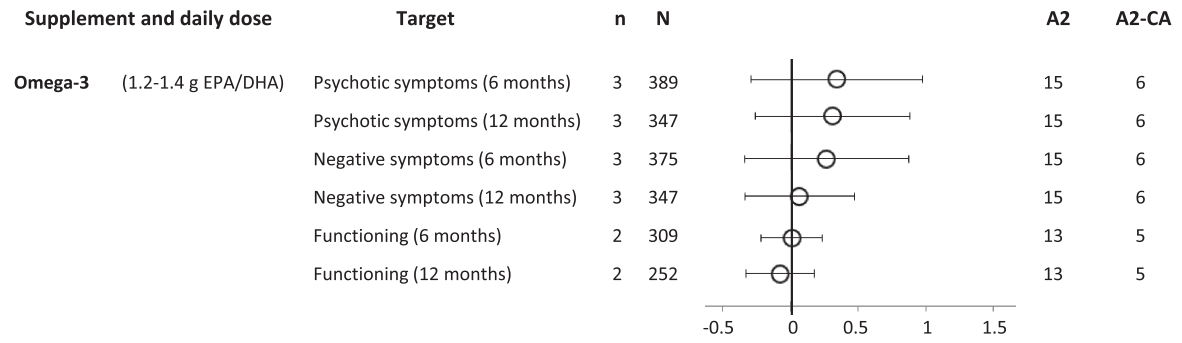

Figure 5 Effects of nutrient supplements in states at risk for psychosis, shown as standardized mean difference with 95% CI. Circles represent no significant difference from placebo. A2 – AMSTAR-2 total score, A2-CA – AMSTAR 2 "critical domains" adhered to, EPA – eicosapentaeonoic acid, DHA – docosahexaenoic acid.

n=11, SMD=0.608, 95% CI: 0.154-1.062, p=0.009, I^2=82%), although there was some indication of publication bias[75]. A subsequent analysis of omega-3 as an adjunctive to antidepressants in MDD produced similar results (N=402, n=10, SMD=0.48, 95% CI: 0.11-0.84, p=0.01, I^2=64%), although again showing evidence of significant publication bias[65]. Adjusting for publication bias produced smaller (but still significant) estimates of effects of omega-3 as an adjunctive treatment for MDD (SMD=0.19, 95% CI: 0.00-0.38, p=0.049).

Subgroup analyses found that omega-3 supplements were only effective as an adjunctive treatment for MDD in cohorts with no reported comorbidities (N=201, n=6, SMD=0.74, 95% CI: 0.34-1.13, p<0.01, I^2=42%), whereas there was no indication of efficacy in samples where MDD occurred in comorbidity with cardiometabolic or neurological diseases (N=201, n=4, SMD=0.05, 95% CI: –0.4 to 0.5, p=0.82, I^2=45%)[65]. Furthermore, omega-3 was ineffective for the treatment of MDD in pregnant women (N=121, n=3, SMD=0.24, 95% CI: –0.73 to 1.21, p=0.63, I^2=85%)[59]. A further subgroup analysis of individuals with indicated depression (but no diagnosis of MDD) found small positive effects of omega-3 for depressive symptoms (N=759, n=12, SMD=0.22, 95% CI: 0.01-0.43, p<0.05, I^2=46%).

In analyses examining different formulations of omega-3 for individuals with any clinical depression, omega-3 supplements containing ≥50% DHA had no benefits beyond placebo (N=469, n=6, SMD=–0.028, 95% CI: –0.21 to 0.16, p>0.1)[51]. However, omega-3 supplements containing >50% EPA had moderately large positive effects on depressive symptoms (N=969, n=23,

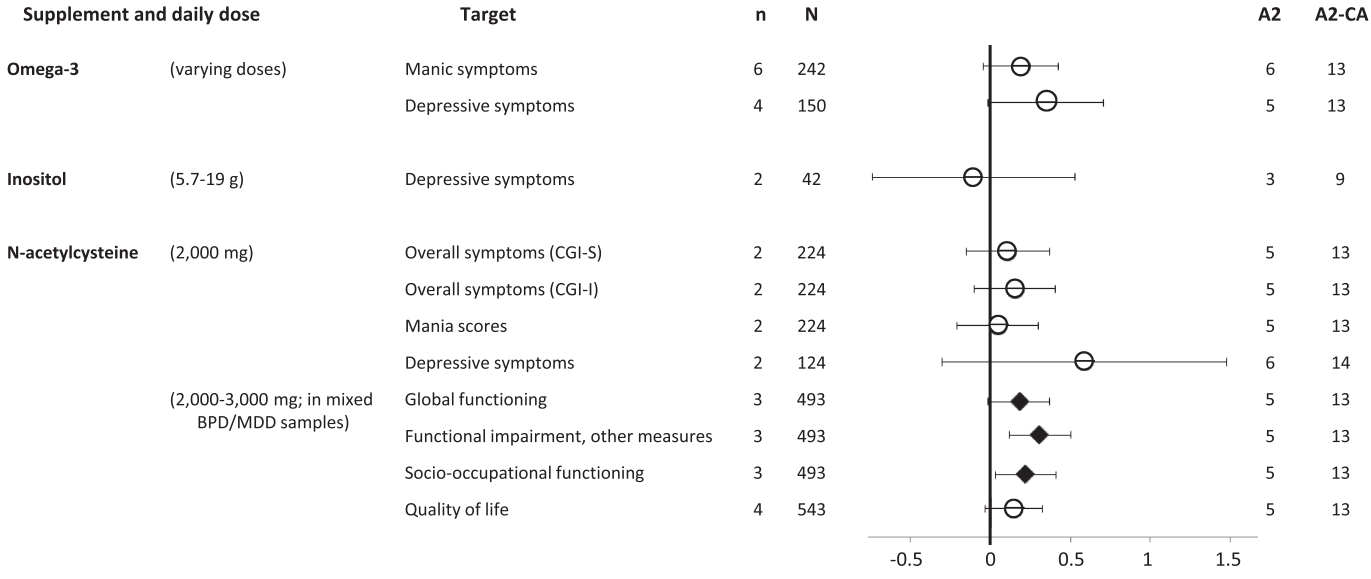

Figure 6 Effects of nutrient supplements in bipolar disorder, shown as standardized mean difference with 95% CI. Circles represent no significant difference from placebo; diamonds represent p≤0.05 compared to placebo. A2 – AMSTAR-2 total score, A2-CA – AMSTAR 2 "critical domains" adhered to, BPD – bipolar disorder, MDD – major depressive disorder, CGI-S – Clinical Global Impression - Severity, CGI-I – Clinical Global Impression - Improvement.

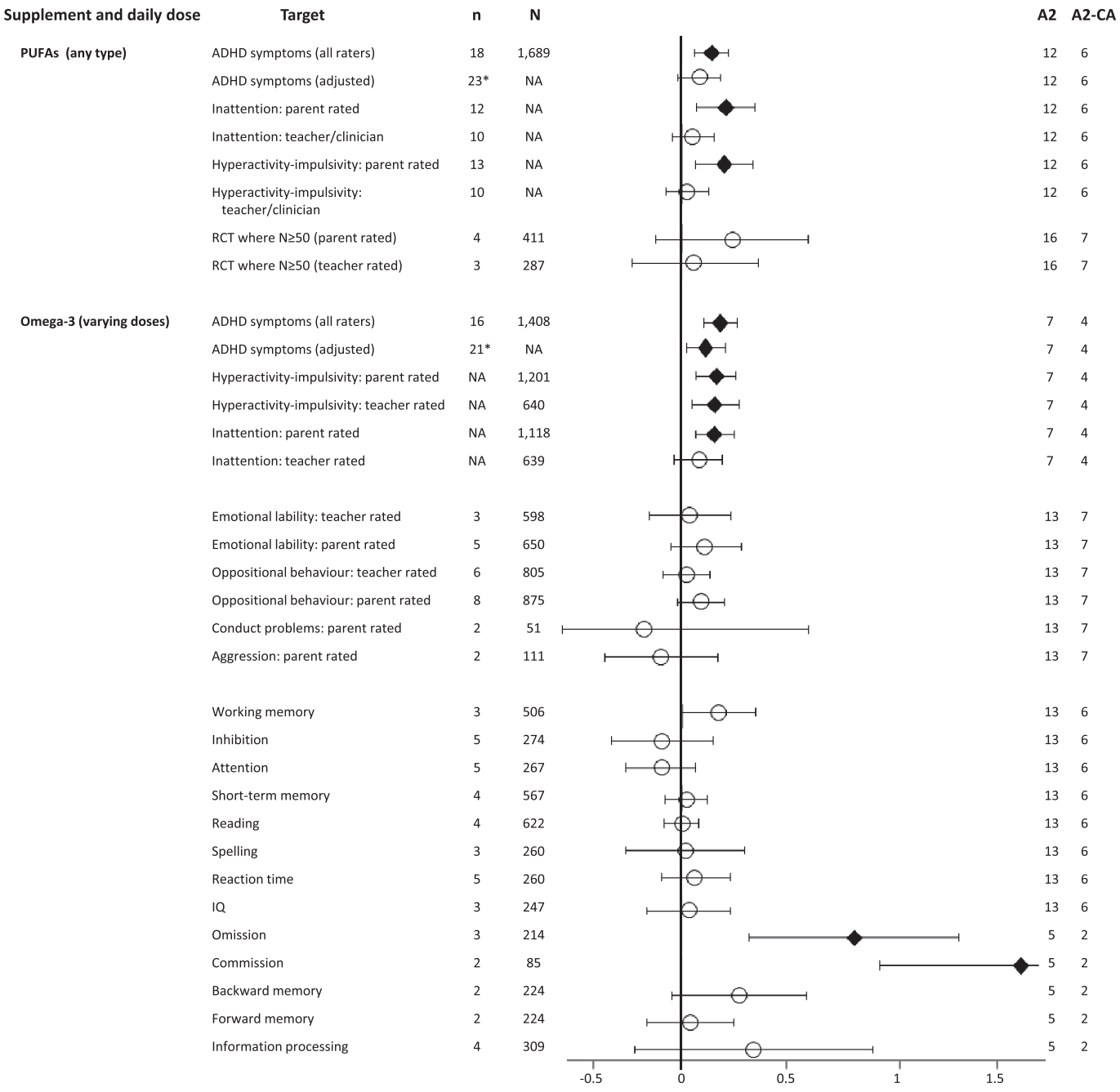

Figure 7 Effects of nutrient supplements in attention-deficit/hyperactivity disorder (ADHD), shown as standardized mean difference with 95% CI. Circles represent no significant difference from placebo; diamonds represent p≤0.05 compared to placebo; * represents trim-and-fill estimate adjusted for publication bias. A2 – AMSTAR-2 total score, A2-CA – AMSTAR 2 "critical domains" adhered to, PUFAs – polyunsaturated fatty acids, NA – not available, RCTs – randomized controlled trials.

SMD=0.61, 95% CI: 0.38-0.85, p<0.001). Again, publication bias was evident, and the estimated positive effects of high-EPA omega-3 was reduced, but still significant, after adjusting for this (SMD=0.42, 95% CI: 0.18-0.65, p<0.001).

Further subgroup analyses of EPA formulas indicated slightly larger effects on depressive symptoms in studies using >12 week treatment periods (N=274, n=4, SMD=1.07, p<0.01) compared to those using ≤12 week periods (N=695, n=19, SMD=0.55, p<0.001), and for those using omega-3 as an adjunctive treatment (N=535, n=15, SMD=0.72, p<0.001) rather than as a monotherapy for depression (N=434, n=8, SMD=0.44, p=0.017)[51].

An analysis in people aged ≥65 years with clinical depression (either diagnosed or meeting thresholds on validated self-report measures) found that omega-3 (averaging 1.3 g/day of EPA/DHA)

Table 2 Key evidence summaries for nutrient supplements with sufficient data (i.e., meta-analyses with >400 participants)

Treatment	Key findings	Indicated usage	Considerations
Depression			
Omega-3	Small-to-moderate positive effects from high-EPA formulas in clinical depression generally, as well as an adjunctive to SSRIs in MDD	>50% EPA formulas providing 2,200 mg EPA/day	• Small but significant effects observed in high-quality meta-analyses even after adjusting for publication bias • Significant heterogeneity in overall analyses • No benefits for MDD in comorbidity to other conditions • No benefits from DHA-predominant formulas
Folate-based supplements	Small overall benefits for unipolar depression, with greatest effects from high-dose methylfolate in treatment-resistant MDD	15 mg/day of methylfolate as adjunctive treatment in MDD	• Overall effects across folate trials become largely non-significant after excluding 15 mg/day methylfolate • Moderate effects of high-dose methylfolate observed only in few small-scale RCTs
Vitamin D	Moderate improvements in major depression, with low heterogeneity between studies	50,000 IU per week as adjunctive treatment	• Examined in only one meta-analysis of four RCTs, with low confidence in findings • All RCTs from China and Iran (given vitamin D levels are influenced by sunlight exposure/region, replication is required in other settings)
Magnesium	No significant benefits for major depression		• Multiple critical flaws in meta-analyses reduce confidence in findings
NAC	Small-to-moderate reductions in depressive symptoms across various psychiatric diagnoses	2,000 mg/day	• Preliminary evidence: low confidence in findings and significant heterogeneity
ADHD			
Omega-3	Small positive effects for total ADHD symptoms, along with hyperactivity-impulsivity and inattention subdomains; no effects on comorbid emotional/behavioural problems	High EPA formulas providing up to 2,513 mg EPA/day	• Low confidence in review findings and negligible effects after adjusting for publication bias • Examined mostly as monotherapy in youths reaching clinical thresholds from self-report measure; difficult to determine efficacy in conjunction with medications
Bipolar disorder			
NAC	Small positive effects for measures of functional impairment; effects on bipolar symptoms examined in <400 patients	2,000 mg/day	• Significant heterogeneity and low confidence in analyses
Schizophrenia			
Omega 3	No significant effects on symptoms of schizophrenia		• Low confidence in review findings • Subsequent research indicates potential benefit in first-episode psychosis
Folate-based supplements	No effects of adjunctive folate supplements on total symptom scores; significant reductions observed for negative symptoms, particularly in methylfolate trials	15 mg/day of methylfolate as adjunctive treatment	• Effects on negative symptoms become largely non-significant after excluding methylfolate trials • Moderate effects of high-dose methylfolate observed only in few small-scale RCTs

EPA – eicosapentaenoic acid, SSRIs – selective serotonin reuptake inhibitors, MDD – major depressive disorder, ADHD – attention-deficit/hyperactivity disorder, DHA – docosahexaenoic acid, RCT – randomized controlled trial, NAC – N-acetylcysteine

had large, significant effects on depressive symptoms compared to placebo (SMD=0.94, 95% CI: 0.5-1.37, p<0.001, I^2=32.7%), although with only a limited number of small studies (N=187, n=4).

Across all placebo-controlled trials of omega-3 PUFAs in people with bipolar disorder, effects on mania were not significant (N=242, n=6, SMD=0.198, 95% CI: –0.037 to 0.433, p=0.10, I^2=0%) although there were small positive effects on depression (N=305, n=6, SMD=0.338, 95% CI: 0.035-0.641, p=0.029, I^2=30%)[75]. An analysis including only double-blind trials found similar positive effects for bipolar depression, although falling just short of statistical significance (N=150, n=4, SMD=0.36, 95% CI: –0.01 to 0.73, p=0.051, I^2=8%)[76]. The majority of studies were identified as low risk of bias, and showed no indication that omega-3 increased rates of adverse events or mania/hypomania

in bipolar disorder[76].

Schizophrenia and states at risk for psychosis

As an adjunctive treatment for people with schizophrenia, the effect of omega-3 (2-3 g/day of EPA) fell short of statistical significance for total symptom scores (N=335, n=7, SMD=0.242, 95% CI: –0.028 to 0.512, p=0.08, I^2=33.8%)[55]. Omega-3 supplements revealed no significant effects on depressive symptoms in people with schizophrenia (N=264, n=4, SMD=0.14, 95% CI: –0.11 to 0.39, p=0.28, I^2=8%)[59].

Three trials (N=512) examining the impact of omega-3 (1,200-1,400 mg/day) as a monotherapy to prevent transition to psychosis in young people meeting "at risk" criteria showed no indication of benefit (all p>0.1) compared to placebo over 26 weeks (OR=0.64, 95% CI: 0.15-2.68) or 52 weeks (OR=0.64, 95% CI: 0.18-2.26)[60].

In youth at risk of psychosis, PUFA supplements were also ineffective for reducing attenuated psychotic symptoms (N=347, n=3, SMD=0.31, 95% CI: –0.26 to 0.88, I^2=80%)[61], negative symptoms (N=347, n=3, SMD=0.06, 95% CI: –0.35 to 0.46, I^2=63%)[62], and functional disability (N=252, n=2, SMD=-0.08, 95% CI: –0.33 to 0.17)[63] over 52 weeks. Similar null effects were also observed over shorter (i.e., 12 and 26 week) time frames[61-63].

Examination of safety profiles found that EPA was well tolerated in psychotic disorders and did not cause adverse effects other than mild gastrointestinal upset[55]. In the at-risk groups, trial attrition in omega-3 treatment conditions was no different to the placebo control conditions[60].

ADHD

In young people and children with ADHD, overall analyses of any PUFA supplementation (including any omega-3 and omega-6 supplements, at varying doses) showed significant effects beyond placebo for composite ADHD symptom scores (N=1,689, n=18, SMD=0.192, 95% CI: 0.086-0.297, p<0.001, I^2=19.3%)[77]. However, after adjusting for publication bias, the effects of PUFAs on composite symptom scores fell short of significance (SMD=0.118, 95% CI: –0.014 to 0.250, p=0.08).

Across the 16 RCTs reporting on ADHD symptom domains, significant benefits were observed for both hyperactivity/impulsivity (SMD=0.209, 95% CI: 0.059-0.358, p=0.006) and inattention (SMD=0.162, 95% CI: 0.047-0.276, p=0.006)[77]. Subgroup analyses revealed that significant benefits from PUFAs were only observed on parent-rated measures, with no effects on teacher/clinician rated measures of overall symptoms, hyperactivity/impulsivity or inattention[77]. A subsequent analysis using stricter inclusion criteria of RCTs (and excluding data from trials with less than 50 participants) found no benefits of PUFA supplementation on teacher-rated measures of ADHD symptoms (N=287, n=3, SMD=0.08, 95% CI: –0.32 to 0.47, p=0.56, I^2=0%), and the benefits for parent-rated measures also fell short of statistical significance (N=411, n=4, SMD=0.32, 95% CI: –0.15 to 0.8, p=0.098, I^2=52.4%).

Omega-3 supplements (120-2,513 mg/day; mean: 616 mg/day) reduced composite symptom scores in ADHD significantly more than placebo (N=1,408, n=16, SMD=0.26, 95% CI: 0.15-0.37, p<0.001, I^2=25%)[79]. Although still statistically significant, the magnitude of benefit was negligible when applying a trim and fill analysis to adjust for publication bias (SMD=0.16, 95% CI: 0.03-0.28). Similar small effects were observed for both symptom domains of hyperactivity-impulsivity (SMD=0.26, 95% CI: 0.13-0.39, p<0.001) and inattention (SMD=0.22, 95% CI: 0.1-0.34, p<0.001). Subsequent analyses (although including fewer trials) replicated these findings of small but significant effects of omega-3 supplements on composite scores, hyperactivity-impulsivity and inattention symptoms[80].

With regards to behavioural comorbidities, there was no indication of effects of omega-3 on emotional lability, conduct problems or aggression in young people with ADHD[80]. Only effects on parent-rated oppositional behaviour approached significance in primary analyses (SMD=0.2, 95% CI: 0.03-0.38, p=0.02, I^2=0.2%). A trend for a positive effect on parent-rated oppositional behaviour was also observed when applying strict inclusion criteria (SMD=0.15, 95% CI: –0.006 to 0.31, p=0.06, I^2=8%), and when examining only high-quality trials (SMD=0.2, 95% CI: 0.03-0.38, p=0.02, I^2=0.2%).

As to cognitive dysfunction, the only positive effects of omega-3 in young people with ADHD were observed in individual task scores for errors of omission (N=214, n=3, SMD=1.09, 95% CI: 0.43-1.75, p=0.001, I^2=75%) and errors of commission (N=85, n=2, SMD=2.14, 95% CI: 1.24-3.03, p<0.001, I^2=63%)[81]. A positive trend was detected for composite scores of working memory (N=506, n=3, SMD=0.23, 95% CI: –0.001 to 0.46, p=0.05, I^2=33.9%)[82] and individual task scores for backward memory (N=224, n=2, SMD=0.37, 95% CI: –0.05 to 0.79, p=0.08, I^2=55%).

Omega-3 conferred no benefits in tasks of forward memory (N=224, n=2, SMD=0.06, 95% CI: –0.21 to 0.34, p=0.66, I^2=0%) and information processing (N=309, n=4, SMD=0.46, 95% CI: –0.29 to 1.21, p=0.23, I^2=89%)[81], and did not produce any improvements in composite cognitive scores for overall IQ (N=247, n=3, SMD=0.05, 95% CI: –0.21 to 0.32, p=0.71, I^2=0%), inhibition (N=274, n=5, SMD=–0.12, 95% CI: –0.44 to 0.2, p=0.47, I^2=42.8%), attention (N=267, n=5, SMD=–0.12, 95% CI: –0.33 to 0.1, p=0.28, I^2=0%), short-term memory (N=567, n=4, SMD=0.03, 95% CI: –0.10 to 0.16, p=0.64, I^2=0%), reading (N=622, n=4, SMD=0.01, 95% CI: –0.09 to 0.12, p=0.79, I^2=0%), spelling (N=260, n=3, SMD=0.03, 95% CI: –0.34 to 0.40, p=0.89, I^2=48.9%), or reaction time (N=260, n=5, SMD=0.09, 95% CI: –0.13 to 0.3, p=0.44, I^2=0%)[82].

Amino acids

N-acetylcysteine

N-acetylcysteine is the nutraceutical form of the amino acid cysteine, found in abundance in high protein foods, and acts

as a precursor to glutathione, which has antioxidant activity throughout the body.

It has been the most commonly assessed amino acid supplement across mental disorders. In a mixed sample of 574 psychiatric patients with high levels of depression (comorbid or primary), adjunctive treatment (2-3 g/day) significantly reduced depressive symptoms (n=5, SMD=0.37, 95% CI: 0.19-0.55, p=0.001, I^2=92.64%), but had no effects on perceived quality of life (N=543, n=4, SMD=0.14, 95% CI: –0.04 to 0.32, p=0.14, I^2=68%)[72]. There was high heterogeneity between studies, but no evidence of publication bias.

In people with mood disorders (including bipolar disorder and MDD; N=493, n=3), N-acetylcysteine at 2-3 g/day had small but significant effects compared to placebo on global functioning (SMD=0.19, 95% CI: 0.01-0.39, p=0.04, I^2=64%) and social functioning (SMD=0.22, 95% CI: 0.03-0.41, p=0.02, I^2=67%). It also significantly improved other measures of functional impairment (SMD=0.31, 95% CI: 0.12-0.50, p=0.002, I^2=86%)[72].

Across three RCTs in people with schizophrenia (N=247), adjunctive treatment with N-acetylcysteine significantly reduced total symptom scores (SMD=0.74, 95% CI: 0.06-1.43, p=0.03). Although included trials were rated as high-quality, the overall strength of evidence was weak due to high risk of publication bias and significant heterogeneity in existing data (I^2=84%)[56]. Regarding symptom subgroups, there was a non-significant trend indication of beneficial effects on negative symptoms (SMD=0.59, 95% CI: –0.10 to 2.00, p=0.08, I^2=93%), but no effects beyond placebo for positive symptoms (SMD=0.16, 95% CI: –0.29 to 0.62, p=0.48, I^2=66%) or general symptomatology (SMD=0.2, 95% CI: –0.21 to 0.62, p=0.34, I^2=59%)[56].

As an adjunctive treatment for individuals with bipolar disorder (N=224, n=2), 2 g/day N-acetylcysteine did not differ from placebo in its impact on overall illness severity (Clinical Global Impression - Severity, CGI-S: SMD=0.11, 95% CI: –0.15 to 0.37, p=0.42, I^2=90%, and Clinical Global Impression - Improvement, CGI-I: SMD=0.16, 95% CI: –0.09 to 0.42, p=0.22, I^2=0%) or mania ratings (N=224, n=2, SMD=0.05, 95% CI: –0.2 to 0.31, p=0.68, I^2=0.01%)[72]. N-acetylcysteine was also found to be ineffective on depressive symptoms in people with bipolar disorder (N=124, n=2, SMD=0.59, 95% CI: –0.3 to 1.48, p=0.19, I^2=83%)[56].

In 155 individuals with OCD taking concomitant medications (mostly SSRIs), 2-3 g/day N-acetylcysteine produced a trend-level effect towards reduction in obsessive-compulsive symptoms (n=4, SMD=0.295, 95% CI: –0.018 to 0.608, p=0.064, I^2=65%)[74]. N-acetylcysteine (2-2.4 g/day) also had no significant effects on symptoms of anxiety in a pooled mixed psychiatric sample (N=319, n=2, SMD=0.03, 95% CI: –0.21 to 0.28, p=0.80, I^2=0%)[72].

Across all the above disorders, the rates of discontinuation and severe adverse events from N-acetylcysteine supplementation did not differ significantly from the placebo conditions[56,72,74]. There was no significant difference in rates of mild adverse events (particularly with regards to gastrointestinal upset) in people with schizophrenia (N=186, n=2, OR=1.56, 95% CI: 0.87-2.80, p=0.14, I^2=0)[56], but N-acetylcysteine supplementation was associated with higher rates of mild adverse events in mood disorders (N=574, n=5, OR=1.61, 95% CI: 1.01-2.59, p=0.049)[72].

N-methyl-D-aspartate receptor modulators

The amino acids sarcosine and glycine (which occur naturally in meat, dairy and legumes) have also been assessed as adjunctive treatments for schizophrenia, due to their potential action as N-methyl-D-aspartate (NMDA) receptor modulators[57]. Neither sarcosine (at 2 g/day) or glycine (at 2.8-60 g/day) had any effect on positive symptoms, although both did significantly reduce total psychopathology as an adjunctive to antipsychotic treatment (sarcosine: N=132, n=4, SMD=0.41, 95% CI: 0.06-0.76, p=0.02, I^2 not reported; glycine: N=159, n=6, SMD=0.66, 95% CI: 0.04-1.28, p=0.04, I^2 not reported)[57].

The effects on negative symptoms fell short of statistical significance (sarcosine: N=132, n=4, SMD=0.32, 95% CI: –0.03 to 0.66, p=0.07; glycine: N=268, n=7, SMD=0.39, 95% CI: –0.11 to 0.9, p=0.13)[57]. However, significant benefits for negative symptoms were observed in individuals treated with non-clozapine antipsychotics (sarcosine: N=112, n=3, SMD=0.39, p=0.04; glycine: N=219, n=5, SMD=0.60, p=0.05; CIs and I^2 not provided)[57].

As an adjunctive to clozapine treatment (N=58, n=3)[58], glycine was ineffective for positive (SMD=0.63, 95% CI: –0.21 to 1.48, I^2 not reported), negative (SMD=0.03, 95% CI: –0.51 to 0.57, I^2 not reported) and total symptoms scores (SMD=0.32, 95% CI: –0.2 to 0.84, I^2 not reported). No eligible data were available for effects of sarcosine as an adjunctive to clozapine.

Prebiotics and probiotics

No meta-analyses on the effects of prebiotics or probiotics in mental disorders were identified in our search. However, in groups of individuals with mild to moderate depression (as determined by thresholds on clinically validated scales), probiotic treatments of varying strains and doses reduced depressive symptoms significantly more than placebo (N=163, n=3, SMD= 0.684, 95% CI: 0.0712-1.296, p=0.029)[71].

DISCUSSION

This meta-review aggregated and evaluated all the recent top-tier evidence from meta-analyses of RCTs examining the efficacy and safety of nutritional supplements in mental disorders. We identified 33 eligible meta-analyses published from 2012 onwards (26 since 2016), with primary analyses including 10,951 individuals with psychiatric conditions (specifically depressive disorders, anxiety and stress-related disorders, schizophrenia, states at risk for psychosis, bipolar disorder and ADHD), randomized to either nutritional supplementation (including omega-3 fatty acids, vitamins, minerals, N-acetylcysteine and other amino acids) or placebo control conditions. Although the major-

ity of nutritional supplements assessed did not significantly improve mental health outcomes beyond control conditions (see Figures 2-7), some of them did provide efficacious adjunctive treatment for specific mental disorders under certain conditions.

The nutritional intervention with the strongest evidentiary support is omega-3, in particular EPA. Multiple meta-analyses have demonstrated that it has significant effects in people with depression, including high-quality meta-analyses with good confidence in findings as determined by AMSTAR-2[64]. Meta-analytic data have shown that omega-3 is effective when given adjunctively to antidepressants[51,64]. As a monotherapy intervention, the data are less compelling for omega-3, while DHA or DHA-predominant formulas do not appear to show any obvious benefit in MDD[51,64].

Omega-3 supplementation appears to be of greatest benefit when administered as high-EPA formulas, as significant relationships between EPA dosage and effect sizes are also observed in high-quality meta-analyses of RCTs[59,64]. Emergent data from RCTs further indicate that omega-3 may be most beneficial for patients presenting with raised inflammatory markers[83]. The available meta-analyses suggest that omega-3 supplementation is not effective in patients with depression as a comorbidity to chronic physical conditions[65], including cardiometabolic diseases, a finding which has been replicated in subsequent trials[84]. In light of current adverse event data, omega-3 seems to represent a safe adjunctive treatment.

More research is needed concerning the efficacy of omega-3 supplements in other mental health conditions. For instance, omega-3 was indicated as potentially beneficial for children with ADHD, again with high EPA formulas conferring largest effects[79]. However, the negligible effect sizes after controlling for publication bias, along with the low review quality identified by AMSTAR-2, reduces confidence in findings. Additionally, whereas the existing meta-analytic data have found a lack of significant benefits in people with schizophrenia[55,59], subsequent trials in young people with first-episode psychosis have reported more positive, though mixed, results[85,86], putatively ascribed to neuroprotective effects[87,88].

Adjunctive treatment with folate-based supplements was found to significantly reduce symptoms of MDD and negative symptoms in schizophrenia[54,67]. However, in both cases, AMSTAR-2 ratings indicated low confidence in review findings, and positive overall effects in these meta-analyses were driven largely by RCTs of high-dose (15 mg/day) methylfolate. Methylfolate is readily absorbed, overcoming any genetic predispositions towards folic acid malabsorption, and successfully crossing the blood-brain barrier[89,90]. Indeed, a placebo-controlled trial of methylfolate in schizophrenia reported significant increases in white matter within just 12 weeks, co-occurring with a reduction in negative symptoms[91].

RCTs not captured in our meta-review[92] and retrospective chart analyses[93] have further indicated benefits of methylfolate supplementation in other mental disorders. Considering this, alongside the lack of detrimental side effects (in fact, significantly fewer adverse events in samples receiving treatment compared to placebo[54]), further research on methylfolate as an adjunctive treatment for mental disorders is warranted.

Regarding other vitamins (such as vitamin E, C or D), minerals (zinc and magnesium) or inositol, there is currently a lack of compelling evidence supporting their efficacy for any mental disorder, although the emerging evidence concerning positive effects for vitamin D supplementation in major depression has to be mentioned.

Beyond vitamins, minerals and omega-3 fatty acids, certain amino acids are now emerging as promising adjunctive treatments in mental disorders. Although the evidence is still nascent, N-acetylcysteine in particular (at doses of 2,000 mg/day or higher) was indicated as potentially effective for reducing depressive symptoms and improving functional recovery in mixed psychiatric samples[72]. Furthermore, significant reductions in total symptoms of schizophrenia have been observed when using N-acetylcysteine as an adjunctive treatment, although with substantial heterogeneity between studies, especially in study length (in fact, N-acetylcysteine has a very delayed onset of action of about 6 months[56,94]).

N-acetylcysteine acts as a precursor to glutathione, the primary endogenous antioxidant, neutralizing cellular reactive oxygen and nitrogen[95]. Glutathione production in astrocytes is rate limited by cysteine. Oral glutathione and L-cysteine are broken down by first-pass metabolism, and do not increase brain glutathione levels, unlike oral N-acetylcysteine, which is more easily absorbed, and has been shown to increase brain glutathione in animal models[96]. Additionally, N-acetylcysteine has been shown to increase dopamine release in animal models[96].

N-acetylcysteine may assist in treatment of schizophrenia, bipolar disorder and depression through decreasing oxidative stress and reducing glutamatergic dysfunction[96], but has wider preclinical effects on mitochondria, apoptosis, neurogenesis and telomere lengthening of uncertain clinical significance.

NMDA receptors are activated by binding D-serine or glycine[97]. Sarcosine is a naturally occurring glycine transport inhibitor and can act as a co-agonist of NMDA[98]. As such, D-serine, glycine and sarcosine may improve psychotic symptoms through NDMA modulation[99]. We found reductions in total psychotic symptoms, but not negative symptoms, with glycine and sarcosine. Additionally, we found that glycine was not effective in combination with clozapine. This may be because clozapine already acts as a NMDA receptor glycine site agonist[97].

The role of the gut microbiome in mental health is also a rapidly emerging field of research[99]. Gut microbiota differs significantly between people with mental disorders and healthy controls, and recent faecal transplant studies using germ-free mice indicate that these differences could play a causal role in symptoms of mental illness[41,100,101]. Intervention trials that aim to investigate the effect of probiotic formulations on clinical outcomes in mental disorders are now beginning to emerge[71]. We included one recent meta-analysis that evaluated the pooled effect of probiotic interventions on depressive symptoms: while the primary analysis reported no significant effect, the moderately large effect in the three included studies suggests that

probiotics may be beneficial for those with a clinical diagnosis of depression rather than subclinical symptoms[71]. However, additional trials are required to replicate these results, to evaluate the long-term safety of probiotic interventions, and to elucidate the optimal dosing regimen and the most effective prebiotic and probiotic strains[102].

While this meta-review has highlighted potential roles for the use of nutrient supplements, this should not be intended to replace dietary improvement. The poor physical health of people with mental illness is well documented[103], and excessive and unhealthy dietary intake appears to be a key factor involved[4,5]. Improved diet quality is associated with reduced all-cause mortality[104]. whereas multivitamin and multimineral supplements may not improve life expectancy[18-20].

A meta-analysis of dietary interventions in people with severe mental illness found benefits on a number of physical health aspects[105]. It is unlikely that standard nutrient supplementation will be able to cover all beneficial aspects of improved dietary intake. In addition, whole foods may contain vitamins and minerals in different forms, whereas nutrient supplements may only provide one form. For example, vitamin E occurs naturally in eight forms, but nutrient supplements may only provide one form. Dietary interventions also reduce dietary elements in excess, such as salt, which is a key driver of premature mortality[13].

While improving dietary intake appears to have a clear role in increasing life expectancy and preventing chronic disease, there is currently a lack of studies evaluating this in people with mental disorders. Additionally, although recent meta-analyses of RCTs have demonstrated that dietary improvement reduces symptoms of depression in the general population[106], more well-designed studies are needed to confirm the mental health benefits of dietary interventions for people with diagnosed psychiatric conditions[25].

Our data should be considered in the light of some limitations. First, although meta-analyses of RCTs typically constitute the top-tier of evidence, it is important to acknowledge that many of the outcomes included in this meta-review had significant amounts of heterogeneity between the included studies, or were based on a small number of studies. A next step within this field of research is to move from study-level to patient-level meta-analyses, as this would provide a more personalized picture of the effects of nutrient supplements derived from adequately powered moderator, mediator and subgroup analyses. Additionally, comparing nutrient supplements in the same trial would be desirable.

It is recognized that people with mental disorders commonly take nutritional supplements in combinations. In some instances, research has supported this approach, most commonly in the form of multivitamin/mineral combinations[107]. However, recent research in the area of depression has revealed that "more is not necessarily better" when it comes to complex formulations[108]. Of note, recent large mood disorder clinical trials have revealed that nutrient combinations may not have a more potent effect, and in some cases placebo has been more effective[47,108,109].

In conclusion, there is now a vast body of research examining the efficacy of nutrient supplementation in people with mental disorders, with some nutrients now having demonstrated efficacy under specific conditions, and others with increasingly indicated potential. There is a great need to determine the mechanisms involved, along with examining the effects in specific populations such as young people and those in early stages of illness. A targeted approach is clearly warranted, which may manifest as biomarker-guided treatment, based on key nutrient levels, inflammatory markers, and pharmacogenomics [83,91,110].

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The efficacy of app-supported smartphone interventions for mental health problems: a meta-analysis of randomized controlled trials

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Although impressive progress has been made toward developing empirically-supported psychological treatments, the reality remains that a significant proportion of people with mental health problems do not receive these treatments. Finding ways to reduce this treatment gap is crucial. Since app-supported smartphone interventions are touted as a possible solution, access to up-to-date guidance around the evidence base and clinical utility of these interventions is needed. We conducted a meta-analysis of 66 randomized controlled trials of app-supported smartphone interventions for mental health problems. Smartphone interventions significantly outperformed control conditions in improving depressive (g=0.28, n=54) and generalized anxiety (g=0.30, n=39) symptoms, stress levels (g=0.35, n=27), quality of life (g=0.35, n=43), general psychiatric distress (g=0.40, n=12), social anxiety symptoms (g=0.58, n=6), and positive affect (g=0.44, n=6), with most effects being robust even after adjusting for various possible biasing factors (type of control condition, risk of bias rating). Smartphone interventions conferred no significant benefit over control conditions on panic symptoms (g=–0.05, n=3), post-traumatic stress symptoms (g=0.18, n=4), and negative affect (g=–0.08, n=5). Studies that delivered a cognitive behavior therapy (CBT)-based app and offered professional guidance and reminders to engage produced larger effects on multiple outcomes. Smartphone interventions did not differ significantly from active interventions (face-to-face, computerized treatment), although the number of studies was low (n≤13). The efficacy of app-supported smartphone interventions for common mental health problems was thus confirmed. Although mental health apps are not intended to replace professional clinical services, the present findings highlight the potential of apps to serve as a cost-effective, easily accessible, and low intensity intervention for those who cannot receive standard psychological treatment.

Key words: App-supported smartphone interventions, mental health problems, depression, anxiety, general psychiatric distress, positive affect, psychological treatments

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The treatment of mental health problems is expected to change considerably over the next few decades as a result of the widespread availability of Internet and mobile-device applications, and their use to deliver psychological interventions[1,2]. This change is predicted to alleviate many barriers that stand in the way of people seeking or receiving treatment under the current model of health care delivery (e.g., insufficient number of trained professionals, geographical constraints, lack of anonymity), thereby vastly increasing the availability of psychological therapies[3,4].

Smartphone interventions, in particular, offer many advantages over other digital interventions (e.g., computer-based), including their ability to allow users to engage in exercises and monitor symptoms *in situ*, in real time, and immediately before and after pivotal events, as well as their capacity to be accessed in private and at a time and location of choice[5]. However, some have noted possible risks with app-based smartphone interventions, a crucial one being the ease with which users may have access to potentially ineffective or harmful interventions[6]. Thus, practitioners and the general population need up-to-date guidance on the evidence base and clinical utility of app-supported smartphone interventions.

The efficacy of smartphone interventions for common and costly mental health problems, such as depressive and anxiety symptoms, was preliminarily documented in two recent meta-analyses. Firth et al[7,8] identified a small number of randomized controlled trials (RCTs) that examined the efficacy of app-based smartphone interventions on symptoms of anxiety (n=9) and depression (n=18) in both clinical and non-clinical samples. Smartphone interventions were found to be significantly more efficacious in reducing symptoms of anxiety and depression than both waitlist (g=0.45 and g=0.56) and active control (mainly attention/placebo-based) groups (g=0.19 and g=0.21). The authors found no evidence that various intervention features (e.g., in-app feedback, mood monitoring features, theoretical orientation) were significantly associated with effect sizes, although larger effects were observed when in-person feedback was not provided[7]. Preliminary findings from these meta-analyses suggest that app-supported smartphone interventions have potential in treating and preventing certain common and debilitating mental health problems.

Since the publication of those two meta-analyses, which included data from RCTs published until May 2017, nearly 50 RCTs evaluating the efficacy of smartphone apps on various mental health outcomes have been conducted. Since most RCTs of smartphone apps have been published within the last couple of years, and interventions delivered through smartphone devices are attracting enormous public, scientific and media attention[9], we expect that a significant number of additional RCTs will be conducted and published in the near future.

It is therefore timely, pertinent and necessary to conduct an updated meta-analysis examining the efficacy of app-supported smartphone interventions not only on symptoms of anxiety and depression, but also on other prevalent, costly and important mental health outcomes not examined in prior meta-analyses, including stress levels, specific anxiety symptoms

(e.g., social anxiety, post-traumatic stress) and well-being/quality of life.

The aims of the present meta-analysis of RCTs were to evaluate the efficacy of app-supported smartphone interventions on a range of mental health outcomes, and to examine whether various features related to the intervention (theoretical orientation, whether professional guidance was offered, whether reminders to engage were sent) and sample (degree of mental health problem) moderated the observed effect sizes.

METHODS

Search strategy and study selection

We searched four major online databases (Medline, PsycINFO, Cochrane databases, Web of Science) in December 2018, using the search terms ("smartphone*" OR "mobile phone" OR "cell phone" OR "mobile app*" OR "iphone" OR "android" OR "mhealth" OR "m-health" OR "cellular phone" OR "mobile device*" OR "mobile-based" OR "mobile health" OR "tablet-based") AND ("random*" OR "trial*" OR "allocat*") AND ("anxiety" OR "agoraphobia" OR "phobia*" OR "panic" OR "post-traumatic stress" OR "mental health" OR "mental illness*" OR "depress*" OR "affective disorder*" OR "bipolar" OR "mood disorder*" OR "psychosis" OR "psychotic" OR "schizophre*" OR "well-being" OR "wellbeing" OR "quality of life" OR "self-harm" or "self-injury" OR "stress*" OR "distress*" OR "mood" OR "body image" OR "eating disorder*"). Reference lists of included studies and previous reviews were also hand-searched to identify any further eligible studies.

A protocol for this review was registered via PROSPERO (CRD42019122136). There were three small deviations to the original protocol. First, we made a *post-hoc* decision to include rather than exclude studies that incorporated an app-supported smartphone intervention within a broader treatment program (e.g., additive or adjunctive designs). Second, we did not conduct meta-analyses of head-to-head comparisons of CBT vs. non-CBT-based apps, as there was an insufficient number of relevant studies. Third, we included an additional moderator, i.e. whether the smartphone intervention was directly aimed at targeting the specific symptom of interest.

Included studies were English language RCTs that examined the effects of an app-supported smartphone intervention, compared to either a control condition or an active intervention, and provided the outcome data required to calculate an effect size.

Both published and unpublished RCTs were eligible for inclusion. Provided the smartphone intervention was designed

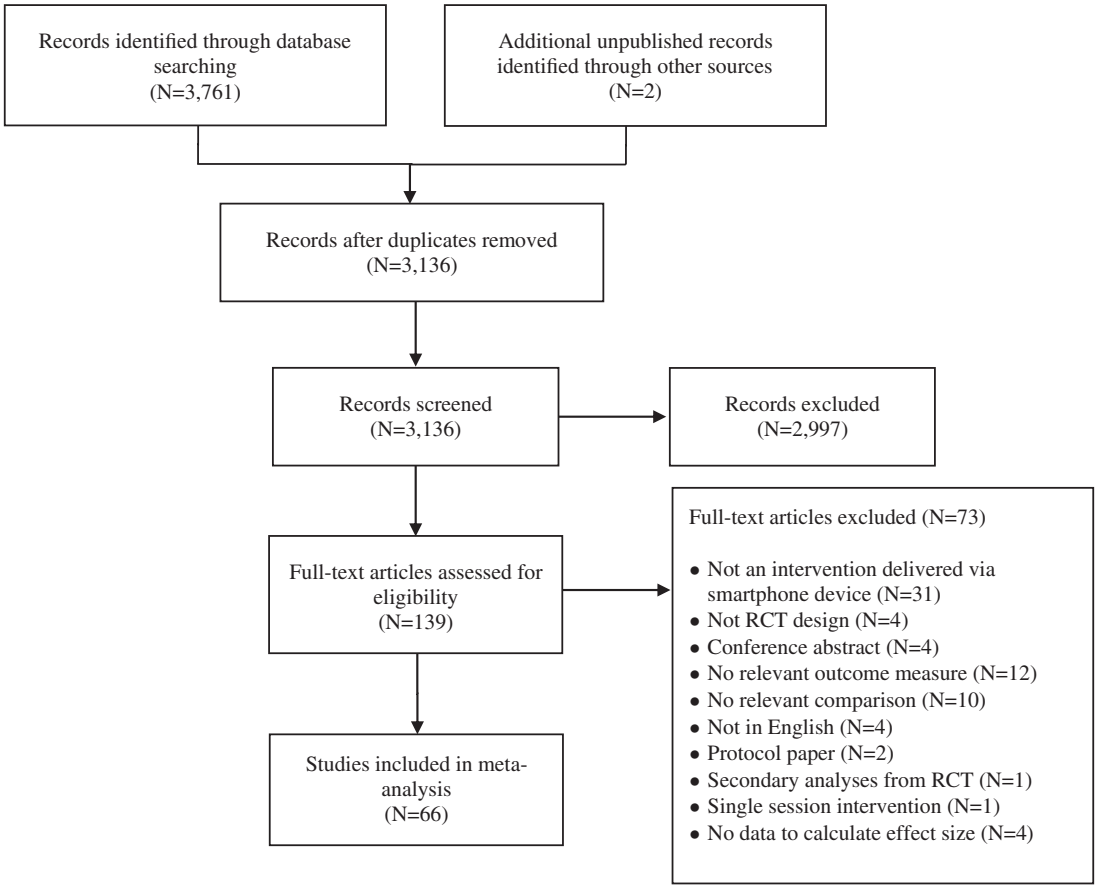

Figure 1 PRISMA flow chart of literature search. RCT – randomized controlled trial

Table 1 Meta-analysis of efficacy of mental health smartphone apps on depressive and generalized anxiety symptoms

	Depressive symptoms				Generalized anxiety symptoms			
	N	g (95% CI)	I^2 (95% CI)	Q	N	g (95% CI)	I^2 (95% CI)	Q
Smartphone vs. controls								
Overall effect	54	0.28 (0.21-0.36)***	54% (38-66)		39	0.30 (0.20-0.40)***	63% (48-73)	
Adjusted for publication bias	37	0.41 (0.32-0.49)			31	0.39 (0.28-0.49)		
Sensitivity analysis								
One effect size per study (smallest)	41	0.28 (0.18-0.37)***	58% (40-70)		28	0.31 (0.18-0.43)***	69% (54-78)	
One effect size per study (largest)	41	0.37 (0.29-0.44)***	41% (15-59)		28	0.38 (0.27-0.49)***	64% (46-75)	
Low risk of bias only (all criteria met)	13	0.43 (0.31-0.55)***	41% (0-68)		7	0.56 (0.39-0.74)***	56% (5-80)	
Control condition type								
Waitlist	34	0.32 (0.22-0.42)***	52% (28-67)		28	0.32 (0.19-0.44)***	63% (45-75)	
Informational resources	8	0.39 (0.21-0.58)***	60% (17-80)		3	0.51 (0.14-0.88)**	72% (17-90)	
Attentional/placebo control	11	0.12 (0.01-0.23)*	6% (0-31)		8	0.18 (0.07-0.29)**	7% (0-20)	
Subgroup analyses								
Target sample				0.151				0.358
Elevated symptoms entry criteria	13	0.38 (0.23-0.52)***	61% (30-78)		10	0.36 (0.25-0.47)***	0% (0-58)	
Elevated symptoms not entry criteria	41	0.24 (0.16-0.33)***	50% (28-64)		29	0.28 (0.15-0.41)***	70% (57-79)	
Smartphone intervention target				0.728				0.319
Directly aimed at targeting this outcome	16	0.26 (0.11-0.41)***	71% (52-82)		12	0.24 (0.09-0.38)**	44% (0-69)	
Not directly aimed at targeting this outcome	38	0.29 (0.21-0.38)***	43% (16-61)		27	0.33 (0.21-0.46)***	68% (53-78)	
CBT-based app				0.125				**0.011**
Yes	26	0.34 (0.23-0.46)***	64% (46-76)		16	0.42 (0.26-0.57)***	76% (57-100)	
No	27	0.23 (0.14-0.32)***	22% (0-50)		23	0.19 (0.11-0.27)***	0% (0-43)	
Contains mindfulness components				0.359				0.952
Yes	28	0.33 (0.24-0.41)***	24% (0-50)		24	0.30 (0.20-0.41)***	43% (8-64)	
No	25	0.25 (0.12-0.39)***	68% (51-78)		15	0.29 (0.10-0.49)**	77% (63-86)	
ACT-based app				0.903				0.967
Yes	9	0.30 (0.08-0.53)**	33% (0-66)		8	0.30 (0.11-0.49)**	1% (0-10)	
No	44	0.28 (0.20-0.37)***	57% (39-68)		31	0.30 (0.19-0.41)***	69% (55-78)	
Reminders to engage provided				0.065				**0.004**
Yes	34	0.32 (0.22-0.42)***	61% (43-72)		23	0.39 (0.27-0.52)***	63% (42-76)	
No	20	0.18 (0.08-0.29)**	16% (0-45)		16	0.15 (0.04-0.26)*	18% (0-50)	
Professional guidance provided				**0.002**				**0.001**
Yes	15	0.48 (0.34-0.62)***	46% (4-69)		12	0.53 (0.36-0.70)***	60% (26-78)	
No	37	0.23 (0.15-0.31)***	32% (0-54)		27	0.21 (0.12-0.30)*	36% (0-59)	
Duration of post-assessment				**<0.001**				**<0.001**
2-6 weeks	33	0.17 (0.08-0.26)***	30% (0-53)		24	0.11 (0.02-0.21)*	12% (0-41)	
7-11 weeks	18	0.46 (0.36-0.55)***	45% (3-66)		15	0.52 (0.41-0.63)***	44% (0-68)	
12+ weeks	3	0.09 (–0.23 to 0.42)	49% (0-80)		0	-		
Apps vs. active comparison								
Overall effect	12	0.13 (–0.07 to 0.34)	60% (27-78)		4	0.09 (–0.21 to 0.39)	32% (0-68)	
Low risk of bias trials only	4	–0.00 (–0.36 to 0.35)	77% (41-90)		0	-	-	

Table 1 Meta-analysis of efficacy of mental health smartphone apps on depressive and generalized anxiety symptoms *(continued)*

	Depressive symptoms				Generalized anxiety symptoms			
	N	**g (95% CI)**	**I^2 (95% CI)**	**Q**	**N**	**g (95% CI)**	**I^2 (95% CI)**	**Q**
Smartphones as an adjunct intervention	4	0.26 (–0.09 to 0.61)	71% (26-89)		1	0.05 (–0.27 to 0.38)	0%	

N – number of comparisons, CBT– cognitive behavior therapy, ACT – acceptance and commitment therapy
*p<0.05, **p<0.01, ***p<0.001. Bold prints indicate significant differences

to improve mental health or general well-being, no restrictions on the samples were applied. Trials of interventions delivered only in part via smartphone devices were also included, such as adjunctive designs (smartphone app + standard therapy vs. standard therapy alone) or blended intervention programs (when participants could access the app-based intervention via smartphones or computers).

Control conditions were categorized as waitlist, assessment only, treatment as usual, informational and educational resources (e.g., website links, health tips), or attention/placebo controls (e.g., gaming apps, music-listening conditions). Active interventions were categorized as standard face-to-face therapy, web-based or computerized interventions, pharmacotherapy, and self-monitoring conditions.

Studies were excluded if: a) the smartphone intervention did not address mental health or well-being (e.g., interventions focusing on weight loss, physical activity, diabetes management, smoking cessation or alcohol use were excluded); b) a computerized intervention, a virtual reality exposure treatment, or a text messaging-only intervention was delivered; and c) there was no relevant comparison condition (e.g., a two-arm trial comparing two apps was excluded) or no outcome measure was reported. If a study did not include data for effect size calculation, the authors were contacted, and the study was excluded if they failed to provide the data.

JL screened all records, and full texts were obtained for potentially eligible RCTs. Two independent assessors (JL and MM) examined the full texts and selected eligible RCTs.

Quality assessment and data extraction

The quality of trials was assessed using four criteria from the Cochrane Risk of Bias tool[10]: adequate generation of allocation sequence, concealment of allocation to conditions; blinding of outcome assessors or the use of self-report questionnaires; and dealing with incomplete outcome data (assessed as low risk when outcome data used to calculate effect size were based on intention-to-treat analyses). JL conducted the quality assessments and MM coded a random 40% of studies, with good agreement observed between raters (kappa = 0.77, 0.69, 1.00 and 0.91, respectively). Disagreements were resolved through in-depth discussion.

We also coded the participant characteristics (target sample, mean age); the characteristics of the smartphone intervention (name, theoretical orientation, whether the app contained mindfulness components); the comparison condition; the outcome measures; and other trial characteristics (sample size, whether guided support or reminders to engage were offered, length of post-assessment).

Meta-analysis

For each comparison between a smartphone intervention and a control or active intervention condition, the effect size was calculated by dividing the difference between the two group means by the pooled standard deviation at post-test. The standardized mean difference (d) was then converted to Hedges' g to correct for small sample bias[11]. If means and standard deviations were not reported, effect sizes were calculated using conversion equations from significance tests (e.g., t statistics).

To calculate a pooled effect size, each study's effect size was weighted by its inverse variance. A positive g indicates that the smartphone condition had better outcomes than the comparison condition. Effect sizes of 0.8 can be assumed to be large, while effect sizes of 0.5 are moderate, and effect sizes of 0.2 are small[12]. If data from both intention-to-treat and completer analyses were presented, the former were extracted and analyzed.

We selected and analyzed the following mental health outcomes, as a sufficient number of trials (≥3) reported these outcomes and allowed for a meta-analysis: depressive symptoms; generalized anxiety symptoms; specific anxiety symptoms (social anxiety symptoms, panic symptoms, post-traumatic stress symptoms); stress levels; quality of life/well-being; general psychological distress; and positive and negative affect. If multiple measures of a given outcome variable were used, the mean of the effect sizes from each measure within the study was calculated, before the effect sizes were pooled.

Comprehensive Meta-Analysis Version 3.0 was used for the analyses[13]. Since we expected considerable heterogeneity among the studies, random effects models were employed. Heterogeneity was examined by calculating the I^2 statistic, which quantifies heterogeneity revealed by the Q statistic and reports how much overall variance (0-100%) is attributed to between-study variance[14]. The 95% confidence intervals (CIs) for the I^2 statistic were also calculated.

Subgroup analyses were conducted to explore sources of heterogeneity under a mixed effects model, which pools studies within a subgroup using a random effects model, but tests for significant differences between subgroups using fixed effects models.

Publication bias was examined through the trim-and-fill procedure[15], as well as Begg and Mazumdar rank correlation test.

Study	Statistics for each study		
	Hedges' g	Variance	p
Bakker et al[16]	-0.213	0.026	0.183
Teng et al[17]	-0.195	0.077	0.481
Krafft et al[18]	-0.182	0.175	0.663
Bakker et al[16]	-0.130	0.025	0.414
Versluis et al[19]	-0.117	0.055	0.618
Kauer et al[20]	-0.108	0.049	0.627
Teng et al[17]	-0.088	0.063	0.725
Krzystanek et al[21]	-0.085	0.030	0.623
Krafft et al[18]	-0.077	0.150	0.841
Faurholt-Jepsen et al[22]	-0.045	0.058	0.852
Enock et al[23]	-0.042	0.013	0.714
Krafft et al[18]	-0.039	0.096	0.899
Oh et al[24]	0.057	0.113	0.864
Ivanova et al[25]	0.071	0.039	0.716
Dennis-Tiwary et al[26]	0.073	0.131	0.839
Versluis et al[19]	0.078	0.058	0.745
Ludtke et al[27]	0.083	0.053	0.718
Arean et al[28]	0.110	0.098	0.725
Carissoli et al[29]	0.126	0.101	0.691
Krafft et al[18]	0.137	0.087	0.641
Flett et al[30]	0.171	0.029	0.317
Mistretta et al[31]	0.195	0.106	0.550
Birney et al[32]	0.197	0.013	0.087
Hirsch et al[33]	0.204	0.050	0.360
Oh et al[24]	0.207	0.111	0.533
Bakker et al[16]	0.225	0.026	0.159
Kuhn et al[34]	0.228	0.033	0.211
Flett et al[30]	0.228	0.027	0.168
Lee & Jung[35]	0.229	0.025	0.143
Moell et al[36]	0.230	0.074	0.397
Guo et al[37]	0.233	0.074	0.392
Boettcher et al[38]	0.296	0.029	0.081
Stolz et al[5]	0.297	0.049	0.180
Cox et al[39]	0.315	0.097	0.312
Roepke et al[40]	0.318	0.077	0.250
Proudfoot et al[41]	0.332	0.013	0.004
Howells et al[42]	0.347	0.033	0.057
Kollei et al[43]	0.390	0.075	0.153
Arean et al[28]	0.417	0.010	0.000
Kahn et al[44]	0.437	0.046	0.041
Proudfoot et al[41]	0.446	0.013	0.000
Bostock et al[45]	0.470	0.019	0.001
Ebert et al[46]	0.528	0.020	0.000
Ebert et al[47]	0.547	0.016	0.000
Horsch et al[48]	0.571	0.027	0.001
Ivanova et al[25]	0.580	0.041	0.004
Ebert et al[49]	0.594	0.016	0.000
Enock et al[23]	0.608	0.044	0.004
Harrer et al[50]	0.625	0.028	0.000
Heber et al[51]	0.639	0.016	0.000
Tighe et al[52]	0.707	0.068	0.007
Roepke et al[40]	0.777	0.087	0.008
Hall et al[53]	0.831	0.112	0.013
Nobis et al[54]	0.855	0.017	0.000
Total pooled effect size	**0.282**	**0.002**	**0.000**

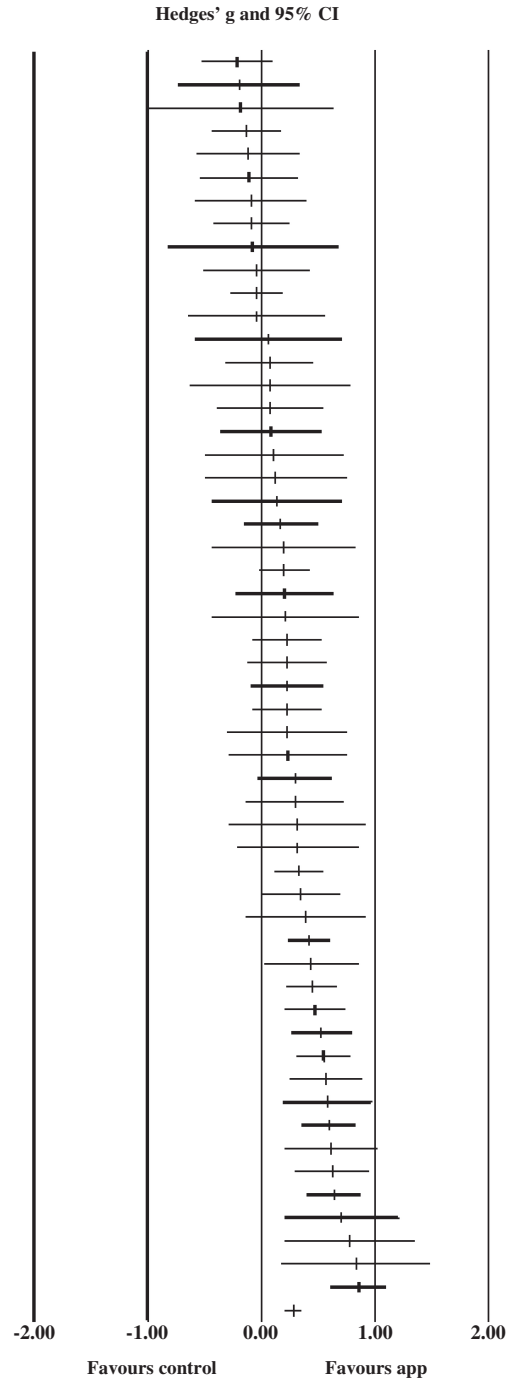

Figure 2 Effect of smartphone apps vs. control conditions on depressive symptoms

RESULTS

Characteristics of included studies

A flow chart of the literature search is presented in Figure 1. Out of a total of 3,136 screened abstracts, 66 RCTs with 77 smartphone intervention conditions were included. A variety of smartphone apps were tested, most of which were based on cognitive and/or behavioral principles (n=35) and/or acceptance- or mindfulness-based principles (n=38).

Numerous trials used some indication of mental health problems as an inclusion criterion for study entry (n=38), which most frequently included those presenting with elevated levels (either at a diagnostic or subthreshold level) of depression (n=14), anxi-

Study	Statistics for each study		
	Hedges' g	Variance	p
Dennis-Tiwary et al[26]	-0.305	0.132	0.401
Bakker et al[16]	-0.234	0.026	0.144
Teng et al[17]	-0.203	0.077	0.465
Krafft et al[18]	-0.187	0.096	0.548
Bakker et al[16]	-0.140	0.025	0.380
Mistretta et al[31]	-0.087	0.106	0.789
Krafft et al[18]	-0.020	0.096	0.950
Krafft et al[18]	0.000	0.175	1.000
Flett et al[30]	0.018	0.029	0.914
Pham et al[55]	0.028	0.062	0.912
Versluis et al[19]	0.047	0.055	0.843
Flett et al[30]	0.081	0.027	0.625
Carissoli et al[29]	0.126	0.101	0.691
Villani et al[56]	0.152	0.006	0.050
Cox et al[39]	0.177	0.096	0.569
Bakker et al[16]	0.179	0.025	0.263
Oh et al[24]	0.182	0.113	0.588
Ebert et al[46]	0.219	0.020	0.117
Moell et al[36]	0.239	0.074	0.380
Ivanova et al[25]	0.273	0.039	0.167
Versluis et al[19]	0.277	0.058	0.250
Roepke et al[40]	0.291	0.076	0.292
Lee & Jung[35]	0.294	0.025	0.061
Oh et al[24]	0.364	0.112	0.276
Proudfoot et al[41]	0.365	0.013	0.001
Bostock et al[45]	0.377	0.019	0.006
Proudfoot et al[41]	0.435	0.013	0.000
Boettcher et al[38]	0.459	0.029	0.007
Teng et al[17]	0.478	0.065	0.060
Ebert et al[47]	0.505	0.016	0.000
Ivanova et al[25]	0.512	0.040	0.011
Roepke et al[40]	0.575	0.084	0.047
Horsch et al[48]	0.647	0.028	0.000
Heber et al[51]	0.677	0.016	0.000
Krafft et al[18]	0.706	0.159	0.077
Harrer et al[50]	0.757	0.028	0.000
Ebert et al[49]	0.792	0.016	0.000
Nobis et al[54]	0.819	0.017	0.000
Hall et al[53]	0.843	0.112	0.012
Total pooled effect size	**0.304**	**0.003**	**0.000**

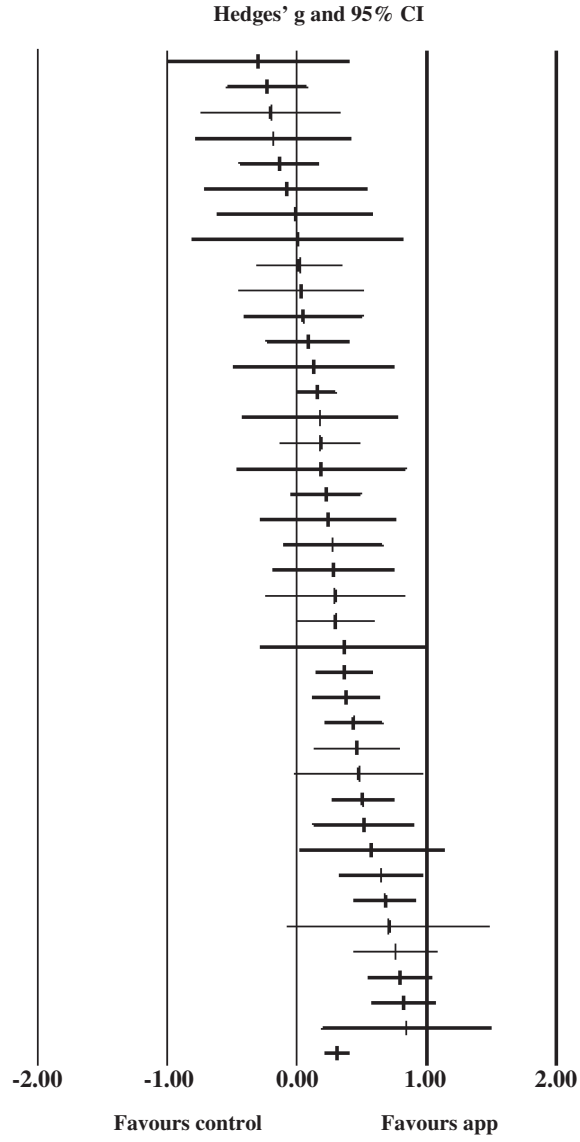

Figure 3 Effect of smartphone apps vs. control conditions on generalized anxiety symptoms

ety (n=9), or stress (n=8). Several trials (n=28) did not use any indication of mental health problems as an inclusion criterion (e.g., general community sample, student samples), but rather targeted general well-being in these samples.

The quality of RCTs varied. Fifty trials (75.7%) reported an adequate sequence generation; 24 (36.4%) used adequate allocation concealment; four (6.1%) reported blinding of outcome assessors and 62 (93.9%) used self-report questionnaires (so that direct interaction with an assessor was not required); and 37 studies (56.1%) reported data needed to calculate an effect size based on the intention-to-treat principle. Seventeen trials (25.7%) met all four criteria, 16 (24.2%) met three criteria, 27 (40.9%) met two criteria, and six trials (9.1%) met one of the criteria.

Efficacy of smartphone interventions on depressive symptoms

Smartphone interventions vs. controls

Depressive symptoms were assessed as an outcome in 47 trials (71.2%), and 11 trials (16 comparisons) delivered an app that was specifically designed to target depressive symptoms.

The pooled effect size for the 54 comparisons between smartphone interventions and control conditions on depressive symptoms was g=0.28 (95% CI: 0.21-0.36), with moderate heterogeneity (see Table 1 and Figure 2). The pooled effect size was somewhat larger when adjusting for potential publication bias

Table 2 Efficacy of mental health smartphone apps on stress levels and quality of life outcomes

	Stress levels				Quality of life			
	N	**g (95% CI)**	**I^2 (95% CI)**	**Q**	**N**	**g (95% CI)**	**I^2 (95% CI)**	**Q**
Smartphone vs. control conditions								
Overall effect	27	0.35 (0.21-0.48)***	69% (55-79)		43	0.35 (0.29-0.42)***	24% (0-47)	
Adjusted for publication bias	22	0.44 (0.30-0.57)	-		37	0.39 (0.32-0.46)		
Sensitivity analysis								
One effect size per study (smallest)	22	0.38 (0.22-0.54)***	72% (58-82)		34	0.36 (0.29-0.44)***	29% (0-53)	
One effect size per study (largest)	22	0.42 (0.28-0.57)***	65% (46-77)		34	0.41 (0.35-0.47)***	0% (0-36)	
Low risk of bias only	4	0.78 (0.63-0.04)***	0% (0-22)		10	0.46 (0.31-0.61)***	50% (1-74)	
Control type								
Waitlist	20	0.47 (0.33-0.62)***	60% (36-75)		37	0.35 (0.28-0.43)***	29% (0-52)	
Informational sources	1	0.06 (–0.32 to 0.44)	0		4	0.41 (0.21-0.61)***	0% (0-84)	
Attentional/placebo control	6	0.09 (–0.05 to 0.24)	0% (0-74)		2	0.23 (0.03-0.42)*	0%	
Subgroup analyses								
Target sample				**0.010**				0.084
Clinical sample	-	-	-		6	0.24 (0.07-0.41)**	0% (0-57)	
Symptomatic/at-risk sample	7	0.59 (0.35-0.83)***	80% (61-90)		12	0.44 (0.33-0.56)***	45% (0-70)	
Non-clinical/non-symptomatic sample	20	0.24 (0.09-0.37)**	45% (9-67)		25	0.31 (0.23-0.39)***	4% (0-46)	
CBT-based app				**0.003**				0.823
Yes	8	0.61 (0.39-0.83)***	77% (56-88)		19	0.37 (0.26-0.48)***	45% (8-67)	
No	19	0.21 (0.07-0.35)**	45% (7-67)		23	0.35 (0.27-0.44)***	0% (0-39)	
Contains mindfulness components				0.371				0.968
Yes	23	0.31 (0.19-0.44)***	58% (33-73)		29	0.36 (0.29-0.43)***	7% (0-33)	
No	4	0.52 (0.09-0.95)*	80% (52-92)		13	0.36 (0.22-0.49)***	48% (4-71)	
ACT-based app				0.252				0.305
Yes	5	0.16 (–0.17 to 0.49)	30% (0-66)		13	0.29 (0.13-0.44)***	15% (0-62)	
No	22	0.38 (0.23-0.52)***	72% (58-82)		29	0.38 (0.31-0.45)***	25% (0-51)	
Reminders to engage provided				0.066				**0.025**
Yes	20	0.41 (0.25-0.57)***	73% (57-82)		29	0.39 (0.32-0.47)***	28% (0-53)	
No	7	0.19 (0.03-0.35)*	1% (0-71)		14	0.24 (0.14-0.35)***	0% (0-41)	
Professional guidance provided				**0.010**				**0.001**
Yes	10	0.57 (0.35-0.79)***	63% (29-80)		13	0.52 (0.39-0.64)***	24% (0-57)	
No	17	0.24 (0.12-0.36)***	42% (0-66)		30	0.29 (0.22-0.35)***	0% (0-21)	
Duration of post-assessment				**<0.001**				0.971
2-6 weeks	19	0.18 (0.06-0.28)**	13% (0-44)		31	0.35 (0.26-0.44)***	30% (0-54)	
7-11 weeks	6	0.63 (0.38-0.88)***	83% (65-91)		11	0.36 (0.26-0.46)***	17% (0-51)	
12+ weeks	2	0.59 (0.35-0.83)***	20% (0-33)		1	0.31 (–0.13 to 0.74)	0%	
Apps vs. active comparisons								
Overall effect	2	0.21 (–0.46 to 0.88)	72% (27-88)		6	0.02 (–0.14 to 0.17)	0% (0-57)	
Low risk of bias trials only	-	-	-		3	–0.08 (–0.27 to 0.12)	0% (0-66)	

N – number of comparisons, CBT– cognitive behavior therapy, ACT – acceptance and commitment therapy
*p<0.05, **p<0.01, ***p<0.001. Bold prints indicate significant differences

Table 3 Meta-analysis comparing the effect of mental health smartphone apps vs. control conditions on other outcomes

Outcome measure	Analysis	N	g (95% CI)	I^2 (95% CI)
General distress				
	Overall effect	12	0.40 (0.24-0.56)***	60% (24-77)
	Low risk of bias trials only	3	0.47 (0.08-0.87)*	70% (15-89)
Social anxiety symptoms				
	Overall effect	6	0.58 (0.25-0.90)***	78% (53-89)
	Low risk of bias trials only	3	0.76 (0.51-1.03)***	0% (0-77)
Panic symptoms				
	Overall effect	3	–0.05 (–0.41 to 0.31)	0% (0-92)
	Low risk of bias trials only	2	0.12 (–0.41 to 0.65)	0%
Post-traumatic stress symptoms				
	Overall effect	4	0.18 (–0.04 to 0.41)	0% (0-86)
	Low risk of bias trials only	0	-	-
Positive affect				
	Overall effect	6	0.44 (0.15-0.73)**	67% (24-85)
	Low risk of bias trials only	1	–0.05 (–0.46 to 0.35)	0%
Negative affect				
	Overall effect	5	–0.08 (–0.48 to 0.32)	76% (45-89)
	Low risk of bias trials only	1	0.26 (–0.14 to 0.67)	0%

*p<0.05; **p<0.01; ***p<0.001

(g=0.41, Begg and Mazumdar test: p=0.087) and when analyzing only low risk of bias trials (g=0.43).

The pooled effect size was small but still statistically significant when attention/placebo control conditions were used (g=0.12), and larger when waitlist (g=0.32) or informational resources (g=0.39) were used as control conditions.

In the previous analyses, we included a few trials in which more than one intervention condition was compared with the same control condition (or vice versa). These comparisons were not independent from each other, which may have artificially reduced the heterogeneity estimate and affected the pooled effect size. To deal with this, we ran sensitivity analyses in which the comparison with the smallest effect size was only included in the analysis, and then repeated this again for the comparison with the largest effect size. These sensitivity analyses ensured that only one comparison per study was included in the meta-analysis. These sensitivity analyses yielded a pooled effect size highly similar to the overall effect (Table 1).

Subgroup analyses

Subgroup analyses were conducted to test whether various participant or trial characteristics were significantly associated with the pooled effect size (Table 1).

Studies that offered professional guidance (e.g., regular supportive text messages, phone calls, or personalized feedback from therapists or research staff) produced larger effect sizes than studies that did not offer guidance. Studies with a follow-up length between 7 and 11 weeks produced larger effect sizes than studies with a follow-up length of 2-6 or ≥12 weeks. No other study characteristics were significantly associated with effect sizes.

Smartphone interventions vs. active comparisons

The pooled effect size for the 12 comparisons between smartphone interventions and active comparisons was g=0.13 (95% CI: –0.07 to 0.34), with moderate heterogeneity. Non-significant effect sizes were observed for low risk of bias trials.

Additive effects of smartphone interventions

Four trials examined whether adding a smartphone intervention to a standard intervention (face-to-face, computerized, pharmacotherapy) was superior to a standard intervention-only condition. The pooled effect size for the four comparisons between smartphone intervention + standard intervention vs. the standard intervention-only arm was g=0.26 (95% CI: –0.09 to 0.61).

Efficacy of smartphone interventions on generalized anxiety symptoms

Smartphone interventions vs. controls

Generalized anxiety symptoms were assessed as an outcome

in 29 studies (43.9%), and eight studies (12 comparisons) delivered an app that was specifically designed to target generalized anxiety symptoms.

The pooled effect size for the 39 comparisons was g=0.30 (95% CI: 0.20-0.40), with high heterogeneity (see Table 1 and Figure 3). It remained statistically significant across all sensitivity analyses. Begg and Mazumdar test was non-significant (p=0.217).

Subgroup analyses

Four statistically significant moderation effects were observed. Larger effect sizes were found by studies that used a CBT-based app, that reminded participants to engage in the app, that offered professional guidance, and that had a longer post-assessment duration (7-11 weeks) compared to those with a shorter duration (2-6 weeks).

Smartphone interventions vs. active comparisons

The pooled effect size for the four comparisons was g=0.09 (95% CI: –0.21 to 0.39), with moderate heterogeneity.

Efficacy of smartphone interventions on stress levels

Stress levels were assessed in 22 trials (33.3%). The pooled effect size for the 27 comparisons was g=0.35 (95% CI: 0.21-0.48), with high heterogeneity (Table 2). The pooled effect size remained statistically significant across the sensitivity analyses. Begg and Mazumdar test was non-significant (p=0.392).

Four significant moderation effects were observed in subgroup analyses. Larger effect sizes were found by studies that used elevated stress levels as an entry criterion for trial inclusion, that used a CBT-based app, that offered professional guidance, and that had a longer post-assessment duration (≥ 7 weeks) compared to those with a shorter duration.

The pooled effect size for the two comparisons of smartphone vs. active interventions was g=0.21 (95% CI: –0.46 to 0.88), with high heterogeneity.

Efficacy of smartphone interventions on well-being/quality of life

Measures of well-being/quality of life were assessed in 36 studies (54.5%). The pooled effect size for the 43 comparisons was g=0.35 (95% CI: 0.29-0.42), with low heterogeneity (Table 2). The pooled effect size remained statistically significant across all sensitivity analyses. Begg and Mazumdar test was non-significant (p=0.622).

Two significant moderators were observed in subgroup analyses. Larger effect sizes were found by studies that reminded participants to engage, and by those that offered professional guidance.

The pooled effect size for the six comparisons of smartphone vs. active interventions was g=0.02 (95% CI: –0.14 to 0.17). A negative, non-significant effect size was observed when restricting these analyses to low risk of bias trials.

Efficacy of smartphone interventions on other outcomes

Table 3 presents the meta-analyses comparing smartphone interventions to control conditions on "other" outcomes.

Smartphone interventions were significantly more effective than control conditions in improving general psychological distress (g=0.40), social anxiety symptoms (g=0.58), and positive affect (g=0.44). No significant group differences were observed for panic symptoms (g=–0.05), post-traumatic stress symptoms (g=0.18), and negative affect (g=–0.08), although the number of studies contributing to these analyses was low.

DISCUSSION

This meta-analysis examined the efficacy of app-supported smartphone interventions for a range of mental health problems. Our search identified 66 RCTs that tested several smartphone interventions on numerous distinct clinical and non-clinical populations. Importantly, the majority of RCTs were published in the last two years, highlighting that this area of research is gaining significant momentum and is growing exponentially.

We found evidence that app-supported smartphone interventions are efficacious for several common mental health problems. They significantly outperformed control conditions in improving depressive symptoms, anxiety symptoms (generalized anxiety and social anxiety), stress levels, general psychiatric distress, quality of life, and positive affect, with effect sizes ranging from g=0.28 to g=0.58. Crucially, these effects were robust even after performing various sensitivity analyses that adjusted for common biasing factors in RCTs, including the type of control condition, trial risk of bias rating, and publication bias[57,58].

The statistically significant effect sizes were observed in both symptomatic (e.g., people meeting diagnostic criteria or reporting elevated mental health symptoms) and non-symptomatic (e.g., university students, general population) samples, further highlighting the potential that smartphone apps could bring within current models of mental health care. For instance, smartphone interventions could eventually serve as a low-cost, easily accessible, and user-friendly option for universal, selective or indicated preventive programs[59]. Smartphone interventions could also fit within the stepped-care model, in which low intensity interventions are offered as a first step in treatment, with more intensive resources reserved for those who fail to respond[60].

Studies that offered professional guidance (e.g., supportive text messages, personalized feedback, telephone calls) and engagement reminders were consistently associated with larger effect sizes on several mental health outcomes, although smart-

phone interventions still significantly outperformed control conditions even in the subset of studies that did not offer guidance or reminders. That therapist guidance and engagement reminders bolster the effectiveness of smartphone interventions is consistent with what has been observed in a series of meta-analyses of Internet-based and computerized psychological treatments[61-64]. However, the involvement of a therapist can be costly and may thus restrict the capacity of smartphone apps to reach the millions of people around the world in need of (and who cannot gain access to) treatment.

It has been suggested that digital interventions may benefit from peer or automated support rather than human support systems[38,65]. The development of automated support systems may be guided by machine learning principles, so that users could receive guidance or prompts that are customized to their own needs and in real time[66]. Automated (and personalized) support has been shown to produce equivalent clinical outcomes to human support in RCTs of computerized treatments[67], which suggests that developing and testing automated support systems for smartphone apps may be an important avenue for future research.

We also investigated whether the theoretical orientation of the smartphone intervention was associated with effect sizes. While interventions containing mindfulness- or acceptance-based components were not associated with effect sizes, CBT-based interventions produced larger effects for anxiety and stress. However, conclusions concerning the relative efficacy of different theoretical orientations would be premature at this stage, as too few head-to-head comparisons of different smartphone interventions have been performed, and those that compared CBT vs. non-CBT-based smartphone interventions reported no differences in level of symptom improvement[68-70].

Smartphone interventions did not significantly differ from active interventions on any outcome. These findings, although preliminary, are in line with reports regarding Internet-based treatments[71], and point further toward the clinical utility of mental health apps. However, we note that few studies contributed to these head-to-head comparisons, so these analyses may have been underpowered. Power may have also been an issue for the other outcomes in which smartphone interventions conferred no benefit over control conditions (panic, post-traumatic stress, and negative affect). Alternatively, it could be that the content quality of smartphone apps for these specific symptoms needs to improve[72].

Limitations to the present meta-analysis must be considered. First, possible negative effects of smartphone interventions (e.g., deterioration rates)[73] were not assessed, since they were not reported in the included studies. Future studies should examine these possible negative effects[74]. Second, we did not analyze the long-term effects of smartphone interventions, due to large differences in follow-up times and since drop-outs were dealt with inconsistently across studies. Thus, it is unclear whether improvements in mental health are sustained after the period of the study. Assessing the long-term efficacy of smartphone interventions is an important future goal, particularly since promising long-term effects have been noted in Internet-based trials[75]. Third, nearly all included studies assessed outcomes via self-report questionnaires. A previous meta-analysis demonstrated that clinician-rated instruments yield significantly larger effect sizes in psychotherapy trials than self-reported measures[76]. So, it is possible that our effect size estimates were slightly underestimated.

In summary, we found evidence for the efficacy of app-supported smartphone interventions. They significantly outperformed (with small to moderate effect sizes) control conditions in improving a range of mental health outcomes, with effects remaining robust even after adjusting for various biasing factors in RCTs. Studies that offered professional guidance and engagement reminders were shown to produce the largest effects, and smartphone interventions did not differ significantly from active intervention comparisons on any outcome.

Although mental health apps are not here to replace professional clinical services, the present findings highlight the potential of apps to serve as a cost-effective, easily accessible, and low intensity intervention for the millions of people worldwide who cannot receive standard psychological treatment.

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The assessment and management of insomnia: an update

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Insomnia poses significant challenges to public health. It is a common condition associated with marked impairment in function and quality of life, psychiatric and physical morbidity, and accidents. As such, it is important that effective treatment is provided in clinical practice. To this end, this paper reviews critical aspects of the assessment of insomnia and the available treatment options. These options include both non-medication treatments, most notably cognitive behavioral therapy for insomnia, and a variety of pharmacologic therapies such as benzodiazepines, "z-drugs", melatonin receptor agonists, selective histamine H1 antagonists, orexin antagonists, antidepressants, antipsychotics, anticonvulsants, and non-selective antihistamines. A review of the available research indicates that rigorous double-blind, randomized, controlled trials are lacking for some of the most commonly administered insomnia therapies. However, there are an array of interventions which have been demonstrated to have therapeutic effects in insomnia in trials with the above features, and whose risk/benefit profiles have been well characterized. These interventions can form the basis for systematic, evidence-based treatment of insomnia in clinical practice. We review this evidence base and highlight areas where more studies are needed, with the aim of providing a resource for improving the clinical management of the many patients with insomnia.

Key words: Insomnia, cognitive behavioral therapy, pharmacotherapy, benzodiazepines, z-drugs, orexin antagonists, antihistamines, melatonin receptor agonists, antidepressants, antipsychotics, anticonvulsants

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Insomnia is defined as a complaint of difficulty falling or staying asleep which is associated with significant distress or impairment in daytime function and occurs despite an adequate opportunity for sleep[1,2]. It is a common condition, with an approximate general population point prevalence of 10%[3-6].

In the vast majority of cases, insomnia co-occurs with psychiatric or physical conditions. Although it had long been believed that, when this was the case, insomnia was a symptom of those conditions, the available evidence suggests that the relationship between such conditions and insomnia is complex and sometimes bidirectional[7-10]. In fact, insomnia is a risk factor for major depression, anxiety disorders, substance use disorders, suicidality, hypertension and diabetes[11-23]. On this basis, as well as due to the fact that insomnia is associated with impairments in quality of life and an increased risk for accidents and falls, it is recommended that treatment be targeted specifically to addressing insomnia whenever it is present, including when it occurs along with physical or psychiatric conditions[24,25].

For those who meet the diagnostic criteria for insomnia, a number of empirically supported treatments are available. These include non-medication therapies as well as medication options[25-28]. The public health impact of this condition in terms of prevalence, morbidity and consequences on health and quality of life highlights the need to effectively diagnose and treat it in clinical practice. This paper reviews the state of the art for optimally diagnosing and treating insomnia based on the available research evidence.

DIAGNOSTIC CRITERIA FOR INSOMNIA

The clinical diagnosis of insomnia is based on the complaint of trouble falling asleep, trouble staying asleep, or early morning awakening, and resultant daytime dysfunction[1,2].

This daytime dysfunction can manifest in a wide range of ways, including fatigue, malaise; impairment in attention, concentration or memory; impaired social, family, occupational or academic performance; mood disturbance, irritability, sleepiness, hyperactivity, impulsivity, aggression, reduced motivation, proneness for errors, and concerns about or dissatisfaction with sleep[2].

The sleep disturbance must occur despite adequate opportunity for sleep in a safe, dark environment. Duration is also key to the diagnosis: to meet criteria for chronic insomnia according to the third edition of the International Classification of Sleep Disorders (ICSD-3) or for persistent insomnia according to the DSM-5, symptoms must be present at least three days per week for at least three months. Short term insomnia (ICSD-3) or episodic insomnia (DSM-5) has the same criteria as chronic insomnia, but lasts for fewer than three months.

If the sleep complaints are completely explained by another physical, psychiatric or sleep disorder, the patient does not meet diagnostic criteria for insomnia. However, insomnia is not solely a symptom of other mental disorders as was once thought[29]. Even if another disorder was the trigger or is present some of the time, if insomnia is sufficiently severe to warrant independent clinical attention, it should be recognized as a separate, comorbid disorder.

Previously, both the ICSD and the DSM described various subtypes of insomnia. These included psychophysiologic insomnia, paradoxical insomnia, idiopathic insomnia, behavioral insomnia of childhood, insomnia due to a mental disorder, insomnia due to a medical disorder, and insomnia due to a drug or substance. However, the mechanism of insomnia is poorly understood, and the various subtypes are difficult to differentiate in clinical practice[30]. Therefore, the subtypes were consolidated into chronic insomnia (ICSD-3) and persistent insomnia disorder (DSM-5) in the most recent editions of the manuals.

A subtype of insomnia with objectively short sleep has been described and stands out for its probable association with increased morbidity. These individuals meet criteria for chronic insomnia and, by objective measure, sleep on average less than six hours per night. This combination of insomnia with short sleep duration has been linked to hypertension, type 2 diabetes, and worse neurocognitive function[17,31,32]. Therefore, this may ultimately become a separate category in future versions of insomnia classifications.

DEMOGRAPHICS OF INSOMNIA

Symptoms of insomnia are common, with about one in three people reporting some symptoms in the previous year[33,34]. The point prevalence of a formal diagnosis of insomnia is 6-15%, though occurrence rates vary by definition used[35].

When looking at only nighttime complaints, rates are far higher. In a large population sample in France, 57% complained of trouble falling asleep, 53% of trouble staying asleep, and 41% of non-restorative sleep, though only 19% met DSM-IV criteria of at least one complaint three times per week for one month[36].

For many, insomnia is a persistent condition, with 74% reporting symptoms for at least one year[37]. Persistence is more common in women, the elderly, and those with more severe insomnia. In a 3-year study, over half of participants did remit, but there was a 27% relapse rate[37]. Family history of insomnia is also common, occurring in 35% of individuals[38].

Women more commonly report symptoms of insomnia and daytime consequences, and are more likely to be diagnosed with insomnia than men. The male-to-female ratio is 1:1.4 for insomnia symptoms and 1:2 for insomnia diagnosis[5]. In both men and women, the prevalence of insomnia increases with age[5,39,40].

Insomnia is associated with lower income, lower education, and being divorced or widowed[5,36,41]. It is also strongly associated with physical disorders, with half of those with insomnia also reporting multiple physical problems[34,41]. People with insomnia are more likely to rate their health poorly[42,43].

Insomnia is very strongly associated with mental disorders, most commonly depression, anxiety and post-traumatic stress disorder. Across cultures, most people with major depression report insomnia[44], and those with insomnia are more likely to have depressed mood[42,43,45-47]. Insomnia is also a predictor for developing mental health problems, including depression, anxiety, bipolar disorder and suicide[45].

CLINICAL ASSESSMENT OF INSOMNIA

Chief complaint

The chief complaint for those with insomnia is typically difficulty initiating or maintaining sleep, early morning awakening or simply unrefreshing sleep. Early morning awakening is waking at least 30 minutes prior to the desired time, accounting for habitual bedtime, total sleep time, and premorbid pattern.

The specific complaint may vary over time and often includes more than one sleep concern. The duration, frequency and severity of this concern should be elucidated as well as exacerbating and relieving factors. Complaints of insomnia often arise only when probed during evaluation of another disorder, despite the impact of insomnia on multiple health issues.

Current sleep history

A good current sleep history is essential to confirm the diagnosis and determine the best treatment for a patient with insomnia. This includes sleep/wake schedule, bedtime routine, nocturnal behavior, and daytime dysfunction.

Sleep/wake schedule

A detailed account of time to bed, time to sleep, frequency of night awakenings, time to return to sleep, time waking in the morning, and time out of bed should be obtained.

What the patient does when not falling asleep is also important. For example, a patient who gets out of bed and eats ice cream or watches a favorite show when not sleeping is providing positive reinforcement for being awake, which is counterproductive. This can be a behavior to target and eliminate during treatment.

The sleep/wake schedule should be obtained for both work/school days and weekends or vacations. A large variation may signal a circadian rhythm disorder and serve as a target for intervention.

Does the patient nap during the day? If taking a nap later in the day, this may be decreasing sleep drive in the evening and can also be a target for intervention. If the patient reports a strong propensity to fall asleep during the daytime, this raises concern for another sleep disorder.

Bedtime routine

It is important to have the right conditions to ensure proper sleep. While someone with true insomnia will not be effectively treated by simply providing a dark, quiet environment, the clinician – in order to confirm the diagnosis – must ensure that poor sleep is not due to poor sleep conditions.

Detailing the bedtime routine may also highlight areas for intervention during the treatment phase. For example, mobile phone use is associated with shorter sleep duration[22].

Nocturnal behavior

What does the patient do when not sleeping at night? Are there other behaviors overnight, such as snoring or leg kicking, that may signal alternative or concomitant diagnoses?

Input from a bed partner can also be helpful. In a patient who reports being awake the entire night, a bed partner often

observes long periods of sleep, suggesting there may be some sleep state misperception.

Daytime dysfunction

Daytime dysfunction is part of the formal criteria for insomnia and must be assessed. This includes worsened quality of life, concerns about memory, fatigue, mood, and success at work or school.

The 3P model

The 3P model, a behavioral model of insomnia developed by Spielman[48], can help the clinician focus a sleep history[49]. The model highlights why insomnia occurs in certain individuals and what allows acute insomnia to become chronic insomnia.

The three Ps occur in temporal order: factors *predisposing* an individual to insomnia, factors *precipitating* an acute episode of insomnia, and factors *perpetuating* the insomnia from acute to chronic. Predisposing factors include genetic and personality traits leading to physiologic and cognitive hyperarousal[50,51]. Precipitating factors are the triggers after which the insomnia cycle begins and are typically stressful events, though they can be positive, ranging from the loss of a loved one to retirement or marriage. Perpetuating factors allow the insomnia to continue, even when the trigger is removed. These factors include behaviors and thought structures that may appear to offer short-term relief yet cause long-term harm, such as increasing time in bed and reducing daytime activity.

Past medical history

There is a large interplay between many physical or psychiatric conditions and insomnia, and typically it is thought that a bidirectional relationship exists in which the physical or psychiatric condition exacerbates insomnia and vice versa. A huge range of physical comorbidities – including pulmonary, cardiac, gastrointestinal, endocrine, neurological, musculoskeletal and genitourinary – can contribute.

It is important to ensure that the management of these comorbid conditions is optimized when treating insomnia.

Medications

Numerous medications can impact sleep, and a thorough medication list, including over-the-counter medications and substances of abuse, should be elicited.

Antidepressants such as selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) and monoamine oxidase inhibitors (MAOIs) can cause sedation or stimulation, with individual variability. Therefore, a patient may consider moving a daily dose from morning to evening or vice versa to determine how this impacts sleep.

Over-the-counter allergy medications often contain stimulants such as pseudoephedrine or phenylephrine, and patients may not realize that this can contribute to insomnia. Withdrawal can also contribute, such as from alcohol, benzodiazepines or opioids. Pulmonary medications, including albuterol and theophylline, can cause insomnia as well.

While insomnia is reported as a side effect of antihypertensive medications, and beta-blockers are known to reduce melatonin levels, there is mixed evidence about the direct impact of these medications on sleep[5,52,53].

Social history

Occupation is key to the sleep history, to ensure driving safety in patients reporting daytime sleepiness. Work or school hours are also important, as variation in these hours, shift work, and frequent travel across time zones can all disturb sleep.

Use of nicotine, caffeine, alcohol and other substances should also be noted.

Physical examination

Insomnia is not associated with any specific features on physical or mental status examination. The examination can, however, provide information about alternative diagnoses and comorbid conditions. Assessments to consider include body mass index, neck circumference and airway exam for obstructive sleep apnea[54].

Differential diagnosis

Three criteria must be met for a diagnosis of insomnia: complaint of trouble falling or staying asleep, adequate opportunity for sleep, and daytime dysfunction. If a patient reports trouble sleeping for the expected 7-8 hours but does not have daytime consequences, he/she may be a short sleeper. On the other hand, if there are insufficient hours of sleep and daytime dysfunction, but the patient is able to sleep when provided opportunity, this is likely to be behaviorally induced insufficient sleep. Function during vacations and weekends can be helpful to differentiate these.

Other sleep disorders that can present with the complaint of insomnia include circadian rhythm sleep-wake disorders, restless leg syndrome, periodic leg movement disorder, and obstructive sleep apnea.

Helpful questions to distinguish circadian disorders include the time to bed and awake on weekends, holidays and vacations in contrast to work or school days and whether there is a normal duration of refreshing sleep once the patient does fall asleep. If sleeping from 3 am to 10 am provides refreshing sleep and yet the patient gets in bed at midnight and hopes to rise at 7 am, but

cannot fall asleep for several hours, a delayed sleep-wake phase disorder may be involved and the misaligned internal rhythm should be the target for treatment.

Symptoms of restless leg syndrome include an urge to move the legs at least partially relieved by moving them, typically preceded by an abnormal leg sensation, and typically occurring during times of rest at the end of the day. As the syndrome can cause trouble falling asleep, it should be ruled out or treated directly.

Obstructive sleep apnea can present with symptoms of insomnia, more commonly in women than men. Presence of snoring, frequent awakenings, witnessed apneas should be discussed and, if concern is present, polysomnography should be performed[55,56].

Insomnia assessment tools

Sleep diary

Sleep diary is a form compiled by the patient, usually for at least two consecutive weeks, in which he/she notes down the time that he/she went to bed, the time of lights out, time to sleep, time and duration of awakenings overnight, time awake in the morning, time out of bed, naps, perceived duration of sleep, and sometimes quality and depth of sleep. The use of sleep aids and alcohol is sometimes included.

This can be very useful for the diagnosis of insomnia and is core to the treatment, because it helps to characterize the specific nature of the sleep problem, delineate maladaptive behaviors and provide an indicator of treatment outcome. If a circadian rhythm disorder is being considered, a sleep diary can be very useful for making the correct diagnosis.

Actigraphy

Actigraphy is a device, typically worn on the wrist, that records movement and employs an algorithm to estimate sleep and wake periods.

It has satisfactory reliability with the "gold standard" polysomnography in good sleepers who spend little time awake and still, but not in those with sleep difficulties where significant periods of waking stillness occur[57-60]. It is often combined with a light sensor to provide an estimate of the latency from lights out to sleep onset.

Actigraphy is not required in the evaluation of insomnia, but it can be useful for a patient whose sleep log or history is not reliable or when circadian disorders are suspected.

Personal monitoring devices

Commercially available devices that purport to measure sleep, often differentiating between light and deep sleep, are increasingly available. There are little published data indicating the performance of nearly all of these consumer devices and thus the accuracy of the information regarding sleep and wake periods is unknown.

Limited data suggest that some of these monitors do not accurately reflect sleep architecture, sleep efficiency or sleep latency, and tend to overestimate sleep duration in normal sleepers with far worse accuracy in insomnia patients[61,62]. Therefore, these devices are not recommended to make clinical decisions until there are rigorous studies establishing validity and reliability. The ease of use and consumer enthusiasm, however, does suggest that these devices may play an increasing role in evaluation and treatment moving forward.

Polysomnography

Polysomnography is the gold standard to distinguish sleep from wake. It is not needed for the diagnosis of insomnia, which is based on patient self-report. This is because indices traditionally derived from polysomnographic data do not reflect the sleep problems reported by approximately 40% of insomnia patients[63].

Polysomnography can be helpful to rule out other possible explanations for poor sleep, such as sleep apnea or periodic leg movement disorder. Therefore, it may be indicated when there is concern for sleep apnea or when a patient is not responding to treatment as expected.

Questionnaires

There are multiple questionnaires that can aid in the evaluation of insomnia.

In many sleep clinics, every patient completes the Epworth Sleepiness Scale[64], given the safety concern of daytime sleepiness when driving or operating heavy machinery. The Insomnia Severity Index[65] is commonly used in research as an outcome measure. The Dysfunctional Beliefs and Attitudes about Sleep[66] can help provide additional information to guide treatment. The Pittsburgh Sleep Quality Index[67] is also commonly used to collect information about self-perceived sleep quality.

MANAGEMENT OF INSOMNIA

When a patient is diagnosed with insomnia, treatment may be initiated with one of a number of available interventions. These can be broadly categorized as non-medication treatments and pharmacological therapies. In the sections below we review these interventions, focusing on the available evidence from blinded controlled trials indicating their efficacy and adverse effects.

Non-medication treatments

There are several different non-pharmacological treatment regimens that have been tested and implemented to treat in-

somnia. Here, we review the components and evidence supporting the non-medication treatment with the best empirical background and most widespread use, i.e. cognitive behavioral therapy for insomnia (CBT-I).

Employed in a variety of formats, CBT-I has been found to be effective in reducing insomnia and improving sleep across a wide array of clinical populations[68-77]. Consequently, the American College of Physicians has recommended this intervention as the first line treatment for adults with insomnia[74].

CBT-I has been found to be as effective in the short term as pharmacological treatments, with better long-term persistence of benefit after the end of treatment[72]. Further, unlike nearly all medications, this therapy has relatively minimal side effects. Here, we provide a clinical review of the components of CBT-I followed by evidence of its efficacy, including its effectiveness among patients with comorbidities, and its use across different treatment modalities.

CBT-I is typically delivered over roughly four to seven sessions. It is unclear how many sessions confer optimal benefit, though evidence suggests that fewer than four sessions are not generally sufficient[69,78].

Educational components of CBT-I

While most patients with insomnia are likely aware of some of the behaviors that fall into the sleep hygiene category, it is important to provide them with the relevant education. This includes the importance of establishing a conducive sleep environment by keeping the bedroom dark, quiet and cool.

Patients should also be reminded not to consume sleep disturbing substances, such as caffeine, nicotine and alcohol, particularly close to bedtime. Similarly, vigorous exercise three to four hours prior to bedtime should be avoided.

Additionally, a wind down routine can be helpful in readying a patient for bed. This should include discontinuation of arousing activities, including exposure to bright light (e.g., computer screen), which can negatively affect one's circadian rhythms.

Behavioral components of CBT-I

Stimulus control

Conditioned arousal is one of the key factors implicated in the pathogenesis of insomnia. Repeated pairing of the bed/bedroom and experiences of physiologic arousal, fear, anxiety and frustration leads to the bed serving as a learned cue or conditioned stimulus for arousal, which is incompatible with sleep onset and maintenance.

In order to eliminate this conditioned response, patients are recommended to remove themselves from the bed and bedroom if not sleepy and sit somewhere quiet until the feeling of sleepiness returns. Similarly, at bedtime, the patients are recommended not to go to bed unless they feel sleepy. Use of the bed and bedroom is restricted to sleep and sex, which means that patients are recommended not to do other activities in bed, including read or watch television. Additionally, patients are recommended to wake up the same time each morning, seven days per week, and get out of bed within 10 to 15 minutes upon awakening.

Sleep restriction

Another common contributor to the development and preservation of insomnia is the tendency for patients to spend excess time in bed. On the surface, this makes reasonable sense given that the patients yearn to "catch" sleep whenever they can. Unfortunately, excess time in bed results in conditioned arousal and fragmented sleep.

In order to effectively carry out this technique, patients should provide at least one week of sleep diaries (though two weeks are preferred). The goal is to reduce a patient's time in bed to the reported total sleep time. For instance, if a patient's diary report indicated an average total sleep time of six hours but a time in bed of nine hours (bedtime 9 pm and wake time 6 am), the new sleep schedule would provide a time in bed of six hours (bedtime midnight and wake time 6 am).

Importantly, patients are recommended to not go to sleep until the new prescribed bedtime and *only* when sleepy. In choosing the sleep opportunity window, it is important to take into account the patient's chronotype.

Due to safety concerns related to sleep restriction (e.g., cognitive deficits, drowsy driving), a minimum time in bed of five hours has been used in the literature[79]. In addition, sleep restriction may exacerbate comorbidities. For instance, sleep restriction has been shown to lower seizure thresholds, increase pain sensitivity, and precipitate mania in patients with bipolar disorder[80-82].

Patients are recommended to complete sleep diaries throughout treatment. Their time in bed schedule should be reviewed in each subsequent CBT-I session, with sessions occurring every one to two weeks. The sleep diaries allow the clinician to calculate their average sleep efficiency, which is the percentage of time a patient is asleep given his/her time in bed. We recommend 85% or higher in average sleep efficiency as a metric for "good" sleep quality and a threshold to be met prior to adjusting the time in bed recommendation.

Once it is established that a patient's sleep efficiency is sufficiently high, the clinician can begin to increase the time in bed, typically by altering the prescribed bedtime by 15 min each time and tracking the patient's improvement in subjective sleep quality and daytime sleepiness.

Sleep restriction is typically the aspect of CBT-I that suffers the most from non-adherence. In the event that a patient is unable or unwilling to carry out the prescribed time in bed, sleep compression can also be used. This technique consists of slowly decreasing time in bed over time in order to meet the original prescribed time, and may be more palatable to patients, particularly those with significant anxiety about losing further sleep opportunity.

Relaxation and paradoxical intention

These behavioral techniques complement stimulus control and sleep restriction by providing the patient with tools for decreasing arousal prior to bedtime and in the event of nighttime awakenings.

Relaxation techniques vary, but typically include diaphragmatic breathing, the tensing and relaxing of muscle groups, and possibly visual imagery. Paradoxical intention is premised on the idea that anxiety about falling asleep is inhibiting sleep onset. Using this technique, patients are asked to stay awake as long as possible, which leads to reduced anxiety and easier sleep onset.

Cognitive components of CBT-I

Maladaptive beliefs and thoughts about sleep are typically addressed throughout treatment. It is important for a clinician to attend to sleep-related worries, as they tend to drive the inappropriate behaviors that perpetuate insomnia. Unrealistic expectations about sleep and catastrophic thinking about the consequences of sleep loss are among these worries.

One technique for countering catastrophic thoughts is by examining evidence from the patient's experience. For instance, if a patient has the belief that a poor night of sleep will leave him/her unable to be effective in his/her job, a clinician could help the patient identify instances when he/she was able to perform sufficiently despite a poor night of sleep. Additionally, providing patients with tools to reduce worry at bedtime can be helpful.

Another technique, known as a constructive worry exercise, requires patients to list in the early evening three or more problems that they believe will likely keep them up at night. For each problem, patients list the next step towards a solution. The exercise is folded and put away and, if patients awake during the night, they are to remind themselves that they have already taken the necessary step towards resolving that problem at their "problem-solving best" (i.e., not in the middle of the night).

Evidence of efficacy of CBT-I

Several meta-analytic reviews support the efficacy of CBT-I compared to active control conditions and usual care[68-70,72,78-81]. In a recent meta-analysis, van Straten et al[69] pooled data from 87 randomized controlled studies that used at least one component of CBT-I, which included 3,724 patients and 2,579 non-treated controls. The strongest effects were improvements in insomnia symptoms, as measured using the Insomnia Severity Index (Hedges' g=0.98), sleep efficiency (g=0.71), wake after sleep onset (g=0.63), sleep onset latency (g=0.57), and subjective sleep quality (g=0.40). A small effect was observed for changes in total sleep time (g=0.16).

Further, data suggest that CBT-I is effective among individuals with psychiatric and physical comorbidities[70], with some accruing evidence that it may have positive effects on comorbid outcomes[82,83]. CBT-I benefits are stronger for psychiatric than physical comorbidities[70].

CBT-I has been delivered using a number of different formats, including face-to-face individual, group and digitally delivered therapy. In addition, self-help manuals, books and videos have been developed, which allow patients to carry out treatment on their own. In general, all modalities are effective, though there is some evidence to suggest that face-to-face therapy outperforms self-help. Digitally delivered CBT-I appears to produce effects comparable to in-person therapy[84,85]; however, it is likely that in-person supervision may be required for more complicated cases[86].

Pharmacological therapies

A number of medications from several different classes have undergone randomized, double-blind, placebo-controlled trials in patients with insomnia. Those for which a statistically significant therapeutic effect compared with placebo was reported appear in Tables 1 and 2. In addition, there are a number of medications commonly used to treat insomnia that have not been demonstrated to have efficacy in at least one double-blind, randomized, placebo-controlled trial. These appear in Table 3.

In this section we review the characteristics of all of these medications (benzodiazepines, "z-drugs", melatonin receptor agonists, selective histamine H1 antagonists, orexin antagonists, antidepressants, antipsychotics, anticonvulsants, and non-selective antihistamines) and present the available evidence regarding their efficacy and safety as a basis for clinical decision making.

Benzodiazepines

Benzodiazepines are a group of compounds with a similar chemical structure. Their sleep enhancing effect is a result of positive allosteric modulation of the gamma-aminobutyric acid (GABA) type A receptor[138,139]. These agents exert this modulation by binding to a specific site on the GABA-A receptor complex (referred to as the benzodiazepine binding site), thereby changing the conformation of the receptor constituent proteins, which leads to an enhancement of the inhibition occurring when GABA binds to these receptors[140,141]. This enhancement of inhibition is associated with a broad set of dose-dependent clinical effects, including sedation, anxiety reduction, seizure inhibition and myorelaxation[139,140,142].

Of the benzodiazepine medications, triazolam, flurazepam, temazepam, quazepam and estazolam have been demonstrated to have therapeutic effects on both sleep onset and maintenance in double-blind, placebo-controlled trials in younger adults (Table 1). In older adults, triazolam and flurazepam have been found to have therapeutic effects on sleep onset and maintenance in double-blind, placebo-controlled trials, whereas temazepam has been demonstrated to have therapeutic effects on sleep maintenance only (Table 2).

Table 1 Double-blind placebo-controlled trials demonstrating efficacy in the treatment of younger adults with insomnia

Medication	Class	Efficacy for sleep onset		Efficacy for sleep maintenance		Primary adverse effects
		Dose (mg)	N	Dose (mg)	N	
Triazolam	BDZ	0.25[87]	1,507	0.5[89]	277	Dose-dependent sedation, psychomotor impairment, abuse potential
		0.25[88]	83			
		0.5[89]	277			
Flurazepam	BDZ	30[90]	60	30[91]	157	Dose-dependent sedation, psychomotor impairment, abuse potential
		30[91]	157			
Estazolam	BDZ	2[91]	148	2[91]	148	Dose-dependent sedation, psychomotor impairment, abuse potential
		1-2[92]	379	1-2[92]	379	
				0.25-2[93]	15	
Quazepam	BDZ	30[94]	57	30[94]	57	Dose-dependent sedation, psychomotor impairment, abuse potential
Temazepam	BDZ	30[95]	75	30[95]	75	Dose-dependent sedation, psychomotor impairment, abuse potential
Zolpidem	z-drug	10[96]	75	10[100]	199	Dose-dependent sedation, psychomotor impairment, abuse potential
		10[97]	203			
		10[98]	615			
		10[99]	163			
		10[100]	199			
Zolpidem (extended release)	z-drug	12.5[101]	212	12.5[101]	212	Dose-dependent sedation, psychomotor impairment, abuse potential
		12.5[102]	1,025	12.5[102]	1,025	
Zolpidem (sublingual)	z-drug			3.5[103]	295	Dose-dependent sedation, psychomotor impairment, abuse potential
Zaleplon	z-drug	10[104]	113			Dose-dependent sedation, psychomotor impairment, abuse potential
		10-20[88]	83			
		10-20[98]	615			
Zopiclone	z-drug	7.5[105]	25	7.5[105]	25	Bitter taste, dose-dependent sedation, psychomotor impairment, abuse potential
		7.5[88]	1,507	7.5[88]	1,507	
Eszopiclone	z-drug	3[106]	788	3[106]	788	Bitter taste, dose-dependent sedation, psychomotor impairment, abuse potential
		3[107]	830	3[107]	830	
		2-3[108]	308	2-3[108]	308	
Ramelteon	MT1/MT2 agonist	4-32[109]	107			
		8-32[110]	65			
		8[111]	451			
		4-16[112]	190			
		8-16[113]	405			
Doxepin	H1 antagonist	6[114]	67	1,3,6[114]	67	Sedation
				25-50[115]	47	
				6[116]	254	
				3-6[117]	221	
Suvorexant	Orexin antagonist	20-40[118]	1,211	20-40[118]	1,211	Sedation, probable abuse potential
		10-80[119]	591	10-80[119]	591	
		40[120]	380	40[120]	380	

BDZ – benzodiazepine

Table 2 Double-blind placebo-controlled trials demonstrating efficacy in the treatment of older adults with insomnia

Medication	Class	Efficacy for sleep onset		Efficacy for sleep maintenance		Adverse effects
		Dose (mg)	N	Dose (mg)	N	
Triazolam	BDZ	0.25[121]	32	0.125[125]	22	Dose-dependent sedation, psychomotor impairment, abuse potential
		0.25[122]	41	0.25[122]	41	
		0.25-0.5[123]	27	0.4-0.8[124]	25	
		0.4-0.8[124]	25			
		0.125[125]	22			
Flurazepam	BDZ	15[122]	41	30[124]	25	Dose-dependent sedation, psychomotor impairment, abuse potential
		30[124]	25			
Temazepam	BDZ			7.5-30[126]	40	Dose-dependent sedation, psychomotor impairment, abuse potential
Zolpidem	z-drug	5[127]	549			Sedation, psychomotor impairment, abuse potential
Zolpidem (extended release)	z-drug	6.5[128]	205	6.5[128]	205	Sedation, psychomotor impairment, abuse potential
Zaleplon	z-drug	5-10[129]	422			Dose-dependent sedation, psychomotor impairment, abuse potential
		10[127]	549			
Zopiclone	z-drug	5-7.5[121]	48	5-7.5[121]	48	Bitter taste, dose-dependent sedation, psychomotor impairment, abuse potential
Eszopiclone	z-drug	2[130]	231	2[130]	231	Bitter taste, dose-dependent sedation, psychomotor impairment, abuse potential
		2[131]	264	2[131]	264	
		2[132]	388	2[132]	388	
Ramelteon	MT1/MT2 agonist	8[133]	829			
		8[134]	100			
Doxepin	Selective H1 antagonist			3-6[135]	76	
				1-3[136]	240	
Suvorexant	Orexin antagonist	15[137]	520	15[137]	520	Sedation, probable abuse potential
		30[120]	319	30[120]	319	
		15-30[137]	819	15-30[137]	819	

BDZ – benzodiazepine

For many years the prevailing view of these medications, and medications used for the treatment of insomnia in general, was that they were inevitably associated with tolerance (i.e., loss of therapeutic benefit over time) and dependence (i.e., withdrawal symptoms upon discontinuation) when used nightly on a long-term basis[143]. Until relatively recently, little data were available to actually assess whether this was the case[25]. As data have become available, it has been clear that tolerance and dependence do not inevitably occur and are not characteristic of long-term nightly insomnia pharmacotherapy.

However, data on long-term treatment are only available for some medications, and the available information leaves open the possibility that dependence does occur in some individuals[25]. This limitation is particularly notable for benzodiazepines: the longest nightly treatment study of a benzodiazepine was an 8-week trial of temazepam, where dependence was not observed[126]. Studies of 2-4 weeks duration were carried out with triazolam (three trials) and flurazepam (one trial), without evidence of dependence occurring[87,121,122].

The adverse effects of benzodiazepines are dose-dependent and reflect their broad central nervous system inhibitory activity. They include sedation, psychomotor impairment, and potential for abuse by a small subset of the population[143]. The anxiolytic and myorelaxant effects can be useful in those with comorbid anxiety or pain.

Among the available options, these agents are relatively effective at treating sleep onset problems and, as a result, may be needed in some individuals with this type of sleep problem. The

Table 3 Medications used to treat insomnia not demonstrated to have efficacy in at least one double-blind placebo-controlled trial in insomnia patients

Medication	FDA approved indication	Primary known side effects
Trazodone	Major depressive disorder	Sedation, dizziness, headache, dry mouth, blurred vision, orthostatic hypotension, priapism
Mirtazapine	Major depressive disorder	Sedation, dry mouth, increased appetite/weight gain, constipation
Amitriptyline	Major depressive disorder	Sedation, dizziness, weight gain, dry mouth, blurred vision, constipation, urinary retention
Gabapentin	Partial seizures, pain	Sedation, dizziness, ataxia, diplopia
Pregabalin	Fibromyalgia, pain, partial seizures	Sedation, dizziness, dry mouth, cognitive impairment, increased appetite, discontinuation effects
Quetiapine	Schizophrenia, mania, major depressive disorder	Sedation, orthostatic hypotension, dry mouth, tachycardia, increased appetite/weight gain
Olanzapine	Schizophrenia, mania	Sedation, agitation, dizziness, constipation, orthostatic hypotension, akathisia, weight gain, increased incidence of cerebrovascular events in dementia patients
Diphenhydramine	Over-the-counter antihistamine	Sedation, dizziness, dry mouth, blurred vision, constipation, urinary retention
Doxylamine	Over-the-counter antihistamine	Sedation, dizziness, dry mouth, blurred vision, constipation, urinary retention
Melatonin	Over-the-counter hormone	Headache, sedation

FDA – US Food and Drug Administration

only relative contraindication to their use is a history of polysubstance abuse or a specific predisposition to benzodiazepine abuse.

"Z-drugs"

These agents are an unrelated group of compounds which act by the same mechanism as benzodiazepines, but do not share the benzodiazepine chemical structure[138-142]. There is some evidence that they may differ somewhat from benzodiazepines in that their action is relatively restricted to subsets of GABA-A receptors. As a result, they may have less broad clinical effects[25,138-142].

Double-blind, placebo-controlled trials demonstrate the efficacy of zaleplon for sleep onset, and of zolpidem extended-release, zopiclone and eszopiclone (the S isomer of zopiclone) for sleep onset and maintenance in both younger and older adults. Zolpidem has a documented efficacy for sleep onset and maintenance problems in younger adults, but for sleep onset problems only in older adults (Tables 1 and 2).

More data on long-term treatment are available for "z-drugs" than for benzodiazepines. The sustained efficacy of eszopiclone and zolpidem has been demonstrated in studies of nightly dosing up to one year in duration without any evidence of dependence occurring, nor was dependence found in a 6-month study of non-nightly treatment with extended-release zolpidem[101,106,107].

The potential adverse effects of the "z-drugs" are the same as the benzodiazepines. Because of the relatively narrower effects of some of these agents, they may not be as helpful as benzodiazepines in addressing concomitant anxiety or pain. This appears to be the case for zolpidem. However, eszopiclone and zolpidem extended-release have been found to have therapeutic effects on pain, anxiety and depression concomitant with insomnia[144-151].

Like benzodiazepines, these agents are relatively more effective than other options in treating problems with sleep maintenance, and may be problematic in those predisposed towards substance abuse.

Melatonin receptor agonists

There are two melatonin receptor agonists used in the treatment of insomnia: melatonin and ramelteon.

Melatonin is a hormone that is taken by many individuals with insomnia. Normally, it is released by the pineal gland during the dark period of the day. It binds predominantly to the MT1 and MT2 receptors, though the mechanism by which this might enhance sleep is not well understood[152].

No clear dose-response relationship has been established for the use of melatonin for treating insomnia, and there is some evidence that sleep enhancement may depend on the time of day and may not occur until 3-4 hours after administration[153-155].

A substantial number of studies have evaluated the effects of a variety of dosages, administration times, and both immediate and prolonged release formulations of melatonin in individuals with sleep problems[156,157]. The available evidence suggests that this agent has a clear therapeutic effect in individuals with delayed sleep-phase syndrome, that it has an excellent safety profile, and that there may be a modest therapeutic effect on sleep onset latency in individuals with insomnia (although it remains unclear whether this effect is of clinical significance). Some preliminary evidence supports the use of melatonin to treat sleep problems in children with neurodevelopmental disorders, in whom this agent has been established to have an excellent safety profile[158-163].

The most common adverse effect of melatonin is headache, and slowing of reaction time and sedation can occur during the day. Melatonin is without abuse potential, so it could be admin-

istered to abuse-prone individuals with insomnia. Because it is a hormone that regulates reproductive function, when taken in higher dosages it can in theory impair fertility. Therefore, it has been recommended that it not be taken in those attempting to conceive[164-167].

Like melatonin, ramelteon is an agonist at MT1 and MT2 receptors. However, it is a substantially more potent agonist at these receptors than melatonin. Double-blind, placebo-controlled trials demonstrate the efficacy of ramelteon for sleep onset insomnia in both younger and older adults (Tables 1 and 2). Efficacy has been more consistently found with polysomnographic measures than self-report measures of sleep onset. Nightly treatment for six months was evaluated and no evidence of dependence phenomena was reported[111].

Ramelteon has a relatively benign profile of adverse effects, among which the most commonly reported are headache, sedation, fatigue and nausea. It does not have significant abuse potential and could be used for abuse-prone individuals with sleep onset problems, though no studies have evaluated its therapeutic effects in this population. Due to its good safety profile, it may be considered for use in individuals with difficulty in sleep onset only.

Selective H1 antagonists

The only highly selective histamine H1 receptor antagonist that has been systematically studied is doxepin in the 3-6 mg dosage range[25].

Doxepin, originally developed as an antidepressant in dosages of 75-150 mg/day, has H1 antagonism as its most potent pharmacological effect[168]. As a result, as the dosage is decreased, this agent becomes an increasingly specific H1 antagonist[168].

Double-blind, placebo-controlled trials carried out in both younger and older adults, using both self-report and polysomnographic endpoints, demonstrate the sleep maintenance efficacy of this medication in the 3-6 mg range (Tables 1 and 2). It is notable that the therapeutic effects appear to be largest towards the end of the night, without increasing morning impairment. As such, this agent appears to be uniquely well suited for use in individuals waking up towards the end of the night and having difficulty returning to sleep. Studies of up to 3-month duration of nightly treatment have been carried out without dependence occurring[136].

The most common adverse effect reported in younger adults is daytime sedation. However, in older adults there were no adverse effects reported more frequently with doxepin 3 mg compared to placebo. As such, older adults with early morning awakening would be a particularly appropriate group to treat with this medication. Also, given its potent H1 antagonism, doxepin could also be considered for use in people with insomnia occurring with allergy symptoms. As this agent is without abuse potential, it could also be used in patients with sleep maintenance problems who are prone to abuse, although no data exist on its use in this population.

Orexin receptor antagonists

The name "orexins" was given to two peptides that were relatively recently discovered to arise from the neurons of the lateral hypothalamus and to promote wakefulness/arousal[118-120]. Agents which are orexin receptor antagonists are sleep promoting, owing to their ability to block the arousal mediated by the orexins.

Suvorexant is an agent which blocks both types of orexin receptors (orexin A and B) and has been demonstrated in double-blind placebo-controlled trials to have therapeutic effects on sleep onset and maintenance (including in the last third of the night) in both younger and older insomnia patients, at dosages from 10 to 40 mg (Tables 1 and 2). This includes a placebo-controlled trial of nightly treatment for a year, which demonstrated sustained therapeutic effects and no significant rebound insomnia on discontinuation[120].

The adverse effect of suvorexant that is of most importance is daytime sedation. Available studies suggest that this agent is associated with some abuse potential that is roughly comparable to that of zolpidem, so that it is probably best avoided in people predisposed to abuse.

Suvorexant is the only agent with therapeutic effects in the last third of the night without substantially increasing morning sedation that also has a robust therapeutic effect on sleep onset. As such, it could be considered for use in those patients with both sleep onset difficulties and early morning awakening.

Antidepressants

There are several medications originally developed for the treatment of major depressive disorder that are commonly used for treating insomnia. These agents may produce sleep enhancing effects by blocking the receptors for neurotransmitters that are wake enhancing, such as norepinephrine, histamine, acetylcholine and serotonin[25].

The antidepressants most commonly used to treat insomnia are trazodone 50-150 mg, doxepin 10-75 mg, mirtazapine 15 mg, and amitriptyline 10-100 mg[25]. Of these agents, only doxepin 25-50 mg has been demonstrated to have therapeutic effects in insomnia patients in at least one placebo-controlled, double-blind, randomized trial, and this study was small (N=47) (Table 1).

Although trazodone is widely prescribed in the treatment of insomnia, it has not been found to have therapeutic effects in insomnia patients in any randomized, double-blind, placebo-controlled trial. It was evaluated in one such trial in younger adults, but significant effects compared with placebo were not found[97]. This should not be interpreted as definitive evidence that it lacks therapeutic effects in insomnia. In fact, that study evaluated only one dose of trazodone (50 mg), whereas clinically a range of doses from 50 to 150 mg is prescribed[25].

There are data available on the efficacy and side effects of the S isomer of mirtazapine, which is not currently available for prescription. S-mirtazapine, like doxepin, is a selective H1

antagonist and has been evaluated in a dosing range far below the antidepressant dosage, at which it is expected to have only H1 antagonist effects of clinical significance[169-171]. Placebo-controlled, randomized, double-blind trials carried out with this agent suggest that, like doxepin, it has robust effects on sleep maintenance, with less pronounced therapeutic effects on sleep onset[169-171].

The adverse effects of the antidepressants used to treat insomnia vary. All of them can cause daytime sedation, and most may cause orthostatic hypotension. The tricyclic antidepressants doxepin (25-50 mg) and amitriptyline can cause dry mouth, constipation, blurred vision, urinary retention, cognitive impairment, arrhythmias, and increased appetite/weight gain[25]. Mirtazapine's most important adverse effects tend to be sedation and increased appetite/weight gain. Trazodone's most important adverse effects include sedation and orthostatic hypotension; it may also induce priapism[25].

As none of these agents has significant abuse potential, they can be considered in people with a predisposition to substance abuse. They can also be considered for use in patients who fail usual therapy or have concomitant conditions such as mood, anxiety or pain difficulties, owing to their broad pharmacological effects[25]. Doxepin and amitriptyline should be used with caution in individuals prone to cognitive impairment, urinary obstruction or glaucoma. The use of all these agents is problematic in patients with bipolar depression, because of the risk of precipitating mania[172].

Antipsychotics

Antipsychotics are a group of medications developed for treatment of psychotic conditions that are sometimes used in clinical practice to treat insomnia, generally at a dosage lower than that typically used to treat individuals with psychosis[25]. These agents may have therapeutic effects in insomnia due to their broad antagonism of wake promoting neurotransmitter receptors, such as dopamine, histamine, serotonin, cholinergic and adrenergic receptors.

The antipsychotic medications that are most commonly used to treat insomnia in clinical practice are quetiapine 25-250 mg and olanzapine 2.5-20 mg. There are no rigorous double-blind, randomized, placebo-controlled trials demonstrating the efficacy of any antipsychotic medication for the treatment of insomnia.

A few small studies of quetiapine have been carried out. This agent was reported to improve wake time after sleep onset as compared to placebo in a trial of 20 patients with alcohol use disorder in recovery and sleep disturbance[173]. A double-blind, randomized, placebo-controlled trial of quetiapine 25 mg was also carried out in 13 patients with primary insomnia and demonstrated an advantage for quetiapine on sleep latency and total sleep time, although neither reached statistical significance[174].

The primary side effects of these agents include sedation, orthostatic hypotension, dry mouth, tachycardia, increased appetite/weight gain, agitation, dizziness, constipation and akathisia. More concerning, though far less common, is the risk of tardive dyskinesia. The increased risk of cerebrovascular events in patients with dementia should also be taken into account.

As these agents are without abuse potential, they can be considered for use in people who are abuse-prone. They are best suited, however, for insomnia occurring in patients with psychosis or bipolar disorder.

These agents should be used with caution in those with dementia, hypotension or at risk for myocardial infarction, closed-angle glaucoma, constipation or urinary retention.

Non-selective antihistamines

Non-selective antihistamines that are often used to treat insomnia include diphenhydramine and doxylamine, which are ingredients in many over-the-counter insomnia therapies. Both of these agents have, in addition to H1 antagonism, clinically relevant M1 muscarinic cholinergic antagonism.

There are highly limited data establishing the insomnia efficacy of these drugs. A therapeutic effect of diphenhydramine 50 mg on self-reported number of awakenings, but not sleep quality, total sleep time or sleep onset latency, was reported in a placebo-controlled cross-over study in 20 older primary insomnia patients[175]. Diphenhydramine 25 mg was also evaluated in a parallel-group study along with a combination of valerian and hops in 184 insomnia patients, and found to have a significant effect vs. placebo on self-reported sleep efficiency, but not self-reported or polysomnographic sleep onset latency, total sleep time, or polysomnographic sleep efficiency[176].

The most important adverse effects of these medications are sedation, dizziness, psychomotor impairment, cognitive impairment, dry mouth, blurred vision, constipation, urinary retention and weight gain. Less common side effects of diphenhydramine include agitation and insomnia, whereas doxylamine has been linked in case reports to coma and rhabdomyolysis[177].

As these agents do not have significant abuse potential, they can, in theory, be considered for use in substance abuse-prone insomnia patients. They are best suited for use in those with insomnia occurring in the setting of allergy symptoms or upper respiratory infections. They are best avoided in those with closed-angle glaucoma, decreased gastrointestinal motility, urinary retention, asthma and chronic obstructive pulmonary disease.

Anticonvulsants

Some agents originally developed for treatment of seizures are at times used in the management of insomnia. They include gabapentin and pregabalin, whose potential therapeutic effects in insomnia are ascribed to a decreased release of glutamate and norepinephrine through binding to the alpha-2-delta subunit of N-type voltage-gated calcium channels[178,179].

There are no double-blind, randomized, placebo-controlled trials evaluating the efficacy of these agents in insomnia pa-

tients. Two double-blind, randomized, placebo-controlled trials were carried out evaluating the effects of gabapentin 250-500 mg on sleep disturbance created by putting people to bed five hours earlier than usual (five-hour phase advance model). They reported that this agent significantly improved both self-reported and polysomnographic wake time after sleep onset and total sleep time compared with placebo, but not sleep onset latency[180,181].

Therapeutic effects of gabapentin and pregabalin on sleep disturbance have also been reported in studies of patients with pain, restless legs syndrome, generalized anxiety disorder, and epilepsy[182-185].

The most important side effects of gabapentin are sedation, dizziness, ataxia and diplopia, whereas the most important adverse effects of pregabalin include sedation, dizziness, dry mouth, cognitive impairment and appetite increase. Pregabalin appears to have some abuse potential, whereas this is not the case for gabapentin[186].

These agents could be considered for use in insomnia occurring in patients with pain, partial seizures or restless legs syndrome. There is some evidence supporting the use of pregabalin to treat insomnia occurring in those with alcohol use disorder[187,188]. Both of these medications should be avoided in patients with impaired renal function.

UNMET NEEDS

Insomnia is a common and often debilitating disorder that is associated with significant adverse consequences for physical health and well-being. Fortunately, there are behavioral and pharmacological treatments available for treating this condition. In this paper we reviewed the evidence base for those treatments in order to provide a resource for practitioners, with the hope that this would improve the clinical management of insomnia. However, our review also illustrates that there are a number of important gaps in the research carried out to date.

We lack information on the specific effects of the various components of CBT-I which might allow greater treatment efficiency and tailoring. While meta-analyses demonstrate the value of CBT-I, they also note significant heterogeneity. Variability in CBT-I components across trials makes it difficult to determine which aspects are most responsible for the observed benefits. As such, there is a need for studies aimed at providing this information.

There are also a number of key gaps related to pharmacotherapy. The most glaring one is that we lack any double-blind, placebo-controlled, randomized trial demonstrating the efficacy of any pharmacological treatment for insomnia in children or adolescents. There is clearly an urgent need to carry out these studies in order to guide effective clinical practice in younger individuals with insomnia.

Another gap in insomnia pharmacotherapy research is that we lack rigorous double-blind, placebo-controlled trials of a number of agents commonly used to treat this condition in clinical practice. This includes agents such as trazodone, quetiapine and gabapentin. It would be of great value to those clinicians who tend to prescribe these medications if they had data delineating their risks and benefits to help guide their clinical decision making.

We also lack studies of the pharmacological treatment of insomnia in the setting of several key conditions where this treatment is very often needed, such as dementia, mild cognitive impairment and substance use disorders.

A final critical gap in our knowledge base reflected in our review is that we lack research to help guide personalization of therapy. The vast majority of studies carried out evaluate a single therapy vs. a placebo or another control intervention. More trials are needed comparing effective treatments and aimed at optimally matching treatments to specific patient types, so that we can move to greater personalization in clinical practice.

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The crossroads of psychiatric epigenomics

Traditionally, the origin of mental disorders has been attributed to the combination of genetic and environmental risk factors. Since environmental effects are difficult to pinpoint, a strong emphasis has been placed on genetics. However, despite the increasing scale and scope of contemporary genetic studies on mental disorders, it is evident that structural DNA differences cannot explain all facets of these disorders.

The beginning of 21st century in psychiatric research was marked by the arrival of epigenetics, followed by its large scale version – epigenomics[1]. The rapidly increasing popularity of epigenetic approaches in psychiatric diseases, and human morbid biology in general, can be explained by several factors. A series of cell biology studies showed that histone proteins are not just passive scaffolds for packing the two sets of 2 meter-long DNA strands into the micrometer-sized cell nucleus. Acetylation, methylation, phosphorylation and other types of chemical modifications of histones determine accessibility to local chromatin, which, in turn, regulates transcription factor binding and gene activation. The discovered regulatory functions of histone modifications resonated well with those of DNA modifications, which included methylation and other covalent chemical attachments to cytosines. By this time, DNA modifications had already been shown to account for monoallelic expression of imprinted genes, suppression of genomic retroelements, and X chromosome inactivation[2]. With some exceptions, the density of modified cytosines in gene regulatory elements correlates with gene transcriptional activity.

The realization that epigenetic factors play a pivotal role in the regulation of genes and genomes put them on par with DNA sequence variation. It has become evident that the failure of epigenetic "software" can be as detrimental as changes in the DNA sequence "hardware". Furthermore, the responsiveness of the epigenetic code to the environment allows it to be an "interface" between genes and the environment, thereby positioning epigenetic studies to offer new insights to DNA-environment interactions in determining complex phenotypes[3]. For example, one of the main mysteries in human morbid biology is why identical twins frequently do not share phenotypes. It has been known from isogenic plants and inbred animal studies that genetically identical organisms can exhibit numerous epigenetic differences, some of which may translate to different phenotypic outcomes[4]. Notably, not all epigenetic variations need to be caused by environmental factors; stochastic errors of maintenance of epigenetic profiles may accrue over time, resulting in significant molecular and, by corollary, phenotypic differences.

Epigenetics has identified some "blind spots" in psychiatric research, with the most notable being age- and time-dependent phenotypic changes in organisms. There is increasing evidence that epigenomes age in a partially deterministic fashion. The best illustration of programmed aging is the epigenetic "clock": age-dependent methylation changes at several hundred cytosines that allow for the precise prediction of an individual's chronological age[5]. Slow deviation from healthy epigenetic aging may not immediately cause health problems, nor even for an extended period of time. Such a mechanism may explain why individuals carrying inherited disease risk factors remain disease-free for several decades after birth. Following disease onset, epigenomes may also fluctuate, which has the potential to translate into disease remissions and relapses. Finally, the accumulation of epigenetic aging changes in elderly adults may surpass the effects of disease epigenomes, resulting in partial recovery of psychiatric symptoms in late life.

The rapidly increasing interest in psychiatric epigenetics and epigenomics is best illustrated by PubMed statistics. Over the last 18 years, the annual number of publications with the key words "epigenetic AND psychiatric" has increased nearly 80-fold (6 and 478 papers in 2000 and 2018, respectively). The majority of studies focus on DNA methylation analysis. The typical study investigates peripheral blood samples collected from hundreds, and in rare cases thousands, of psychiatric patients and controls, with the use of Illumina microarrays that interrogate ~450,000 cytosine sites in gene regulatory and coding regions. It is worth noting that Illumina microarrays profile only a small fraction of cytosines with the potential to carry brain disease-relevant epigenetic changes. Analysis of the entire methylome of multiple individuals in populational studies has thus far been prohibitively expensive, leaving large parts of the epigenome unexplored.

Despite significant efforts, psychiatric epigenetic and epigenomic findings are modest thus far, and their interpretation is difficult[6]. The majority of studies have been performed using white blood cells. To date, it is still not clear whether such "surrogate" tissues can be useful for mental disorder studies, given that epigenetic status and dynamics in neurons and glial cells are distinct from those of white blood cells. The studies performed in post-mortem brain are of particular interest, but they also face the issue of separating genuine disease-causing epigenetic signals from those that result from living with the disease or unrelated processes taking place over an individual's lifetime. Another concern is brain cell type heterogeneity – the mixture of many different subtypes of neurons and glial cells. If proportions of such cell subtypes were to vary, the detected epigenetic differences may reflect cellular differences, rather than the sought-after disease-related epigenetic changes. Finally, even in large and well-designed studies, the mean DNA methylation differences between psychiatric patients and controls rarely exceeded 1%[7], which has made biological interpretation difficult, especially considering the large variation exhibited by epigenetic marks across individuals.

At the same time, basic epigenetics is progressing rapidly. Recent large epigenomic studies such as PsychENCODE documented numerous new layers in epigenetic and chromatin organization of the brain[8]. The list of epigenetic marks is increasing, and it has been recently detected that major monoaminergic

neurotransmitters, such as serotonin, can be attached to histones and facilitate gene expression in neurons[9].

In parallel, experimental approaches have become more sophisticated and informative. Several laboratory innovations are of particular interest for psychiatric epigenomics. First, single-cell approaches are redefining the meaning of epigenetic stochasticity and directly address the issues of cell type differences in the brain. Second, easily available somatic cells, such as fibroblasts, can be reprogrammed into neurons, partially addressing the need for brain tissue. Third, CRISPR-Cas9 technology can be used not only for editing genomes, but also epigenomes, which is of considerable interest for modeling disease components in tissue culture and animals. Fourth, progress in computational strategies has enabled the integration of epigenomic data with genomics, transcriptomics, and metabolomics. The comprehensive trans-omic approaches enable the identification of hub elements and cellular pathways centrally involved in disease. Given the rapid developments in molecular biology and brain imaging technologies, an ideal experiment – a prospective epigenomic study in the living brain of psychosis-predisposed individuals – may not be science fiction in the near future.

Despite the challenges thus far, epigenetics and epigenomics remain an important part of the psychiatric research agenda. There are still no better ways to explain the numerous dynamic features of complex diseases, which by definition do not conform with the stability of DNA sequence. Uncovering the mechanisms of discordance in monozygotic twins or the delayed age of psychosis onset would be of major importance for precision psychiatry. The success and progress of psychiatric epigenetics relies on the ever improving experimental and computational tools and, more importantly, on the diligence and creativity of scientists working on this very interesting, but also challenging, part of human biology.

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What is treatment resistance in psychiatry? A "difficult to treat" concept

Since the year 2000, there has been an exponential increase in papers on treatment resistant psychiatric disorders. It is unclear to what degree this is guided by unmet clinical need, by regulatory bodies looking for more homogeneous patient groups, or by budget limitations imposed by health care payers on first line treatments.

A more fundamental question is whether a categorical definition of treatment resistance makes sense[1,2]. Do we have evidence to delineate such an entity and, if so, what is the possible clinical practice benefit? When it results in putting a threshold before more effective treatment options can be implemented, why should those options not be chosen as an earlier treatment step? Anyhow, the concept underscores that currently available treatment options are suboptimal.

The evidence for a distinct psychopathological or neurobiological nature of treatment resistant psychiatric disorders, and hence for a categorical definition of treatment resistance, is limited and, outside of a clinical trial context, not very useful[3]. In depression, in anxiety disorders and in schizophrenia, the standard categorical definition is "an inadequate response to at least two adequate (appropriate dose and lasting for at least six weeks) treatment episodes with different drugs". In eating disorders, where psychopharmacology is not the main treatment option, treatment resistance has been poorly defined and shown to be mainly related to the severity of associated psychopathological features. In personality disorders, treatment resistance is often mentioned, but in the sense of resistance to entering or to pursuing psychotherapy.

What is supposed to be an inadequate response differs from disorder to disorder and is sometimes defined differently in a first step treatment versus a treatment resistant patient. A response can be considered inadequate on the basis of an absolute threshold of symptom severity or a percentage change from baseline in symptom severity[4]. In major depression and in generalized anxiety disorder, response is usually defined as a 50% decrease in symptom severity (but it has also been defined as a 25% decrease in patient selection for trials focusing on treatment resistant depression). In obsessive-compulsive disorder, it is usually defined as a 35% decrease in symptom severity, and in schizophrenia as a 30% decrease (or a 20% decrease in treatment resistant schizophrenia).

"Response" defined as a percentage improvement in the global score of a rating scale can obscure clinical reality: a response can be seen in a depressed patient despite high residual cogni-

tive symptoms or severe residual anhedonia, or in a patient with an anxiety disorder despite increased avoidance behavior, or in a patient with schizophrenia despite high levels of negative or cognitive symptoms. Functioning or distress are often not taken into account when defining an (in)adequate response, while, in some patients with schizophrenia, learning to cope with a treatment resistant hallucination can significantly decrease distress and hence improve quality of life[5].

The reason why most definitions of treatment resistance require two previous unsuccessful treatment episodes is also unclear. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial documented that, with each treatment step, an incremental gain in the response rate is observed, but there is also an incremental dropout rate and a higher and faster rate of relapse[6].

Furthermore, in defining treatment resistant schizophrenia, only pharmacotherapy is considered, while, in defining treatment resistant anxiety disorders, both pharmacotherapy and psychotherapy are taken into account. It is remarkable that, in treatment resistant depression, psychotherapy or neuromodulation (except electroconvulsive therapy) are most often not considered.

The fact that outcome in trials with treatment resistant patients provide different results depending on whether the two treatment episodes with inadequate response were both retrospective or whether one was retrospective and the other one prospective further documents the difficulty in obtaining a homogeneous patient population.

The recommendation that each of the two treatment episodes should have lasted "at least six weeks" is understandable from both a trial design and a clinical point of view, since few non-responders within the first six weeks will respond later, but again is far away from daily practice: health insurance databases show that a third treatment step is on average started after 43 weeks, which is important to take into account, since duration of an illness episode predicts outcome[7].

It is understandable that classification attempts are now moving away from two categories (non-resistant or resistant) versus staging and "levels of resistance" approaches. These are based on number of treatments (with different treatments getting differential weights), episode duration and symptom severity.

More fundamentally, it has been suggested that the expression "treatment resistance" is "devoid of empathy"[8]. Indeed, the expression seems to blame the disorder or even the patient: for example, a lay press article mentioned that a new antidepressant "can cause rapid antidepressant effects in many people with 'stubborn' depression"[9].

Finally, the concept of "treatment resistance" stems from an acute illness model with remission or cure as the goal. Unfortunately, not all patients with psychiatric disorders can reach that symptom-free goal. That's why the use of the more collaborative expression "difficult to treat" psychiatric disorders could be preferred.

This expression may fit better with the recurrent or chronic nature of some psychiatric disorders. Achieving a meaningful life in spite of limitations can be(come) the ultimate treatment goal. This also resonates with the "recovery" movement, which identifies regaining personal control and establishing a personally meaningful life, with or without residual symptoms, as the objective to pursue.

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Factors facilitating or preventing compulsory admission in psychiatry

A large majority of mental health professionals have a positive attitude towards compulsory admission of people with mental disorders, when some conditions specified by the law are present[1]. However, most professionals are not aware that the circumstances under which compulsory admissions actually occur worldwide are very different, as reflected by the wide variation of the numbers of these admissions in the various countries[2], which cannot be explained by clinical variables.

The factors which impact on the threshold for compulsory admissions, either facilitating or preventing them, can be classified into three levels: a macro-level, including the wider societal perspective and the national legislation; a meso-level, including the organization of mental health care and in particular the implementation of intervention strategies aimed to reduce those admissions; and a micro-level, including the socio-demographic and clinical features of the affected persons as well as the attitudes of their caregivers.

At the macro-level, the assumption that people with severe mental disorders, in particular schizophrenia, are unpredictable and dangerous is still widespread in the general population in many countries. This is the background on which national mental health legislations often identify the risk of harm to others as the main criterion for compulsory hospitalization, in order to ensure protection of the general public. The threshold for perceived danger may vary substantially from context to context and from professional to professional, and this will ob-

viously influence the likelihood of involuntary hospitalization.

In most mental health laws, compulsory hospitalization also serves the purpose of protecting a person with a mental disorder from self-harm. However, the conceptualization and perception of self-harm may again vary substantially from context to context and from professional to professional, so that compulsory admission may be restricted to an imminent and/or serious danger or otherwise focus on possible long-term threats to the affected person's mental and/or physical health. This, again, may affect the rate of involuntary admissions.

Finally, the formal procedural act, i.e., which legal authority takes the responsibility for the involuntary hospitalization, such as an independent authority or the medical system itself, and the safeguards that are provided, including the right by the patient to oppose the decision, also contribute to set the threshold for compulsory hospitalization.

At the meso-level, the organization of the mental health care system is a crucial factor affecting the rate of compulsory admissions. Continuity of care, and in particular an effective integration between the inpatient and outpatient components, is likely to be a crucial factor. However, a meta-analysis of randomized controlled trials of "integrated treatment" (actually including only one study on crisis resolution teams, two studies on integrated treatment in first-episode schizophrenia, and one study on psychoeducation combined with focused monitoring) found no significant reduction in the risk of compulsory admissions[3].

This meta-analysis also found no significant risk reduction in two studies on compliance enhancement (focusing respectively on treatment adherence therapy and on financial incentives for improving adherence to antipsychotic treatment), and three studies on "community treatment orders" (i.e., orders for the patient to receive involuntary treatment in the community)[3].

Why these strategies are ineffective remains unclear. Most of the above studies were conducted in Anglo-Saxon countries, and it is possible[4] that in those countries certain staff characteristics facilitate compulsory admission, such as weekend working, burnout and lack of contact with other services. In other cultural settings with less distressing service characteristics, similar intervention strategies might be more successful[5].

In some countries, a significant increase in compulsory admissions has been observed during the process of deinstitutionalization[2], which has revived the old debate on whether community mental health care facilitates "revolving door", i.e. repetitive – including involuntary – hospitalization as a consequence of too early discharge from inpatient units into the community. However, the above increase seems to reflect a more general increase in psychiatric service use rather than a failure of community psychiatry[2].

At the micro-level, it has been repeatedly documented that persons who are male, younger, unemployed, from an urban environment, from lower social classes, and from a diverse ethnic and linguistic background, are at higher risk of compulsory hospitalizations[6]. However, most of these risk factors are likely to be proxies, standing for social exclusion and isolation, which, in a complex interaction with clinical features, may facilitate compulsory admissions.

A potentially effective approach for users to prevent compulsory admissions are advance statements. These are documents which allow persons at risk to state their future treatment preferences in the case they will not be able to make considered decisions. A meta-analysis of four randomized controlled trials on advance statements[3] found a statistically significant and clinically relevant 23% reduction in compulsory admissions in adult psychiatric patients. Advance statements are currently advocated also by international bodies, such as the World Health Organization[7].

On the other hand, user-held records (i.e., the person holding the information about the course and care of his/her illness) have been found to have no significant effect on compulsory admissions in three randomized controlled trials versus treatment as usual[8].

Whether the involvement of caregivers in treatment planning may have an impact on compulsory hospitalizations remains unclear. The caregivers' appraisal of compulsory admissions is in general quite favorable[9], as they are regularly the first line who have to cope with patients' acute episodes and carry most of the associated burden. As such, their attitude might, at least in part of the cases, facilitate compulsory admissions, although this issue has never been explored systematically.

From the above synthetic review, it is clear that the literature on factors facilitating or preventing compulsory admissions in psychiatry is more speculative than based on empirical findings, and that the few data available are often controversial and of difficult interpretation. Moreover, cross-cultural studies are very rare, although they may be extremely useful to clarify several aspects. Given the high clinical and ethical relevance of the issue, further research in this area is obviously warranted.

It is likely that many of the factors we have briefly considered contribute with a small effect to facilitate or prevent compulsory admission, and that interventions will need to be likewise differentiated and take place at different levels.

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Systematic inclusion of culture-related information in ICD-11

The experience and presentations of mental disorders are affected by culture and the social milieu, not only of patients and families, but also of the individuals and health systems providing care. These cultural views impact what is considered normal or pathological. The salience of cultural considerations has therefore been increasingly reflected in modern classification systems.

The two dominant classification systems in psychiatry, in their earlier editions, took somewhat different approaches to reflecting cultural influences on diagnosis. The Clinical Descriptions and Diagnostic Guidelines (CDDG) for ICD-10 Mental and Behavioural Disorders did not include a classification of culture-specific disorders, but rather noted the presence of cultural variations in expression under broad disorder groupings (e.g., somatoform disorder) and in help-seeking and illness-related behaviour. However, consideration of culture was not systematically incorporated in the manual. In contrast, the DSM-IV incorporated brief descriptions of cultural features under specific disorders, outlined components of a cultural formulation approach, and listed twenty-five "culture-bound syndromes"[1].

The development of the ICD-11 has emphasized the principle of global applicability, i.e., the need for the diagnostic guidelines to function well across global regions, countries and languages[2]. Reflecting the cultural context in which clinical encounters take place is likely to enhance this goal. However, there is an inevitable tension between the incorporation of locally relevant material and the essential purpose of an international classification system, which is to reliably convey clinical information across diverse boundaries. Responding to this challenge requires a pragmatic balance that involves recognizing cultural differences where these are clinically important without allowing them to detract from the goal of a common global diagnostic language[3].

As a way of including meaningful consideration of culture in the diagnostic process, the World Health Organization (WHO) Department of Mental Health and Substance Abuse constituted a Working Group to develop guidance on cultural considerations for the ICD-11 CDDG, based on the current state of clinically applicable information for individual disorders and/or disorder groupings.

The focus was on providing pragmatic, actionable material to assist clinicians in their evaluation of patients using the ICD-11 guidelines and reduce bias in clinical decision-making by facilitating diagnostic assessment in a culturally informed manner. Thus, for example, while recognizing that specific idioms relating to mental illness are always influenced by culture, what the guidance describes are emotions, cognitions or behaviours that are broadly universal and therefore not "culture-bound" in the sense of being unique.

The Working Group developed the following set of questions to guide the generation of the material on culture:

- Is there evidence that culture exerts a strong influence on the presentation of the disorder? For example, is there notable cross-cultural variation? Is a mechanism known for how culture might influence the symptoms or presentation of the disorder?
- Is there evidence that the prevalence of the disorder is particularly high or low in specific populations? What caveats should be considered in interpreting these data (e.g., misattribution of symptoms by clinicians unfamiliar with cultural expressions of distress)? Is it possible to link prevalence variation to information on mechanisms (e.g., available data suggesting that prevalence of anorexia nervosa is higher in societies where thinness is idealized)?
- What are the cultural concepts of distress (idioms, syndromes, explanations/causes) identified in various cultural groups that are related to the disorder?

To generate the guidance, the Working Group conducted extensive consultation with experts and reviewed the literature on cultural influences on psychopathology and classification of each diagnostic grouping as well as the texts provided in the ICD-10 CDDG and the DSM-5. Information was also derived from materials produced by various ICD-11 Working Groups as part of their generation of ICD-11 content forms[4]. The resulting guidance is designed to help the clinician make informed decisions which are likely to foster patient-centered care that is sensitive to the cultural and social milieu of the clinical encounter.

The following is an example of the resulting material on cultural considerations for adjustment disorder:

- Adjustment disorder may be exacerbated by limited family or community support, particularly in collectivistic or sociocentric cultures. In these societies, the focus of the worry may extend to stressors affecting close relatives or friends.
- Adjustment disorder reactions that include dissociative symptoms may be more prominent in some cultural groups.
- Symptoms of the disorder may be influenced by local idioms (e.g., *susto* or *espanto* (fright) in Central America) that are associated with fear or subsequent worry regarding a stressor with strong cultural connotations (e.g., becoming suddenly frightened when crossing an unpopulated area alone at night). These idioms are also applicable to anxiety disorders.

While the guidance can enhance the global applicability of ICD-11, it is not sufficient to meet this goal. The limitation of current scientific knowledge means that robust validating data for most diagnostic categories is lacking[5,6]. Classification of mental disorders has therefore entailed best judgment of existing information, usually by groups of experts. The data on which such judgment is commonly based are largely derived from the West, with large sections of the world contributing very little to the information pool. Just as we know that psychiatric diagnosis is not

value-free[7], there can be little doubt that psychiatric nosology is embedded in the culture of its derivation and that where the data come from is important.

One way of alleviating the limitation of the sources of data is to ensure that diverse cultural groups bring their experiences to the decision-making process[8]. Within the constraints of our imperfect present state of knowledge, the WHO has sought to address this need by ensuring that all ICD-11 Working Groups included members from all global regions, with a substantial proportion from low- and middle-income countries, and through the flexible design of the ICD-11 CDDG, which allows more scope for clinical judgment to take account of contextual, including cultural, factors[4].

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Transdiagnostic psychiatry: premature closure on a crucial pathway to clinical utility for psychiatric diagnosis

There is no doubt that psychiatric diagnosis faces a crisis and needs a new way forward which is grounded in clinical utility[1-3]. We have proposed a transdiagnostic approach built upon a clinical staging framework[3,4], which, while reflecting strongly the dimensional nature of the clinical phenotypes, retains a categorical or syndromal approach and many of the existing concepts, such as depression and psychosis. This is a heuristic strategy which seeks to pave the way to improved clinical utility. Transdiagnostic clinical staging is a relatively recent proposal and data is accumulating which will test its validity.

Fusar-Poli et al[5] create the impression that they are addressing this question in the introduction to their recent systematic review of transdiagnostic research. However, it soon becomes clear that their expedition has captured research which is of quite a different nature and has little bearing on the higher order challenge facing psychiatry. Conceptually, they have ignored most of the literature on contemporary transdiagnostic thinking and new nosological approaches (e.g., clinical staging, Hierarchical Taxonomy of Psychopathology (HiTOP), network theory, p factor). The one exception is the Research Domain Criteria (RDoC) project, which, while transcending DSM categories for research purposes, is fully dimensional and does not claim to provide any usable framework for clinical purposes.

The authors characterize the origins of transdiagnostic approaches in an idiosyncratic manner. Their gold standard definition is drawn from a reference in the cognitive behavioral therapy (CBT) field[6], and the search they conducted yielded material largely from the CBT space. The critique in their discussion focuses strongly on dimensional vs. traditional categorical approaches, rather than acknowledging that transdiagnostic categorical approaches which respect dimensionality might be possible. It becomes apparent that, despite their claim to be relevant to the wider issues in nosology and diagnosis, they are really talking about the psychotherapy field, providing a critique of recent trends. Hence, their comments about rediscovery versus true innovation are arguably correct in that context.

The authors acknowledge that the quality of the studies they accessed was low, that one fifth were not even transdiagnostic at all, and that only 3 of the 111 studies included met their gold standard definition. Their search, which put undue emphasis on article titles, actually captured only a limited number of relevant studies. It is premature to conduct such reviews with such narrow search terms and confused focus, and we suggest that the field would benefit more from high quality knowledge-generating research aimed at developing and evaluating emerging approaches.

Some form of transdiagnostic paradigm is clearly required, and perhaps Fusar-Poli et al were motivated to stimulate a renewed effort to develop one. However, there is also a risk that their review might dampen enthusiasm for the great challenge of creating and testing a simpler, more useful approach to diagnosis and understanding the process of disorder onset and evolution. Our traditional diagnostic systems are categorical and siloed, consisting of polythetic operational definitions of clinical phenotypes. They have not worked for patients, clinicians or researchers. Boundaries between syndromes and phenotypes are not clear, as the authors correctly point out, and comorbidity is the rule rather than the exception. Syndromes are not discrete disease entities, and we know that dimensionality underlies most of these phenotypes, even though a dimensional approach is too unwieldy for clinical care, and that distress, impairment and need for care are not limited to the full threshold versions of these phenotypes.

This means that some version of a transdiagnostic approach is going to be necessary. The dynamics of early psychopathology are complex, and emerging microphenotypes ebb, flow, and evolve through many patterns, which do not follow rigid train tracks to discrete macrophenotypes such as schizophrenia or bipolar disorder. Ubiquitous comorbidity and heterotypic evolution of syndromes over stages of illness underline the flaws of current diagnostic systems[7]. The reification of these late macrophenotypes has led to a spurious certainty about the indications, specificity and timing of drug therapies (less so psychosocial therapies), with risks of premature treatment, overtreatment, undertreatment, and mismatched treatment.

Emerging psychopathology is a mixture of anxiety, affective dysregulation, aberrant salience, cognitive impairment, and motivational changes that dynamically influence one another over time, creating a range of clinical patterns. Despite this complexity and dimensionality, treatment decisions are largely binary, and clinicians need useful categories for guiding these decisions[8]. This is why clinical staging has emerged as a potentially useful model.

Clinical staging has been adapted from mainstream health care as a framework to facilitate early intervention, enhancing prediction and personalization of care through profiling within stages, and guiding research[9]. It has particular value when applied in the *early stages* of illness, where it supports the proportional yet proactive treatment of young people experiencing distress, a need for care, and an unstable and fluctuating collection of microphenotypes which nevertheless connotes substantial risk of suicidal behaviour and functional impairment.

Some authors have attempted to mould the staging idea to the procrustean silos of existing late macrophenotypes. However, the essential feature of the model is that it is transdiagnostic. This does not mean that late macrophenotypes such as mania, psychosis and anorexia cannot be accommodated as they differentiate out and stabilize. The specificity of treatment approaches or otherwise can be examined and the spurious

precision of the licensing of medications and other therapies replaced by a more flexible and accurate evidence-based approach as in mainstream health care.

The potential value of such an approach for the redesign of mental health care cannot be overestimated, as we struggle to replace 50-year-old mindsets and work practices with a modern, dynamic 21st century approach.

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Transdiagnostic psychiatry goes above and beyond classification

For the last decade or so I have been involved in developing the science and practice of psychological interventions that apply across psychiatric disorders[1,2]. These developments, known collectively as the transdiagnostic approach, have recently been challenged in this journal within a systematic review[3]. The review extracted research studies that used the term "transdiagnostic" in their title to include a heterogeneous mix of methodologies and samples. The authors report that few studies met the "Mansell criteria"[4] for transdiagnostic research in psychiatry. In particular, the studies were critiqued for their limited use of standardized diagnostic interviews, and the lack of any alternative classification system. Treatment studies in the review generally found that the outcomes of transdiagnostic and disorder-specific interventions were equivalent.

Each of the above points were presented as shortcomings of the transdiagnostic approach. I will explain here the conceptual foundations of the transdiagnostic approach in more depth to challenge that conclusion.

The "Mansell criteria" were initially developed by A. Harvey and colleagues[1] to organize the existing research literature on cognitive and behavioural processes across psychiatric disorders. At the time, that review provided evidence that twelve different processes were shared across multiple (at least four) disorders. In other words, the transdiagnostic basis of psychological processes across psychopathology was already established.

The literature that is relevant to the transdiagnostic approach goes well beyond the articles that use the word "transdiagnostic". For example, there is a large, replicated literature on "p", the general psychopathology factor, which rarely uses the term "transdiagnostic"[5]. These studies show that a single factor underlying the diverse symptoms of psychiatric disorders can be identified and predicts a range of medical, health and socioeconomic outcomes. In addition, one could mention the human connectome research: large-scale studies of brain networks have identified the same disrupted neural pathways across different psychiatric disorders. Most recently, a study of 402 patients with a range of affective and psychotic disorders, matched with 608 healthy controls, identified a single network (across the frontoparietal regions) that was shared across disorders, and its level of disruption scaled with severity[6].

Earlier critiques of current classification systems have typically attempted to replace them with a new classification system, such as a dimensional system. Yet, the aim of the transdiagnostic approach is different. It is to identify, utilize and test a general theory of psychopathology[4]. This involves trying to understand the shared, overarching processes that cut across the classification system. This scientific approach is analogous to understanding evolution by natural selection as the mechanism of change that accounts for variation in all the living organisms that are classified[7]. Transdiagnostic interventions then aim to harness a general, neurally mediated, change process, regardless of psychiatric diagnosis. Furthermore, most transdiagnostic approaches posit a mechanism that is on a continuum with the general population, so the strict delineation between a clinical diagnosis and a sub-clinical issue is less critical to this field of research[1].

The most commonly assessed impact of transdiagnostic interventions is still symptom reduction. Yet, symptom relief is only one possible variable to compare and evaluate treatments. Other valuable variables include efficiency, cost-effectiveness, accessibility, and reduction in patient-reported distress. Patients, public, clinicians, service providers and policy makers need to be consulted to determine what is valued. One consequence of this broader perspective is that showing equivalent symptom reduction to a disorder-specific intervention is a particularly positive outcome for transdiagnostic treatments, because by definition they have a reduced need for diagnostic assessment and no requirement for training in multiple diagnostic treatment models[4]. Furthermore, emerging evidence indicates that some transdiagnostic treatments are more efficient, since they may achieve the same reduction in distress through fewer numbers of sessions[8].

It is commonly held that randomized controlled trials are

the gold standard of treatment evaluation. However, on their own, they do not provide evidence that a psychological therapy works through the mechanisms that it claims. The effect could result from the expectation of the therapy working (placebo effect), or through simply talking to a professional. Again, if we follow the successful examples of other sciences, such as chemistry, physics and engineering, the most robust test of a theory is to build and assess a working model of a process[9]. This tradition started with Galileo, continued with prototyping in machine design, and today is typically carried out within computer simulations. If the model behaves the same way as the real system under natural conditions, then the theory informing the model must be correct. There is no *a priori* reason why this should not apply as well to human behaviour as it does to the theory of aerodynamics informing airplane design, for example. Our clinical research team uses Method of Levels (MOL) as a transdiagnostic intervention which we disseminate widely[2,8]. This therapy is based on perceptual control theory, a general theory of behaviour drawn from control engineering. Its key principles of control, conflict and reorganization have been assessed through testing computational models against behavioural data[9].

In sum, transdiagnostic psychiatry is well established, but to understand its transformative potential requires adopting the appropriate scientific approach. Future reviews need to evaluate a broad literature including general psychopathology and shared neuropsychological pathways, and to separate the evaluation of treatment and process studies. Treatment research needs to consider the multiple perspectives of different stakeholders when determining how to index evidence for the potential benefits of a transdiagnostic approach. Process research, on the other hand, needs to be theory driven, hypothesis-led, and ideally emulate the model-testing paradigms of other sciences. A transdiagnostic approach of this kind has the potential to generate a genuine, interdisciplinary, paradigm shift in psychiatry and mental health.

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TRANSD recommendations: improving transdiagnostic research in psychiatry

There is no doubt that transdiagnostic research in psychiatry has gained momentum over recent years. However, what is meant by transdiagnostic research, and the impact it has on current psychiatric practice, is much less clear. The adjective "transdiagnostic" itself does not exist in English dictionaries, and even online medical dictionaries recommend searching the words "trans" and "diagnostic" separately. The word "transdiagnostic" is not only a neologism, but it also exclusively applies to psychiatry. While diagnoses are ubiquitous in medical research and practice, there are no consolidated exemplars of transdiagnostic research in other branches of medicine.

To characterize the actual meaning and the clinical impact of transdiagnostic research in psychiatry, a systematic review was recently conducted following state-of-the-art evidence synthesis guidelines[1]. Although, as a matter of fact, the word "transdiagnostic" has been historically introduced by cognitive behavioral theories and treatments for eating disorders[2], in that review[1] there was no restriction on any *a priori* definition of transdiagnostic research. On the contrary, the review focused on articles reporting on any transdiagnostic topics: interventions (45%), cognition and psychological processes (28%), neuroscientific topics (13%), classification (4%) and prediction studies (10%).

To systematically appraise the evidence without superimposing *a priori* conceptual schemata of transdiagnostic research, the review performed an epistemological test and empirically included and interrogated articles that self-proclaimed transdiagnostic by explicitly using the word "transdiagnostic" in their title[1]. High-order conceptual reviews of research initiatives that have implicitly adopted a transdiagnostic approach, such as the Research Domain Criteria (RDoC) project, the Hierarchical Taxonomy of Psychopathology (HiTOP) approach, the p-factor construct (none of which have yet replaced the current classification systems in clinical routine), and the clinical staging model, have been recently presented and fully debated in this[3-5] or other[6] journals, and as such were not the main focus of the systematic review[1].

The core finding of this review was that transdiagnostic designations in psychiatry are applied in a loose and unstandardized way, encompassing several different and often incoherent conceptualizations[1]. For example, one would expect studies that self-proclaim transdiagnostic to somewhat address issues relating to the diagnosis of mental disorders. Paradoxically, some of the studies reviewed were intrinsically incompatible with a transdiagnostic framework because they investigated symptoms and not disorders or, to the extreme, reported no diagnostic information at all[1].

Another illustrative example is the fact that authors themselves disagree on the ultimate aim of transdiagnostic research. Some of them claim that transdiagnostic research is a fundamental pathway to clinical utility for improving psychiatric classification and diagnosis[7], while others argue that the transdiagnostic approach does not primarily target the improvement of psychiatric classification and diagnosis, but rather tests a general theory of psychopathology[8]. A further example is the fact that, until the publication of this systematic review[1], the empirical limitations and reporting quality of transdiagnostic research remained unaddressed: appraising and acknowledging the specific limitations of a certain domain of knowledge is equally, if not more, important as celebrating its successes.

It may well be that some versions of a transdiagnostic approach are going to be necessary to improve psychiatric classification and care[7]. What is certain is that, until studies continue to loosely and incoherently self-proclaim transdiagnostic without acknowledging any diagnostic information, it is unlikely that transdiagnostic research will bear any real-world meaning for clinicians, patients, and medical practice. Similarly, poor reporting on the number and type of (trans)diagnostic spectra prevents the appraisal, refinement, and eventual integration of categorical and dimensional approaches in psychiatric classification.

The systematic review acknowledged that transdiagnostic categorical approaches that respect dimensionality are possible in organic medicine as well as in psychiatry[1], but this requires transparent reporting of the results. For example, the largest transdiagnostic study published to date demonstrated that it is possible to report the diagnostic information for almost all ICD-10 mental disorders[9]. Furthermore, while it is possible that transdiagnostic interventions may display superior efficiency, cost-effectiveness, accessibility, and patient-reported satisfaction compared to specific-diagnostic interventions[8], demonstrating this would require robust comparative analyses specifically conducted to test the non-inferiority or superiority of the transdiagnostic approach. These analyses are infrequent in the current literature[1].

The systematic review leveraged these caveats to put forward six empirical transdiagnostic research recommendations: TRANSD[1]. The TRANSD recommendations are pragmatic and focus on improving the quality of appraising and reporting transdiagnostic constructs. Importantly, they do not provide any *a priori* restrictive definition of the transdiagnostic schemata; as such, they can be applied to different topics and stimulate critical research in the field.

The first recommendation is to have a transparent definition of the gold standard (ICD, DSM, other), including specific diagnostic types, official codes, primary vs. secondary diagnoses, and diagnostic assessment interviews. Second, the primary outcome of the study, the study design, and the definition of the transdiagnostic construct should be reported in the abstract and main text. Third, the conceptual framework of the transdiagnostic approach – across-diagnoses (comparing different ICD/DSM categorical diagnoses against each other), beyond-diagnoses (employing ICD/DSM diagnostic information to go beyond it, testing new diagnostic constructs such as biotypes), other (with an explanation of the conceptual framework) – should be appraised. Fourth, the diagnostic categories, diagnostic spectra, and non-clinical samples in which the transdiagnostic construct is being tested and then validated should be indicated. Fifth, the degree of improvement of the transdiagnostic approach should be shown against the specific diagnostic approach through specific comparative analyses. Sixth, the generalizability of the transdiagnostic construct should be demonstrated through external validation studies.

It is hoped that these recommendations will improve the transparency and consistency of the next generation of transdiagnostic research, overcoming the current limitations of knowledge and benefitting psychiatric care.

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Mental illness among relatives of successful academics: implications for psychopathology-creativity research

The relationship between creativity and psychopathology is a long standing topic of research[1]. Creativity is defined as the ability to produce something novel, original, useful and valued, for instance in the domains of art, science or technology. It is being debated if the nature of creativity is general or domain-specific[1]. The assumed relationship between creativity and psychopathology is depicted as an inverted U curve, i.e. vulnerability to or low levels of psychopathology are believed to be associated with creativity, which declines with increased psychopathology[1].

Kyaga et al[2] coupled register information on psychiatric diagnosis with census information on self-reported occupational status. They found that individuals with bipolar disorder and

healthy siblings of people with schizophrenia or bipolar disorder were overrepresented among the scientific and artistic professions. Power et al[3], in a population study in Iceland, found that higher polygenic risk scores for schizophrenia and bipolar disorder were associated with artistic society membership or creative profession, which could not be accounted for by increased relatedness between creative individuals and those with psychoses.

Typically, we consider someone to be creative *post hoc*, on the basis of his/her recognized achievements. However, the contemporary measures of creativity typically rely on psychometric tests[1] or self-reported occupational status[2,3]. Such approaches have limited validity because they may, in fact, measure either a hypothetical disposition or personal aspiration.

We therefore applied a novel approach to the issue by studying the frequency of mental illness among the relatives of successful academics, i.e., people employed in tenured positions at universities. We assumed that such population would reflect a quasi-objective creative achievement compared to the background population.

We designed a study with elements from matched cohort studies and case-control studies. We received the personal identification numbers of all scientific employees in tenured positions at three Danish universities: Copenhagen, Aarhus and Southern Denmark. They were in total 11,803 individuals (referred to as "academics"). These academics were matched 1:6 on age, gender and municipality of residence with randomly selected controls from the background population. Through the Danish Civil Register, we identified first- and second-degree relatives of academics and controls. We divided this population into five subgroups: children, parents, grandparents, siblings and nephews/nieces. Grandchildren were excluded due to low age.

From the Psychiatric Central Research Register, we obtained information on psychiatric diagnoses in academics, controls and their relatives, and grouped these diagnoses following the ICD-10 hierarchy: schizophrenia, non-affective psychosis, bipolar disorder, melancholia, any other mental disorder, or no psychiatric diagnosis.

In comparing the relatives of academics and controls, we adjusted for age and gender. Furthermore, we adjusted for intelligence level, as this has been shown to be a significant epidemiological risk factor for schizophrenia[4] and therefore represents a confounder. We used the educational level (obtained from Statistics Denmark) as a proxy for intelligence.

The five subgroups of relatives were analyzed in a logistic model, with "relation to academic or control" as the dependent variable and the six diagnostic outcomes as the independent variable, adjusted for education, gender and age. The academics and controls were analyzed separately without covarying for educational level.

All data were anonymized, and the authors had no access to any data that could identify individuals. The study was approved by the Danish National Committee on Health Research Ethics and by the administrations of the Universities.

The total population comprised 588,532 individuals: 11,805 academics; 70,818 controls; 69,325 relatives of academics and 436,584 relatives of controls. The odds ratio (OR) for the academics to be diagnosed with any mental disorder was significantly ($p<0.05$) lower than for the controls (OR: 0.44, 95% CI: 0.40-0.49). This also applied to both bipolar disorder (OR: 0.43, 95% CI: 0.27-0.70) and schizophrenia (OR: 0.17, 95% CI: 0.11-0.26).

There was a significantly increased risk for schizophrenia among siblings (OR: 1.92, 95% CI: 1.62-2.27), children (OR: 1.85, 95% CI: 1.38-2.48) and nephews/nieces (OR: 1.50, 95% CI: 1.15-1.96) of the academics. For bipolar disorder, the OR was significantly increased among the academics' parents (OR: 1.38, 95% CI: 1.10-1.74), grandparents (OR: 1.43, 95% CI: 1.03-1.98) and nephews/nieces (OR: 1.62, 95% CI: 1.04-2.50), while significance was borderline ($p=0.05$) for the academics' siblings. The risk for schizophrenia was significantly increased in academics' maternal, but not paternal, half-siblings. The risk for any other mental disorder was significantly lower among the academics' children (OR: 0.75, 95% CI: 0.69-0.82) and nephews/nieces (OR: 0.72, 95% CI: 0.67-0.78).

This study shows that, while successful academics as a group are less prone to mental disorders than the background population, there are increased rates of schizophrenia and bipolar illness among their biological relatives. Other mental disorders, on the other hand, are less frequent among the relatives of academics. Because of our *a priori* hypothesis, we believe that this study supports the idea of a link between creativity and vulnerability to mental illness. We acknowledge, however, that the association between academic status and increased rates of schizophrenia and bipolar disorder in the relatives may be caused by multiple other factors.

The hypothesized relationship between creativity in successful academics and the increased risk for schizophrenia and bipolar disorder in their relatives seems to be mediated by a vulnerability that is not manifested as overt mental disorder in the academics, consistent with the inverted U curve model.

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Embodiment and the Other's look in feeding and eating disorders

Feeding and eating disorders (FEDs) are mainly defined on the basis of behavioural abnormalities, yet there is a general agreement that these are secondary epiphenomena to a more basic psychopathological core, i.e., an anomalous concern about one's body appearance and weight[1]. Theoretical and empirical evidence is increasingly available to better characterize FEDs by specific disorders of embodiment[2].

To determine the kind of bodily disorder characterizing people with FEDs, we need to preliminarily distinguish between the subject-body as experientially different from the object-body[3]. With the former we designate the unmediated, first-person experience of oneself as a spatiotemporal embodied agent. With the latter we indicate the body investigated from a third-person perspective as an entity existing in the outside world (e.g., by natural sciences), or perceived from without (e.g., when I look at myself in a mirror). *Sight* is the sense modality through which I perceive my body from without as an object-body, whereas I apprehend my subject-body from within via *coenaesthesia*.

In addition to these two dimensions, I can apprehend myself as my own body when *it is looked at by another person*[4]. Feeling looked at by another can be experienced as threatening. The Other may threaten me with bodily harm, but he can also be a threat to the arrangement of my world. When I feel looked at by the Other, all of a sudden the world may come on to me differently. No longer comfortably arranged around my point of view, the world is now arranged around the Other's vantage. I feel judged by the Other's look. I may feel ashamed or proud, and those feelings reflect the Other's meanings and values. Yet, I recognize myself in the Other's look. His look *defines* me, it cuts me to the core.

The phenomenon of the look is apparently specific to human beings, yet also non-human primates exhibit signs of corporeal arousal in situations in which they are looked at. Staring seems to be a salient stimulus that arouses tension and induces behavioural responses, e.g. flight or fight. What is specific in humans is that the Other's look is not only a threat to physical integrity, but also to selfhood and identity. I may feel reified by the Other's gaze, and reduced to the external appearance of my own body. My body may take the shape that the Other's look imposes upon it.

In our species, the negative effect of feeling a *body-for-Others* are reification, negation of freedom and reduction to appearance. When I feel looked at by the Other, I feel the negation of my possibility to imagine to be "something else" than the "what" or "mere object" I am. The power of the Other's look may produce an unbalance between the "I-am" and the "I-can".

Under normal conditions, the way I experience my body is the outcome of the dialectics between coenaesthesia and sight. Bodily experience is not only influenced by the way I feel myself, but also by the way I feel looked at by the Others – my being a *body-for-Others*.

As the first-person apprehension of my body is based on coenaesthesia, whereas the third-person one is based on the sense of sight, we may call this dynamic balance between the apprehension of one's body through coenaesthesia and through the Other's look the *optical-coenaesthetic proportion* – a prerequisite for constructing a safe and dependable sense of bodily self and personal identity.

At the roots of the abnormal bodily experience in persons with FEDs there is a disorder of the optical-coenaesthetic proportion. Persons with FEDs experience their body as an object being looked at by another, rather than coenaesthetically or from a first-person perspective[5]. What they seem to lack is the coenaesthetic apprehension of their own body as the most primitive and basic form of self-awareness[6]. Their bodily feelings are discontinuous over time and feel extraneous from their own body[7].

Since their experience of their body from within is flawed or inconsistent, they cope with this by apprehending their body from without through the Other's look. The way they feel looked at by the Others is the principal mode to feel themselves and define their identity[8]. Their body is principally given to them as an object "to be seen". It is a body exposed and subjected to the Other's gaze and thus reduced to its appearance.

Particularly relevant to understanding persons with FEDs is to envision in the Other's look a kind of *visual prosthesis* that helps them feel their own body. Feeling one's body as an object being looked at by another has a twofold effect: it makes them feel embarrassment and repulsion for their own body, but it also helps them recover a sense of selfhood, "unity" and "condensation". This phenomenon is epitomized by the following micro-narratives: "The way I feel depends on the way I feel looked at by the others", "Sometimes I focalize myself through the gaze of the others", "Even if I think that the way the others evaluate me is wrong, I can't do without it".

Persons with FEDs are concerned with public self-consciousness, as opposed to private self-consciousness. In our culture, the predominance of sight is claimed to affect self-experience and self-understanding[9]. Our era can be seen as the time of the *optical-coenaesthetic disproportion*. An analogous tendency to attend to those aspects of one's own bodily self that are matters of public display (namely bodily appearance), rather than to more covert aspects (e.g., bodily sensations, emotional feelings and privately held beliefs about oneself), also affects persons with a diagnosis of FED.

In these persons, the optical-coenaesthetic dialectical proportion is flawed because their possibility to feel themselves is weakened or threatened by coenaesthopathic and emotional paroxysms. These persons feel extraneous from their own body, and their bodily feelings are discontinuous over time. This suggests that the Other's look is not only a source of intimidating and shameful "negation" of their capacity to transcend their mere objective corporeality, but also a longed-for device

through which they can finally define themselves – an optical self-prosthesis.

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iSupport: a WHO global online intervention for informal caregivers of people with dementia

In 2015, it was estimated that worldwide 47 million people had dementia, increasing to 75 million in 2030 and 132 million by 2050. Nearly 9.9 million people are expected to develop dementia each year, which translates to one new case every three seconds. While dementia occurs across all levels of socioeconomic status, nearly 60% of people with dementia currently live in low- and middle-income countries (LMICs) and most new cases (71%) are expected to occur in those countries[1]. The majority of people with dementia in those countries do not have access to care and support[2].

To foster a world in which dementia is prevented and people with dementia and their caregivers live well and receive the care and support they need, the World Health Organization (WHO) developed a Global Action Plan on the Public Health Response to Dementia 2017-2025[1]. Support for family and other unpaid caregivers is included as one of the seven action areas. Research in countries with different levels of development has shown that being a caregiver can affect physical and mental health, well-being and social relationships[1].

In the Global Plan, the target for 2025 is that 75% of WHO's 194 Member States provide support and training programmes for caregivers of people with dementia tailored to their needs. Research in different resource settings around the world has shown that programmes improving knowledge and caregiving skills, such as coping with behavioural changes, have beneficial impact on caregivers' burden, depression and well-being[3].

Although face-to-face training programmes have shown beneficial impact, to implement these in LMICs is challenging, because preconditions for sustainable delivery are lacking. There is limited awareness on dementia and the need for training and support of unpaid caregivers[1]. But, even when countries are aware, limitations in long-term care funding and infrastructure, including a shortage of trained professionals, will hamper implementation[4].

Using the Internet might have advantages to overcome the challenges associated with face-to-face training and support programmes for caregivers of people with dementia in LMICs[5]. It may help to reach more caregivers and increase service coverage, as the number of Internet users and Internet penetration are rapidly increasing worldwide, estimated at over 4.2 billion users and 55% penetration in 2018 by Internet World Stats. As the WHO states, e-health is crucial to achieve universal health coverage.

Although the use of Internet interventions to improve mental health in LMICs is still low, initial studies show its potential to improve caregivers' mental health, coping and self-efficacy, at least in high-income countries[6]. In order to address the urgent needs for carer support worldwide, the WHO has developed iSupport, as a first step to filling this gap. Additionally, a small pilot study was carried out to study its usability and impact in India[7].

The content of iSupport is based on the ground-breaking Kitwood's model[8], in which the personhood of someone with dementia is central, and in which care is essentially thought of as interaction, according to each individual's needs, personality and ability. The behaviour of people with dementia is not only a reflection of the functioning of their brain, but also a result of their personality and coping, life history, health status, and social and physical environment. In iSupport, these elements are integrated in the exercises.

The techniques that served as the therapeutic foundation for the development of iSupport are based on programmes that showed some beneficial impact, including elements of cognitive behavioural therapy, such as psychoeducation, relaxation, behavioural activation, cognitive reframing, and some problem-solving elements[6].

iSupport is meant for caregivers with feelings of stress or burden, or mild to moderate mental health problems, such as symptoms of depression or anxiety. People with severe mental health symptoms are probably better served by a mental health professional. However, when the accessibility of mental health professionals is low, they might still want to participate in iSupport and benefit from it.

The generic version of iSupport is freely accessible at www.isupportfordementia.org. The online programme includes five themes: a) what is dementia (one lesson); b) being a caregiver

(four lessons); c) caring for me (three lessons); d) providing everyday care (five lessons); and e) dealing with changing behaviour (ten lessons). Each lesson presents information about a specific topic and provides engaging, interactive exercises related to this topic. The user is given instant feedback.

Since attrition is common in online programmes, tailoring components and duration of the lessons to the individual is important, the more so because caregivers often experience time constraints due to their caregiving role[6]. iSupport enables caregivers to choose lessons that are appealing and most relevant to them.

iSupport has been developed as an online or web-based self-help programme, but it can also be linked to a caregiver platform (for example a Facebook group), a coach or a face-to-face support group. Contacts with other caregivers or a coach might have added value; however, the human resources that are needed to moderate or guide are not always available, in particular in less developed countries.

When countries want to implement iSupport, translation and adaptation of the programme is needed. We assume that iSupport can be useful in different cultural contexts for different groups of caregivers, if appropriate adaptations to context and culture are made for ecological validity[9]. For example, for caregivers of people with dementia, generational differences within cultures should be examined.

The WHO provides a standardized guide for translation and adaptation (available upon request from whodementia@who.int) to ensure that the local version of iSupport is accurate and in line with the generic version, but at the same time appropriate for the local target group of family caregivers. The guide describes the process to translate and adapt the generic English version and the actual changes that might be (in)appropriate in the programme, such as specific words, names, and links to local Alzheimer's organizations and care and support services.

In several countries, iSupport is currently being adapted and implemented, for example in India, China, Japan, Portugal, Brazil, Australia and the Netherlands. In a next step, the usability and effectiveness of iSupport will be studied and will guide the further improvement of this global course. Upon request by some countries, a generic hardcopy manual of iSupport for adaptation and implementation to local contexts will become available shortly.

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Evocative gene-environment correlation between genetic risk for schizophrenia and bullying victimization

Bullying victimization (BV) is a risk factor for the development of psychotic experiences and psychotic disorders[1,2]. We used data from TRAILS (TRacking Adolescents' Individual Lives Survey), a longitudinal cohort study of Dutch pre-adolescents[3], to study the relationship between polygenic risk score for schizophrenia (SCZ-PRS) and BV, and the possible role of BV in mediating the effect of genetic risk for schizophrenia on the development of psychotic symptoms later in life.

Three assessment waves of TRAILS – T1 (10-12.5 years old), T2 (12.4-14.6 years old) and T3 (14.8-18.3 years old) – were considered. We assessed IQ using the Wechsler Intelligence Scale for Children (WISC), administered at T1; BV through peer nomination scores at T1 and T2; social competence at T1 using the Revised Class Play (RCP); teacher-reported relational aggression by Likert scales at T2; and lifetime psychotic experiences using the Community Assessment of Psychic Experiences Scale at T3.

We imputed TRAILS genotypic data using Sanger Imputation Service (1000 Genomes Project Phase 3 reference GRCh37/hg19). We excluded siblings and pupils on special education, checked genotype quality, derived genomic components to control for ancestry, and computed individual polygenic risk scores (PRS) for schizophrenia, attention-deficit/hyperactivity disorder, autism, bipolar disorder, major depression, and obsessive-compulsive disorder, using standard procedures[4]. We focused on PRS-6 (including variants with association p-value <0.05), a measure of genetic risk yielding the highest prediction

accuracy for schizophrenia[5]. We divided the sample into PRS tertiles, reflecting low, medium and high risk.

We explored whether BV was uniformly distributed across genetic groups, and whether BV mediated the path from genetic risk to psychotic experiences. For the former assessment, we computed an ANOVA using BV at T1 and T2 (separately) as dependent variables; PRS tertiles as factor; gender, WISC and five genomic ancestry components as nuisance covariates (bias corrected-accelerated bootstrap, 1000 runs). For the latter assessment, we computed mediation analyses using psychotic experiences at T3 as dependent variable, BV at T1 and T2 (separately) as mediators, and the PRS as multi-categorical predictor (sequential contrast; same covariates as above plus victimization-psychosis time interval; mean-centering; bootstrap with 5000 runs; Cribari-Neto correction).

To account for different BV reporters, we additionally computed a mediation model using the rank product of peer nomination and relational aggression scores at T2. We tested other peer nomination scores and genetic risk for other disorders to assess specificity of the effects. We additionally explored whether the effect of the SCZ-PRS on BV was mediated by social competence assessed at T1.

Analyses at T1 returned no significant PRS effects (N=650, all p>0.05). ANOVA at T2 returned a significant PRS effect on BV (N=625, $F_{2,611}$=3.4, p=0.033, partial η^2=0.011; observed power = 64%). High PRS individuals had greater peer nomination scores compared to medium PRS subjects (N=417, p=0.017) as well as to a merged sample of low/medium risk individuals (N=625, $F_{1,613}$=6.3, p=0.012, partial η^2=0.01, observed power = 71%). SCZ-PRS was directly associated with BV at T2, without significant mediation by social competence at T1 (N=558, partially standardized effect = 0.011). T2 mediation analysis revealed a significant indirect effect of genetic risk on psychotic experiences at T3 (N=610, partially standardized effect = 0.031). Victims suffered more frequent psychotic experiences at T3 (N=610, p=0.018). These results suggest that BV partially mediated the effect of SCZ-PRS on the frequency of psychotic symptoms developed at T3.

When BV was assessed based on both peer and teacher report at T2, the effect was even larger, despite the reduced sample size (N=390, p=0.002). Only genetic risk for schizophrenia, and not for other disorders, was associated with BV. Only BV peer nomination, not other peer nomination measures, was associated with later psychotic symptoms.

In summary, we found that 13-14-year-old adolescents with greater SCZ-PRS experienced more severe bullying than their peers with lower SCZ-PRS, and that BV partially mediated the effect of genetic risk on the development of later psychotic symptoms. A possible mechanism through which this mediation may occur is evocative gene-environment correlation, i.e., the genetic risk carrier evoking particular reactions of other individuals, such as bullying. The effect is small (1% of the variance), but it is in line with other reported effects, e.g., SCZ-PRS explains at most 1.2% of the variance in symptoms across patients with schizophrenia.

Our sample sizes are small for a behavioral genetics study, a limitation we attempted to address by cumulating risk variants into PRS tertiles. Peer nomination is just one way to assess BV and results may differ based on other reporters[6,7]. However, findings persisted when assessing BV based on peer/teacher reports. Importantly, we did not use self-reports, which may be influenced by paranoia. The prospective data collection reduced the risk of retrospective memory bias.

We studied risk for schizophrenia, but used psychotic episodes as a clinical proxy. Schizophrenia risk may overlap only partially with risk for psychosis, but risk variants for psychosis are not known. To the extent that genetic risk translation into clinical symptoms is mediated by environmental risk[8], our findings call for efforts to antagonize BV of vulnerable individuals to support mental health prevention[6,9].

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Psychiatry, human rights and social development: progress on the WPA Action Plan 2017-2020

Activities are underway on several fronts to bring the WPA Action Plan 2017-2020 to fruition. While human rights and social development are front and centre in our activities, this is also a period of change and institutional strengthening for WPA. The WPA website is revamped to suit contemporary uses, communications with Member Societies and other components of WPA are modernized, public service materials more readily accessed, and the early career psychiatrists in our ranks are making good use of the leadership opportunities offered to them[1,2]. The management of WPA Congresses has changed to serve a diverse and growing membership across the world regions. The signature change is the annual convening of the World Congress of Psychiatry, bringing world psychiatry to each region in turn.

At the same time, we are making progress with significant initiatives to advance a range of strategic mental health and professional objectives, as anticipated in the plan and described in previous reports[3-5]. One of these objectives is successfully positioning psychiatry as a partner in improving mental health for young women and men in adversity. Our aim is twofold. We wish first to engage with groups previously in limited contact with psychiatry, and second to provide opportunities for those psychiatrists interested to participate in this community-oriented work. Evidence and experience from post-disaster and emergency settings provide a framework for action with the young people. We continue this work in partnership with citiesRISE and thereby link psychiatry more fully to social development – to achieving the UN Sustainable Development Goals – and to the sources of support for that work[5,6].

The work is proceeding on establishing a service user and family carer advisory group to the President[4], extending WPA's sustained interest in best practices in working with service users and family carers. The Lancet-WPA Commission on depression[7] continues its work. I am indebted to Prof. Mario Maj, who has agreed to chair one of the four writing groups. Following review and discussion of a preliminary document at its third meeting in mid 2019, the Commission is formulating recommendations to be published and disseminated in coming months.

In another initiative, the Executive Committee has approved plans, supported by the Standing Committee on Ethics and Review, to establish a taskforce on minimizing coercion in mental health care. The WPA is working with the Royal Australian and New Zealand College of Psychiatrists (RANZCP) on this topic, leading to a joint project linked to the activities of the taskforce. This joint initiative emerged from a desire on both sides to test and demonstrate a stronger role for psychiatry in implementing the positive provisions of the United Nations Convention on the Rights of People with Disabilities (CRPD).

While continuing to advance the importance of the range of matters associated with implementing the CRPD, by concentrating on minimizing coercion we have decided to tackle an issue that is most acutely associated with violations of human rights[8]. We also understand that this is a problem manifest in various ways in countries across the world, and recognize efforts to redress these[9]. We believe that there is a paucity of practical and demonstrable approaches, methods and standards that apply to coercion. While recognizing the diversity of views on the subject among mental health professionals, civil society groups and those responsible for public safety, the WPA and the RANZCP see an important need for a clear framework on minimizing coercion and for support for that framework to be built.

The taskforce will conduct its work in two phases. In Phase 1 (Research, development and publication), it will produce a discussion paper on the current situation relating to coercion in mental health care and strategies to reduce and minimize it. The paper will consider how best to discern and support the contribution of psychiatrists and other mental health professionals to implementing the provisions of the CRPD. This will include improved practice, conditions, care and links with community supports in institutional and other settings for people with early-onset and long-standing mental illnesses and disabilities, and their carers. The WPA will send the paper to its Member Societies to request comments and also collect and develop examples of how the recommendations can be adopted in each country.

In Phase 2 of its work, the taskforce will advise on the development of the joint project (Practical resources and implementation). The project will build on the recommendations of the discussion paper to develop practical resources and tools for psychiatrists, and conduct a pilot field work study of these resources in one or more countries.

Through the two phases of work, we are seeking not only to raise the profile and importance of the subject of minimizing coercion, but also to demonstrate, test and validate approaches that can be adopted by mental health professionals and their organizations. Ultimately, we want to build a movement for positive change that achieves enduring benefits for individuals and their families who are receiving mental health care and may be vulnerable to coercion.

To achieve truly global influence, it is very important to invite participation from diverse nations. We will encourage the engagement of people with lived experience of coercion in mental health care, and their family carers, so that the work of the taskforce is informed by perspectives from civil society as well as those of mental health professionals.

Achieving tangible results from the project will rely on maintaining a clear vision of what is feasible and will have the most impact over time. We envisage that the work will represent a transformative step for mental health care in three ways: a) by establishing a strong commitment to and

leadership for a significant improvement in practice on the subject; b) through supporting and building a network of practitioners and those with lived experience of mental ill health and their supporters, in effect a movement for better practice to minimize coercion; c) by developing new materials, testing them and learning from their use in a way that strengthens knowledge on human rights and mental health more broadly, of which minimizing coercion is a central element.

Ultimately, the impact we seek is that an understanding of ways to minimize coercion is developed by mental health professionals internationally, in collaboration with civil society, and that better practices are adopted. As a result, the dangers of coercive practices will also be minimized, and the supports available to people experiencing mental health problems and their families will increase significantly over time.

There are people and groups across countries working actively to promote these and other initiatives that contribute to the common goal of the advancement of psychiatry and mental health for all people. All of us in the WPA leadership welcome comments and engagement from readers and colleagues.

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Evidence and perspectives in eating disorders: a paradigm for a multidisciplinary approach

The WPA Section on Eating Disorders is primarily concerned with the prevention of these disorders, the assessment of their psychopathology and psychiatric and physical comorbidities, the identification of pathways to specialist care, the organization of integrated multidisciplinary approaches to their management, and the promotion of information on evidence-based treatments and strategies to support caregivers and to facilitate treatment adherence and effectiveness.

Eating disorders are complex mental diseases growing on a psychopathological core, i.e. the overconcern with body weight and shape in determining self-esteem, as recently confirmed through network analyses[1]. This psychopathological core also includes maladaptive perfectionism, impulsive traits, dysfunctional emotion regulation strategies, and social cognitive deficits, which lead to a number of abnormal behaviors ranging from extreme diet restriction to uncontrolled overeating with or without purging, vomiting and laxative or diuretic misuse, as well as excessive exercising.

Anorexia nervosa, bulimia nervosa and binge eating disorder are the most well-known eating disorders, although other disorders have been included in the DSM-5. Eating disorder types differ in terms of lifetime prevalence and age at onset, but the peak age at onset of both threshold and subthreshold anorexia and bulimia nervosa occurs during adolescence. In this period, eating disorders are recognized as being the third most common chronic illness[2]. Moreover, they often co-occur with other psychiatric disorders, particularly anxiety and depression, over the lifespan. Hence, they have a considerable impact on personal, family, working and social life. On the other hand, treatment may promote recovery in 40-50% of adult people and higher percentages of adolescents[3].

Eating disorders are marked by a high rate of physical comorbidity[4], with anorexia nervosa reaching the highest mortality rate of all mental disorders. This highlights the need for multiple levels of treatment, including outpatient facilities as well as rehabilitation and hospital units, depending on the severity of the clinical picture. In addition, a multidisciplinary approach, which includes access to physical, nutritional, psychological and psychiatric interventions, is recommended in order to achieve full recovery[5]. Psychiatrists with adequate training and expertise are in the best position to build links with general practice, medical/emergency wards, mental health settings and specialist services. They play a key role in coordinating other clinicians in both diagnosis and treatment processes.

Unfortunately, the current access rate to specialized services is unsatisfactory. Possible reasons for this are the complexity of the pathways to care and the patients' ambivalence towards change or denial of their illness, but also some deficiencies in the transition between adolescent and adult mental health care. The relevance of this issue is higher in eating disorders than in other mental diseases, as there is evidence that early intervention, i.e. in the first three years, yields more favorable outcomes[6].

Trained mental health professionals are essential in addressing these problems through the promotion of educational programs for health care practitioners, which may facilitate knowledge and identification of the disorders, and through support to patients in their therapeutic engagement. For the latter purpose, offering shared decision-making and creating supportive environments may be particularly effective. The application of evidence-based treatments for these disorders is a critical area that needs to be pursued[7], but therapeutic alliance has been identified as a non-specific therapeutic factor that significantly contributes to promoting recovery[8].

The relevance of family involvement is unquestioned, especially in adolescents. Family members are important in identifying the disorder and facilitating access to specialist care, particularly in youth. Hence, it is essential that psychiatrists provide them with appropriate support and information, reducing the fear and stigma associated with eating disorders. Furthermore, there is a need to promote prevention programs such as school-based interventions and e-health projects, although the settings and the means of delivery need to be further explored.

In accordance with the staging model of eating disorders[6], the persistence of the illness is associated with neurofunctional changes (especially with respect to reward learning habits) and social exclusion, which may contribute to the disorder evolving into a severe and enduring stage. These processes, as well as variables such as body mass index, binge-purging behaviors, interpersonal functioning, psychiatric comorbidities, family problems and motivation to recovery, need to be taken into account by psychiatrists and specialized mental health professionals in order to tailor treatment to the individual patient[9]. Although treatment guidelines provide specific parameters to assess the level of medical risk and hospital admission requirements, psychiatrists are advised to consider the current definition of eating disorder severity still in development.

The WPA Section on Eating Disorders was founded in 2002 and includes 172 members. It organizes symposia and section meetings at WPA conferences in order to provide a multidisciplinary discussion of the most relevant research topics and clinical advances in the field. It also promotes research activities aimed to assess differences among countries in pathways to specialist care, choice of specialist treatments and organization of inpatient and outpatient facilities. The Section aims to disseminate knowledge on the clinical management of eating disorders among psychiatrists as well as psychologists, other specialist physicians, general practitioners and nurses, highlighting the crucial role that psychiatrists must play in the multidisciplinary approach to these complex mental disorders.

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The role of the evolutionary approach in psychiatry

Evolutionary psychiatry concerns the application of the principles of evolutionary biology to the understanding of mental health, psychological dysfunction, and mental disorder. It is neither a sub-specialty of psychiatry nor a separate field of clinical practice. However, as vulnerability to mental disorder has arisen through evolutionary processes, the whole of psychiatry (and medicine) benefits from being informed by evolutionary science. In one sense, therefore, all psychiatry is evolutionary, but some approaches are more explicitly so than others. Nevertheless, as the term has been in use for more than three decades, our WPA Section adopted it when it was set up in 2011.

The aims of the WPA Section on Evolutionary Psychiatry include raising awareness of the importance of evolutionary biology to psychiatric theory and practice, and encouraging research into domains of psychiatry that can be meaningfully understood if viewed from an evolutionary perspective. These domains include, among the others, gene-environment interactions, ecological aspects, social interactions and nonverbal behaviour, and the interactions between the immune system, the microbiome, and the central nervous system. The Section also fosters cross-disciplinary networking with evolutionary scientists across a range of academic specialities as well as collaboration with national associations in the field existing around the world.

Evolutionary psychiatrists call for the integration of the evolutionary perspective into psychiatric thinking, with the aim of supplementing and augmenting, rather than replacing, current mainstream psychiatric conceptualizations. To achieve this aim, our Section advocates for the inclusion of evolutionary biology as a basic science into both undergraduate medical education and psychiatric training curricula around the world.

The evolutionary approach seeks to extend the concept of causation to incorporate phylogenetic (historical) as well as adaptational (functional) causes of mental disorders (referred to collectively as ultimate causes) alongside the proximate, mechanistic and developmental (ontogenetic) causes familiar to current mainstream psychiatry[1].

While the application of the principles of evolutionary biology to psychology and psychiatry was heralded by Bowlby's seminal work on attachment theory, this trend significantly gathered pace in recent years, evidenced by the publication of several textbooks in addition to numerous articles in peer-reviewed journals.

A major insight of evolutionary thinking is the realization that selection shapes

traits aimed primarily at reproductive success and not good health, happiness or longevity[2]. Hence, if negative emotions aided survival and reproductive success in the ancestral environment, they would have been selected for. It is safe to assume, for example, that humans in the ancestral environment who lacked the capacity for anxiety left either many fewer descendants or no descendants at all. The same logic may be applied to the capacity for low mood, although, compared to anxiety, the function of low mood remains less well-understood[3].

Hence, evolutionists would argue that any understanding of the human emotional system in both its functional and dysfunctional states will remain incomplete without asking crucial questions as to why most humans have the capacity for anxiety, low mood and psychic pain that can be activated under a range of predictable circumstances.

The additional dimension of evolutionary or ultimate causation enables asking "why" questions alongside the "how" questions that are focused on proximate causes, and this enables the construction of more accurate and complete models of biological systems.

The advantages of evolutionary science also include the fact that it offers a functional understanding of behaviour, provides a way to think clearly about developmental influences, proposes a functional approach to emotions and their regulation, and importantly provides a foundation for a scientific classification system[2].

Unlike existing classification systems that are either deliberately atheoretical or syndromal (ICD and DSM) or take a bottom-up biological approach (Research Domain Criteria), evolutionary approaches to classification tend to utilize high-level organizing principles derived from evolutionary insights regarding the adaptive significance of various brain systems, while remaining compatible with existing classification systems[4].

Importantly, an evolutionary approach to classification will prompt us to consider the functional significance of psychopathological signs and symptoms by comparing them with their evolved (adaptive) equivalents, alongside the current focus on symptomatology, candidate genes/biological markers and environmental risk factors[5].

We suggest that the neglect of evolution can result in equating distress with disorder, which runs the risk that some negative but functional emotional states be misclassified as pathological, with negative consequences for individual patients[2,6-8]. Evolutionists strongly emphasize the importance of context, especially in mood and anxiety disorders. It may be argued that the reduced emphasis on context in current approaches to classification has been instrumental in the controversial removal of the bereavement exclusion in DSM-5, thus enabling a diagnosis of major depression disorder two weeks after a major loss. We are mindful, however, of the concerns that a greater emphasis on context can have a detrimental effect on inter-rater reliability of diagnostic categories.

Aside from the various theoretical and research benefits of evolutionary science, we propose that there are also potential benefits to patients in applying evolutionary insights in clinical settings. We would argue that an understanding of the emotional functionality – why they exist, in addition to in-depth knowledge of signs and symptoms – can result in greater clinical efficacy. Examples of evolutionary models useful in clinical settings include the "smoke detector principle" in patients with anxiety disorders[2] and the harm prevention model in patients with obsessive-compulsive disorder[9].

The WPA Section on Evolutionary Psychiatry has held a number of symposia at WPA conferences (Madrid, 2014; Cape Town, 2016), and some of its members have been involved in producing textbooks in both psychiatry and medicine as a whole, as well as publishing research and theoretical articles. The Section actively collaborates with the Evolutionary Psychiatry Special Interest Group of the UK Royal College of Psychiatrists.

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The ICD-11 has been adopted by the World Health Assembly

The 11th revision of the International Classification of Diseases and Related Health Problems (ICD-11) has been adopted unanimously by the 72nd World Health Assembly in Geneva on May 25, 2019.

The endorsement of the new classification will not come into effect until January 1, 2022. Until that date, the Member States of the World Health Organization (WHO) will keep on using the ICD-10 for reporting data.

In the new classification, there are chapters on conditions related to sexual health and on sleep-wake disorders, separate from that on mental and behavioural disorders. This latter chapter includes the following groupings: neurodevelopmental disorders, schizophrenia and other primary psychotic disorders, mood disorders, anxiety and fear-related disorders, obsessive-compulsive and related disorders, disorders specifically associated with stress, dissociative disorders, feeding and eating disorders, elimination disor-

ders, disorders of bodily distress and bodily experience, impulse control disorders, disruptive behaviour and dissocial disorders, personality disorders, paraphilic disorders, factitious disorders, neurocognitive disorders, and mental and behavioural disorders syndromes due to disorders or diseases not classified under mental and behavioural disorders.

The finalization of the ICD-11 chapter on mental and behavioural disorders has been preceded by a vast programme of international field studies. These included Internet-based field studies, implemented through the Global Clinical Practice Network, including nearly 15,000 clinicians from 155 countries, which used the case vignette methodologies to examine clinical decision-making in relationship to the proposed diagnostic categories and guidelines[1,2], and clinic-based (or ecological implementation) field studies, assessing the reliability and clinical utility of the diagnostic guidelines with real patients[3,4].

The Internet-based field studies reported that the diagnostic agreement for several groups of disorders (e.g., disorders specifically associated with stress, and feeding and eating disorders) was consistently higher for the ICD-11 compared with the corresponding ICD-10 categories (see https://gcp.network).

The ecological implementation field studies found that the interrater reliability for the main groups of mental disorders ranged from moderate to almost perfect (.45 to .88) and was generally superior to that obtained for ICD-10[3]. Concerning clinical utility, the diagnostic guidelines were perceived as easy to use, corresponding accurately to patients' presentations, clear and understandable, providing an appropriate level of detail, taking about the same or less time than clinicians' usual practice, and providing useful guidance about distinguishing disorder from normality and from other disorders[4,5].

Several WPA officers and experts have served as chairpersons or members of ICD-11 Working Groups and have been involved in ICD-11 field studies. Before that, WPA Member Societies participated in the WPA/WHO Global Survey of Psychiatrists' Attitudes Towards Mental Disorders Classification, whose results have strongly influenced the process of development of the ICD-11 chapter on mental and behavioural disorders.

World Psychiatry has been one of the main channels through which the international mental health community has been informed about the development of the ICD-11. In particular, the debate has focused on some crucial differences between the ICD-11 and the DSM-5, such as the inclusion in the former of the new categories of complex post-traumatic stress disorder and prolonged grief disorder, and of a subtype "with chronic irritability-anger" of oppositional defiant disorder in the place of the DSM-5 category of disruptive mood dysregulation disorder; the absence in the former of a category for attenuated psychosis syndrome, present instead in the DSM-5 section III; and the introduction in the former of a different approach to personality disorders, bodily distress disorders, disorders due to addictive behaviours, and disorders related to sexuality and gender identity[6-12]. The worldwide interactive process which has led to the ICD-11 approach to the classification of neurocognitive disorders has also been discussed[13], as well as the usefulness of a dimensional approach, recently advocated by several experts[14,15], and partially implemented in the ICD-11.

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Correction

It has been brought to our attention that in Table 1 of the paper "Management of common adverse effects of antipsychotic medications", by Stroup and Gray, published in the October 2018 issue of the journal, the profile of quetiapine concerning sedation was incorrectly reported as "++b" instead of "+++".

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