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World Psychiatry

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3. Fraeijs de Veubeke B. Displacement and equilibrium models in the finite element method. In: Zienkiewicz OC, Hollister GS (eds). Stress analysis. London: Wiley, 1965:145-97.

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Shared decision making: everyone wants it, so why isn't it happening?

M. Slade[1] makes a strong case, in this issue of the journal, for a wider adoption of shared decision making (SDM), while acknowledging the particular problems that must be overcome if it is to become the dominant mode in mental health care. I believe the arguments for this approach are even more compelling than he demonstrates, but implementation remains a key challenge.

It is true, as Slade argues, that evidence of the impact of SDM on clinical outcomes in psychiatry is mixed, but the wider body of SDM research leads to a more positive assessment. Most of the studies he cites were primarily concerned to evaluate the use of specific tools to inform one-off treatment decisions, such as patient decision aids. These are information packages designed to inform patients about their treatment options and help them determine which they would prefer. They take a variety of forms, spanning from one-page sheets, more detailed leaflets or computer programmes, through to DVDs and interactive websites. Some are designed for use by patients at home, while others are intended to guide discussions in medical consultations. They are not absolutely essential for SDM but, by packaging evidence-based information in an accessible form, they certainly make it easier.

A recently-updated Cochrane review across all conditions, not just mental health, combined results from 115 randomized controlled trials of patient decision aids, most of which focused on discrete choices and decisions made at a single point in time[2]. The review found that use of decision aids led to improvements in patients' knowledge, more participation, more accurate risk perceptions, fewer people remaining undecided, and greater comfort with decisions. However, none of these trials had looked at whether consultations exhibited the full range of SDM characteristics (defining the problem, outlining the options, checking understanding, eliciting values, supporting deliberation, reaching mutual agreement) and few had looked at longer term clinical outcomes. In other words, these studies looked at only one component of this highly complex intervention.

These decision aid trials tell us something about the potential benefits of SDM, but this is only part of the story. SDM involves a conversation, or more likely a series of conversations, between patients and clinicians: it is a relationship and a process, not a tool or a one-off event. This is especially pertinent in the case of long-term conditions, such as most mental health problems. Relevant outcomes may include physical and emotional effects, subjective health status, knowledge and understanding, self-management capabilities, treatment burden and resource use, as well as experience of the decision-making process.

We looked at these outcomes in another Cochrane review focused on people with long-term conditions[3]. We searched for randomized controlled trials that had evaluated personalized care planning (SDM by another name), which we defined as anticipatory, negotiated discussions to clarify patients' goals and priorities, agree realistic objectives, solve specific problems, identify relevant sources of support, document agreed action plans, and implement these, including follow-up and review. Nineteen trials met our inclusion criteria. These showed evidence of small, but beneficial effects on emotional health (depression), physical health (blood glucose, blood pressure), and self-efficacy (self-management knowledge and skills). The effects were greater when all stages of the care planning cycle were completed, when the process included more contacts over a longer time period, when it was fully integrated with routine care, and when both clinicians and patients were well supported. We rated this evidence as promising, albeit not yet conclusive, but we hope we have pointed the way towards a more sophisticated evaluation of SDM and its effects than simply looking at the impact of patient decision aids on one-off treatment decisions.

We need to give serious consideration to the issue of how conclusive evidence has to be before we attempt to implement it. If patients want it, the ethical case is strong, there is evidence of some beneficial effects and no likelihood of harm, is that sufficient? Most of those arguing for SDM base their case on ethical justifications rather than clinical ones – patients do want it, it is important to respect their autonomy (right to be informed and involved in decisions that affect them), and it also promotes beneficence (balancing benefits, risks and costs), and non-maleficence (avoiding harm)[4]. As Slade demonstrates, these arguments may be somewhat more nuanced in the case of people with psychosis or those who lack mental capacity, but few would argue that people with mental health problems should not be given the opportunity to shape their own care whenever feasible.

In the UK, ethical and legal guidance from various authorities, including the UK Supreme Court[5], the General Medical Council[6], and the Mental Capacity Act[7], is now fully aligned: SDM should be the default and very few exceptions are permitted. Despite this, as Slade's paper makes clear, around half of mental health service users said they were not involved in treatment decisions to the extent they wanted to be[8]. Why then has it proved so difficult to secure widespread implementation of SDM?

I agree with Slade's contention that the barriers are as much attitudinal as practical and organizational. Commonly voiced objections include concerns about lack of time, lack of skills, lack of resources and misapprehensions about patients' ability to make appropriate choices, all of which act as powerful disincentives to change practice. Most of these perceptions are not supported by the evidence. For example, SDM does not necessarily require longer consultations than more traditional forms of decision making[2], and several studies have shown that it is possible to inform and engage patients from all ages, walks of life and educational backgrounds, with benefits accruing to all, including those with low health literacy[9].

A comprehensive strategy is required to promote wider uptake of SDM. In a recent review of experience in various SDM demonstration sites in North America and Europe, we described ten components that are required to encourage widespread adoption[10]: a) research evidence showing that it can be effective in a specific clinical or local context; b) medical leadership willing to encourage it; c) demand for SDM from patient leaders and organizations; d) incentives for clinicians to change their practice – ethical, financial or professional; e) training for clinical staff in SDM and risk communication skills, plus support and supervision for practising and maintaining these competencies; f) availability of patient decision aids; g) integration of patient decision aids into electronic medical record systems; h) institutional support for developing and updating patient decision aids; i) certification scheme to assure the quality of patient decision aids; j) validated outcome measures to monitor the extent to which patients feel informed and involved in decisions about their care, plus feedback to enable clinicians to monitor progress.

All patients, including users of mental health services, should be encouraged and supported to prepare themselves for an active role in treatment selection. SDM theory, skills and competencies (risk communication, options appraisal, goal setting, care planning and outcomes assessment) should be taught in medical schools, in post-registration training, and in continuing professional development, aligned with support for self-management and patient engagement.

Quality-assured patient decision aids should be made available at specific decision points via electronic medical records, so that they are readily accessible during clinical consultations. Appropriate patient reported outcome measures (PROMs) should be used in routine care as a feedback loop to check that patients are actively engaged and receive treatments that reflect their goals and preferences.

The tensions that Slade outlines are real, but so is the need to work together to find ways to overcome them to ensure the delivery of appropriate, efficient and effective mental health care.

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Migration and psychosis: our smoking lung?

To read the history of humankind is to read a history of migration. From the first human exoduses out of Africa, to Greek and Roman empires which sought territorial expansion, to the Ming dynasty's pioneering voyages of exploration, to the flight of ethnic, religious, political and sexual minorities escaping persecution from various authoritarian regimes or internal conflicts, to the economic migrants from continental Europe, Asia, the Middle East, and South and Central America who sought better lives for themselves and their families on new continents, migration is arguably the defining feature of a singular human experience that binds our past, present and future. The drivers and consequences of migration also leave indelible marks on the history of humankind. Perhaps in equal measure, they result in leaps forward for civilization – enriching cultural, social, genetic and economic diversity and human development – and pockmarks which serve to remind us of the seemingly ceaseless bounds of human savagery and brutality (see also Silove et al[1] in this issue of the journal).

To a psychiatric epidemiologist, migration is arguably associated with one of the defining public health inequalities of the last 100 years: that certain migrants, their children, and their children's children are as much as 10 times more likely to meet diagnostic criteria for psychotic disorder than the majority (usually white Caucasian) population in a given setting[2]. The exact magnitude of this risk varies, depending on the given migrant group and setting in which the study is conducted. In the UK, for example, psychosis risk ranges from slight increases (of 1.5 or less) for white migrants, to 2-4 times greater risk for people of Pakistani and Bangladeshi origin, and up to 10 times higher rates amongst black Caribbean and African groups[3]. Elsewhere, elevated risk also follows historical migration flows, such as amongst the Surinamese and Moroccan populations in the Netherlands[2], or East African migrants to Sweden[4]. Emerging research from countries which have experienced unprecedented contemporary immigration pressures[5] also shows that incidence rates are elevated amongst migrant groups.

It is only right that this epidemiological literature is subject to proper scrutiny to determine whether these patterns are causal. If they are not, then the alternatives are no less palatable: that other social or economic exposures are so entrenched within certain black and ethnic minority (BME) sections of society that they are powerful enough to increase the chance of experiencing a psychotic disorder by up to 1000%; or that the tools, practitioners and institutions tasked with making reliable and valid diagnostic assessments are so unfit for purpose, or so grossly inept at differentiating between normal cultural mores of behaviour and psychotic symptoms, that for every one migrant correctly diagnosed, a further nine may be misdiagnosed with psychotic disorder.

Scrutiny of the evidence in relation to misdiagnosis does not strongly support this as an explanation of higher rates. There may be poor inter-rater reliability between psychiatrists in agreeing on a specific psychotic diagnosis, but this does not appear to be racially biased[6]. Further, few modern epidemiological studies rely solely on clinician-rated diagnoses to measure outcomes, instead using carefully operationalized criteria to reach standardized diagnoses[3,7]. Finally, in the UK and elsewhere, the ethnic composition within clinical psychiatry is increasingly diverse, far from the monochromatic contrast that implicitly surrounds the misdiagnosis debate. In a recent study, for example, which also found elevated rates of psychotic disorder in BME groups in rural England[7], operationalized diagnoses were made by a panel of psychiatrists from over 13 different ethnic backgrounds.

Further new empirical data offer important directions. For example, raised rates do not seem to be entirely attributable to socioeconomic differences between BME groups and the majority population[8]. Other recent research, from Sweden, has demonstrated that refugee migrants are at considerably elevated risk of non-affective psychotic disorders compared with both the Swedish-born population and, importantly, other migrants from the same regions of origin[4]. The implication is that severe exposure to pre-migratory adversities, including war, famine and persecution, or the hazards involved in the transitory process of migration itself, may be aetiologically relevant to psychosis risk. Exposure to other severely traumatic migration-related experiences, such as witnessing genocide[8], also increases schizophrenia risk. Nonetheless, these data would not explain why elevated rates persist in successive generations following the index immigration event. Other factors must be relevant, possibly including experiences of racism and discrimination, although further research is needed on this issue.

We also require more integration of observational data with sociological, ethnographic, experimental psychology and neuroscience research to shed light on the possible pre-, peri- and post-migratory factors that increase psychosis risk amongst BME groups. A recent study from social neuroscience, for example, suggests that healthy volunteers from second generation migrant backgrounds exhibit elevated neural responses to stress following a sociocultural challenge[9]. If we can elucidate whether these putative stress pathways also contribute to the onset of psychosis – potentially encompassing complex interactions between genetic, biological and social factors – this will not only move us closer to understanding the excess risks among BME communities, but in society at large. Aside from psychosis (and, perhaps, post-traumatic stress disorder), there is less consistent evidence that migrants are at higher risk of other mental health conditions; this specificity would be one of several important criteria helping to establish causation.

Further studies are also required in settings where the increased psychosis risk amongst migrants is not observed, such as in people of Indian descent in the UK[3], Turkish descent in the Netherlands[2], or Hispanic origin in the US[10]. Canada is another putative counterfactual setting, given both its foundation on a

relatively recent migration history, and the effects on mental health of indigenous First Nations people in this context.

Studies in settings where white migrants form the minority group would also shed further light on the role of migration in psychosis risk. South Africa provides a possible example. Nonetheless, while white migrants in this context would be the minority in terms of population size, they also continue to hold a disproportionate balance of socioeconomic capital, which may negate any effect; in either case, the aetiological implications would be illuminating. For various reasons, and not without considerable challenges, Brazil, China, Japan and Zimbabwe present other settings for such counterfactual study.

Using data from the UK, we have previously estimated that, if we could identify the drivers of the elevated psychosis risk in BME groups, we could prevent up to 22% of new cases of first episode psychosis in the general population, and up to two thirds in BME groups specifically[11]. This major health inequality may be to psychiatry what nicotine exposure was to bronchogenic carcinomas over 65 years ago[12]: our smoking lung. The psychiatric research community has an unparalleled duty to advance our aetiological understanding on this issue in order to eradicate this gross social injustice.

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Etiology in psychiatry: embracing the reality of poly-gene-environmental causation of mental illness

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Intriguing findings on genetic and environmental causation suggest a need to reframe the etiology of mental disorders. Molecular genetics shows that thousands of common and rare genetic variants contribute to mental illness. Epidemiological studies have identified dozens of environmental exposures that are associated with psychopathology. The effect of environment is likely conditional on genetic factors, resulting in gene-environment interactions. The impact of environmental factors also depends on previous exposures, resulting in environment-environment interactions. Most known genetic and environmental factors are shared across multiple mental disorders. Schizophrenia, bipolar disorder and major depressive disorder, in particular, are closely causally linked. Synthesis of findings from twin studies, molecular genetics and epidemiological research suggests that joint consideration of multiple genetic and environmental factors has much greater explanatory power than separate studies of genetic or environmental causation. Multi-factorial gene-environment interactions are likely to be a generic mechanism involved in the majority of cases of mental illness, which is only partially tapped by existing gene-environment studies. Future research may cut across psychiatric disorders and address poly-causation by considering multiple genetic and environmental measures across the life course with a specific focus on the first two decades of life. Integrative analyses of poly-causation including gene-environment and environment-environment interactions can realize the potential for discovering causal types and mechanisms that are likely to generate new preventive and therapeutic tools.

Key words: Psychiatric genetics, environmental risk factors, gene-environment interactions, classification of mental disorders, life course research, schizophrenia, depression, bipolar disorder, autism

(World Psychiatry 2017;16:121–129)

Major depressive disorder, schizophrenia, bipolar disorder and autism are among the most disabling and costly diseases[1]. They affect individuals from young age, and are associated with physical morbidity and early death[2]. The causal mechanisms underlying mental illness may hide keys to effective prevention and treatment, but remain poorly understood.

The last two decades have seen an expansion of knowledge punctuated by surprises that challenge previously held assumptions about mental illness. In this paper we provide a synthesis of current knowledge and direct further research to maximize the potential for meaningful discovery. While the focus is on generic principles underlying the causation of any mental illness, the majority of information comes from studies of schizophrenia, bipolar disorder, major depressive disorder and autism, on which most data have been accumulated.

We first review the genetic and environmental factors implicated in the etiology of mental illness, before adopting an integrative perspective that jointly considers genetic and environmental elements of causation. We conclude by outlining a framework for productive causal research.

GENETIC FACTORS IN THE CAUSATION OF MENTAL ILLNESS

All types of mental illness have a tendency to run in families, and the risk of developing an illness is associated with the degree of biological relatedness to the affected individual[3,4]. This pattern of transmission strongly suggests genetic causation. Twin studies consistently show that monozygotic twins who share 100% of their nuclear DNA are more likely to be concordant on each disorder than dizygotic twins who share 50% of their genetic material[5]. This difference suggests that the causation of mental illness is to a large degree attributable to genetic factors.

There is a gradient of genetic contribution, with higher estimates of heritability for the more severe and less common disorders (autism, schizophrenia, bipolar disorder) and a lesser degree of heritability for more common and less severe disorders (anxiety, major depressive disorder)[5].

The large heritability estimates promised an easy identification of the molecular genetic variants responsible for the causation of mental illness. Influential authorities estimated that severe mental illness, such as schizophrenia, was likely to be caused by several (2 to 9) genetic loci[6], while others argued for a single gene causing most cases of schizophrenia[7].

Three assumptions have shaped the field of genetic discovery: a) severe mental illness is caused by a small number of genes; b) there is a specific relationship between genotype and the type of mental illness and c) the genetic variants lead to mental illness through biological pathways independent of environment. Consequently, most genetic research has studied one mental disorder at a time by comparing cases with a specific diagnosis to controls, without accounting for environmental influences.

Over the last decade, the molecular genetic technology has offered the tools to study the genetic variants responsible for the transmission of liability for mental illness from parents to offspring. This decade of research has brought surprising findings that challenge the assumptions on which psychiatric genetics has been based. Genome-wide association studies have

Table 1 Genetic variants associated with mental illness

	Autism	Schizophrenia	Bipolar disorder	Depression
Number of individuals in largest genetic sample to date	13,088 cases with autism spectrum disorders and 16,664 controls	36,989 cases with schizophrenia and 113,075 controls	7,481 cases with bipolar disorder and 9,250 controls	121,380 cases with depression and 338,101 controls
Number of genetic variants associated at genome-wide level of statistical significance	4	128	18	17
Odds ratio of the most strongly associated genetic variant	1.17	1.21	1.15	1.05
Proportion of variance explained by common genetic variants across the genome	14%	23%	25%	5%

identified more than a hundred variants associated with severe mental illness (Table 1)[8-11]. Each of the variants has small effect and the number of associated variants keeps increasing with growing sample sizes[8].

Polygenic risk scores analyses consistently show that the prediction of mental illness improves by including more weakly associated genetic variants, suggesting that many thousands of genetic variants are involved in shaping the risk for most mental disorders[12,13]. These involve both common single nucleotide polymorphisms and rare structural variants, such as deletions and insertions of stretches of DNA[14].

Another consistent finding is that most common and rare genetic variants are non-specifically associated with a range of mental disorders[15,16]. Overall, approximately two thirds of genetic associations are common to schizophrenia, bipolar disorder and major depressive disorder[15]. There are also overlaps with genetic variants contributing to autism, attention-deficit/hyperactivity disorder, and intellectual disabilities.

It has also become clear that the heritability estimates derived from twin studies do not translate into direct effects of molecular genetics variants[15]. The estimates based on case-control studies with molecular genomic data suggest that genetic variants contribute only a fraction of the effect that was suggested by heritability estimates from twin studies (Figure 1). The most likely explanation for this "heritability gap" is that a large fraction of genetic effects are contingent on factors that are common to individuals growing up in the same family but not to unrelated individuals who participate in case-control studies[17,18]. A picture is emerging of a complex etiological mechanism, where genetic influence is thinly distributed across thousands of genetic variants of small effects that are contingent on environment and not specific to any single form of psychopathology.

ENVIRONMENTAL FACTORS IN THE CAUSATION OF MENTAL ILLNESS

The same twin studies which confirmed that mental illness is heritable have also demonstrated that environment matters. Concordance of genetically identical twins is far from perfect even for the most heritable types of mental illness, such as autism or schizophrenia[5]. While it is not possible to completely separate the effects of environment from errors in diagnosis, a realistic assessment suggests that environmental and genetic factors contribute equally to the causation of mental illness.

Since the 1960s, researchers have been identifying strong relationships between adverse social environment and mental illness. The bulk of the research on social causation has been based on the assumption that a single environmental factor may explain the causation of a specific diagnosis, irrespective of enduring characteristics of the exposed individual. Thus, social researchers tended to examine one aspect of environment and one mental disorder diagnosis at a time. The highlights of this research included identification of strong associations between severe adverse life events and depression[19].

A number of studies of environmental factors have included longitudinal follow-ups and documented both the long-term effects of adversity in childhood and the close temporal rela-

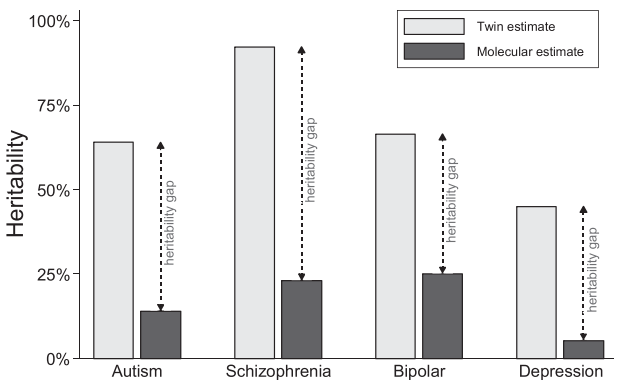

Figure 1 The heritability gap. Heritability (the proportion of causation attributable to genetic factors) has been estimated from differences of concordance between identical and fraternal twins (twin estimates) and from hundreds of thousands of single nucleotide polymorphisms across the human genome (molecular estimates). The large difference between the twin and molecular estimates is referred to as the "heritability gap". Twin estimates are based on same-sex twin pairs from a recent comprehensive meta-analysis[5]. Molecular estimates are from large case-control genome-wide association studies[8-11].

Table 2 Environmental factors associated with mental illness

	Autism	Schizophrenia	Bipolar disorder	Depression
Pregnancy risk factors				
Infections	+	+++	++	+
Malnutrition		+++	++	++
Heavy metals	+++	++		
Perinatal risk factors				
Preterm birth	++	++	++	++
Season of birth	++	+++	++	+
Birth complications	+++	+++	0	
Childhood environment				
Urbanicity	+++	+++	+	+
Poverty	++	+++	+	+++
Maltreatment	N/A	++	++	+++
Bullying	N/A	++	+	+++
Drug use in adolescence				
Cannabis	N/A	+++	++	+
Stimulants	N/A	+++	++	0

The number of + marks the strength of evidence (+ means some evidence of association/single report; ++ means moderate replicated evidence of association/multiple reports; +++ means strong evidence of association/multiple replications or good meta-analysis). Evidence of no association is noted as 0. Empty cells reflect absence of evidence for or against association. No factor has been negatively associated with any of the disorders. Because of the early age at onset of autism, environmental factors occurring after age 3 cannot be reliably studied and are marked as not applicable (N/A).

tionship between severe life events and psychopathology onset in adulthood[20,21]. With larger and more representative studies, additional and diverse environmental risk factors have been identified, including exposure to viral infections during gestation, vitamin D deficiency, growing up in urban environment, ethnic minority status, childhood maltreatment and bullying victimization (Table 2)[22-25].

Several general principles emerged. First, the same type of environmental exposure increases the risk of many different mental disorders. For example, urban environment was first identified as a risk factor for schizophrenia, but a systematic analysis showed that it is associated with increased risk of all types of mental disorders[25]. Second, many different types of environmental exposures contribute to the same disorder. For example, the risk of schizophrenia increases with maternal malnutrition, vitamin D deficiency and viral infections during pregnancy, low socio-economic status, urban upbringing, minority status and childhood maltreatment, as well as exposure to stimulants, cannabis and tobacco[26]. Third, no constellation of adverse environmental exposures will result in psychopathology among all exposed individuals. Many individuals appear to be resilient and do not develop any mental disorder even if they are exposed to multiple adverse environmental factors[27,28].

Resilience appears to be related to a number of enduring personal characteristics that are partly heritable and partly shaped by previous environmental exposures[28,29]. Experiences early in life may make a person more vulnerable or resilient to exposures later in development, resulting in a sequential environment-environment interaction. For example, exposure to maltreatment in childhood may cause sensitization to the effects of specific types of stressful life events in adulthood[30]. The observation that unshared environment has greater influence on intellectual ability among twins growing up in families with low socio-economic status also suggests a complex interplay between multiple environmental factors[31].

A synthesis of current knowledge on environmental causation of mental illness suggests a complex picture with a multitude of social, physical and chemical exposures occurring at different stages of life, affecting the risk for a range of mental disorders. It is becoming increasingly unlikely that any given environmental factor could be a necessary and sufficient cause of any mental disorder. Instead of searching for single disorder-specific environmental causes, researchers who want to explain or predict mental illness may need to jointly study a multitude of environmental influences across the life course, that may be summed up in cumulative poly-environmental scores (E-scores)[32] or grouped in unique environment-environment constellations[31].

While the array of environmental factors that are known to be involved in the causation of mental illness is impressive, it may still only be the tip of an iceberg. Research designs to date have only been powered to detect environmental factors that are harmful for the vast majority of individuals. The types of environments that may good for some and bad for others are still waiting to be discovered.

GENE-ENVIRONMENT CAUSATION OF MENTAL ILLNESS

No genetic variant and no environmental exposure on its own is a sufficient cause of mental illness. While it is possible that some cases of mental illness are caused by a combination of many genetic variants or a combination of multiple environmental exposures, the most likely scenario by far is that both genetic and environmental factors jointly contribute to the causation of mental illness. A causal mechanism where one or more genetic factors and one or more environmental factors are required to produce an outcome is gene-environment interaction (GxE).

A ubiquitous role of GxE in the causation of mental illness is suggested by a contradiction between the results of epidemiological studies and twin studies that we call the shared environment paradox. Epidemiological research shows that a substantial proportion of cases of mental illness are attributable to environmental factors which are typically shared by whole families, such as socio-economic class, poverty, urban environment, minority status, neighbourhood characteristics and childhood maltreatment[22,25,33]. Yet, twin studies allocate only a very small role to shared environmental factors[5] (Figure

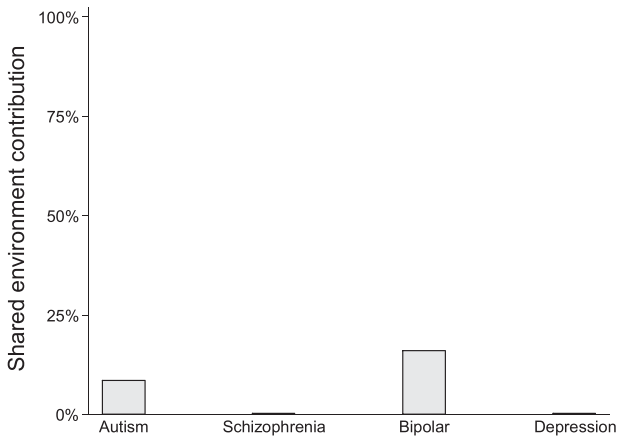

Figure 2 Shared environment paradox. Twin studies have consistently allocated little or no role in the causation of mental illness to environmental factors that are shared by members of the same family. The estimates plotted here are from a recent comprehensive meta-analysis of twin studies[5], based on same-sex twin pairs. Estimates for schizophrenia and depression were actually negative, but since a negative contribution to variance is not possible, we plotted them at 0%.

2). One explanation of the shared environment paradox is that the impact of the family-wide environment depends on factors that are shared more between monozygotic than between dizygotic twins, i.e. genetic polymorphisms. If the effects of shared environment are conditional on genetic variants, the statistical models used in twin studies will fully attribute the joint effect to the genetic component, thus inflating heritability and reducing the estimate of shared environment[34]. In this way, GxE provide the most parsimonious explanation for both the shared environment paradox and the heritability gap.

In the last 15 years, researchers have started to identify specific genetic variants that may sensitize individuals to environmental factors. Like most molecular genetic research, the search for GxE started with tests of candidate polymorphisms in candidate genes. The success of such studies depends not just on picking the correct combination of a genetic variant and an environmental factor based on prior knowledge, but also on sampling and design that allows an approximation of a biological interaction with a statistical test.

Remarkably, some of these studies appear to have been successful in finding causal mechanisms. Some candidate gene GxE have been consistently replicated. For example, the interaction between low activity variants of the X-chromosome-linked monoamine oxidase A (MAO-A) gene and childhood maltreatment leading to antisocial behavior in males has been replicated multiple times and confirmed in meta-analyses[35,36]. The interaction between brain derived neurotrophic factor (BDNF) gene variants and severe life events leading to depression has also been replicated and confirmed in a meta-analysis[37].

Other GxEs have proven less robust or more specific than originally reported. For example, the interaction between short variants of the serotonin transporter gene length polymorphism and adversity leading to depression has seen similar number of replications and non-replications and it may be specific to childhood maltreatment leading to persistent depressive disorder[38-40]. Yet other reported GxE have proven unreplicable. For example, the interaction between catechol-O-methyltransferase (COMT) gene and cannabis use leading to psychotic symptoms has been reported, but not replicated in subsequent studies[41].

More recent studies have screened a larger number of genes and polymorphisms to search for GxE. Such systematic search has led to the identification, among 152 polymorphisms in 42 genes related to cannabinoid signalling, of an interaction between a single nucleotide polymorphism in the serine/threonine kinase encoding gene AKT1 and cannabis use leading to psychosis[42]. This GxE has been replicated in independent samples[43,44], suggesting that this polymorphism sensitizes individuals to the psychosis inducing effects of tetrahydrocannabinol.

Finally, several genome-wide environment interaction studies (GWEIS) have been completed to search for GxE without any pre-existing hypothesis about the genetic variants involved. The first GWEIS concerned interactions of common genetic variants with prenatal exposure to cytomegalovirus and with stressful life events in the causation of schizophrenia[45] and depression[46], respectively. The existing GWEIS have limited statistical power, because most large genotyped samples are missing adequate measures of environment. At present, it is unclear whether the results of GWEIS will be more replicable than those of candidate GxE studies. An interim synthesis suggests that multiple GxE contribute to most types of mental illness, but no specific GxE explains a substantial proportion of cases.

Several studies suggest that multiple genetic variants shape the susceptibility to harmful and protective environmental factors. One study has shown that a score derived from over 2,800 schizophrenia-associated variants in coding or regulatory genomic regions interacted with winter birth to increase the risk of schizophrenia[47]. In another study, a polygenic risk score of tens of thousands of common variants tapping the overall sensitivity to environment predicted the effects of negative parenting on emotional psychopathology as well as the effectiveness of intensive psychological treatment for anxiety[48]. As in studies of direct polygene-disorder associations, the GxE increased in strength with more genetic variants being included in the polygenic risk score. The emerging pattern of findings suggests that sensitivity to environment is a highly polygenic trait with contributions from thousands of common genetic variants.

The examination of gene-environment interplay is still in its infancy, and research available to date leaves many unanswered questions. The specificity of polygenic GxE to the type and timing of environmental exposures, the specificity or pleiotropy of GxE across types of mental disorders, and the role of rare structural variants in sensitivity to environment remain largely unexplored.

BOUNDARIES AND OVERLAP BETWEEN DISORDERS

The review of genetic and environmental factors above has concluded that most factors are associated with most types of mental illness. The apparent overlaps in causation has been generally ascribed either to pleiotropy, i.e. the same factors having the potential to cause multiple types of illness, or to the lack of validity of the diagnostic criteria for specific disorders.

Pleiotropy at the level of a single causal factor has been well documented: for example, the same variant (A-allele of rs1006737) of the calcium channel gene CACNA1C has been associated with increased risk of bipolar disorder, schizophrenia, depression, anxiety and autism[49-51]. While inadequate validity of boundaries between diagnostic categories has also been amply demonstrated[52], evidence supporting validity also exists, e.g. in the specificity of therapeutic response to lithium in bipolar disorder but not schizophrenia.

While both pleiotropy and inadequate validity of categorization are likely to be at play, the multifactorial causation also leaves the possibility of unique combinations of causal factors. For example: even if most risk factors are shared between bipolar disorder and schizophrenia, the loading and combination of factors that give rise to each of the two disorders may still be unique.

Since hundreds or thousands of environmental and genetic factors are likely involved in the causation of each disorder, the number of possible combinations is extremely large. The examination of these possible combinations has only just begun. One example involves both a mental disorder and a physical disorder: individuals with schizophrenia have less than half the risk of developing rheumatoid arthritis compared to the general population, even though schizophrenia and rheumatoid arthritis share environmental risk factors, including winter birth and tobacco smoking. Recently it has been shown that a polygenic risk associated with the immune system is associated with both increased risk of rheumatoid arthritis and reduced risk of schizophrenia. In addition, a polygenic risk score for schizophrenia interacts with winter season of birth to increase the likelihood of schizophrenia[47]. In this case, some environmental factors are shared, but genetic disposition distributed across thousands of variants may determine the relative risk of two competing outcomes.

Even if we are able to examine combinations of genetic and environmental factors, the question remains about the level of outcomes that is most likely to lead to success in etiological research. Most of the debate to date has focused on the distinction between categorical diagnoses and dimensional measures. This may have been a false focus. At present, it is unclear whether one of the approaches is more advantageous than the other. The experience with dimensional constructs introduced as part of the Research Domain Criteria framework over the past five years does not inspire hopes for major advances in etiological research. While dimensional measures may be more powerful for examining variation in common traits across the general population, the categorical diagnostic constructs remain more relevant to the severe types of mental illness that are most pertinent to psychiatry. When it comes to psychopathology, it is unlikely that the difference between complete absence of pathological symptoms and population average matters as much as the difference between average and severe psychopathology. Yet, the number of categories in the current classifications are too large and the boundaries between them lack validity[52].

Because psychiatric research to date has been based on the now refuted assumption of diagnostic specificity, most studies are uninformative about the validity of specific diagnostic categories or dimensions[52]. The potential for discovery will likely be enhanced if researchers refocus on examining broad and heterogeneous samples of mental illness without exclusions based on diagnostic criteria and without constraining their measurement to consensus based constructs, categorical or dimensional. Shedding the constraints of diagnosis-specific research does not require adopting another set of constraints and it does not necessitate transition from a categorical to a dimensional framework of inquiry. Examination of overlaps in etiological factors between disorders suggest that higher level broad categorical constructs may be more appropriate targets of etiological research than specific diagnostic categories. For example, the major overlap in both genetic and environmental contributors between major depressive disorder, bipolar disorder, schizophrenia and other types of psychotic illness suggests that a broad category of severe mental illness that encompasses major mood and psychotic disorders may be an appropriate unit of investigation.

DEVELOPMENTAL CONTEXT AND CLINICAL COURSE

Two major discoveries in psychiatry remain underrated and are not reflected in most etiological research. The first one is the continuity of pathology over the life course. From cohorts with complete and intensive long-term follow up, it has become clear that most cases of mental illness start in childhood and adolescence. The early manifestations of psychopathology typically differ in kind from the eventual diagnoses in adulthood, yet are very strongly predictive of mental illness diagnosed across the life course.

Heterotypic continuity is the rule. For example, anxiety in childhood is a strong predictor of both major depressive disorder and bipolar disorder in adulthood. Oppositional defiant disorder in childhood predicts a broad range of psychopathology in adults, including depression, bipolar disorder, anxiety, substance use disorders and antisocial personality disorder. Yet, there is also a degree of specificity, with a systematic correspondence between the profile of childhood symptoms and the type of adult disorders[53].

The fact that most individuals with mental illness will go through a number of diagnostic categories over their life course adds to the problems associated with diagnosis-specific research[52]. It highlights the need to examine psychopathology

broadly and in a developmental context. Since most mental illness starts in childhood and retrospective report is inaccurate, etiological research needs longitudinal designs that start in childhood, at birth or even earlier[54].

The second discovery is that the course of mental illness varies between individuals and is only loosely related to the diagnostic category. Traditionally, some disorders have been conceptualized as episodic and other disorders as persistent, but longitudinal follow-ups suggest that this conceptual distinction has limited validity. Mood disorders have been codified as episodic, yet on follow-up they are marked by chronicity, with most individuals spending most of their time with depressive symptoms[55,56]. Personality disorders have been conceptualized as persistent, but on follow-up their symptoms show similar rates of remission and relapses as mood disorders do[57].

Yet, within the same disorder, episodic and persistent cases may have distinct etiologies. For example, episodic cases of major depressive disorder are more strongly heritable[58] and persistent cases are more strongly linked to childhood maltreatment[59]. The interaction between serotonin transporter gene length polymorphism and childhood maltreatment also appears to be specific to persistent depressive disorder[39,40]. On the other hand, there is evidence that cycloid psychosis, a type of mental illness marked by a characteristic highly episodic course in spite of varied symptom content, may have distinct genetic underpinning[60,61]. These examples suggest that time course of illness may be at least as important in etiological studies as the symptom profile.

The findings of longitudinal research outlined above highlight a massive caveat in prior etiological studies that grouped individuals into cases and controls based on symptom content in adulthood without reference to developmental context or time course of symptoms. Future etiological research will be improved by the systematic incorporation of a temporal dimension that has been conspicuously missing from both categorical and dimensional classifications used by most etiological studies to date.

LIMITS OF CURRENT APPROACHES

The last decade has seen a large amount of criticism of psychiatric research. It may be important to own up to both successes and failures and take a stock of what might have hindered the field from knowing more. Based on the review of etiological research in psychiatry outlined above, we conclude that four factors are limiting further progress.

One of the major limiting factors is assumed knowledge. Over the past five decades, psychiatry researchers have built their studies around the following assumptions: causes are diagnosis-specific, disorders are caused by a small number of factors, and genetic factors have primacy over environmental influences. It is remarkable that some of the greatest discoveries in psychiatry occurred before these assumptions were established. For example, the discovery of lithium efficacy for bipolar disorder occurred thanks to investigation in an unselected group of patients[62].

Another limiting factor lies in omissions. The diagnosis-focused approach of the 20th century and the ensuing categories-vs.-dimensions discussion might have led to the neglect of the developmental context and the temporal dimension of psychopathology.

The final limitations we will discuss are related: statistical power and quality of measurement. Since many genetic and environmental factors contribute to most cases of mental illness, large representative samples with accurate measurements of genetic variation, environmental exposures and psychopathology over the life course are needed for etiological research. We have many studies with good measurement of environment, but they do not overlap much with studies with high standard of genetic measurement. We have some longitudinal studies with high quality measurements and we have some studies with a large number of individuals. Unfortunately, there has been little overlap between the two. The largest studies in psychiatry are either pulled together from many variably assessed samples or they suffer from large dropout rate and less accurate measurement. We may not get the answers about causation of mental illness unless experts in developmental psychopathology, environment and genetics join forces to work together on large longitudinal studies. Early examples of such collaborations are emerging and hopefully will be completed.

FRAMEWORK FOR DISCOVERY

To substantially advance our understanding of mental illness, the next generation of studies will need to embrace the complexity of poly-gene-environmental causation. The technology and methodological knowledge available today enables studies of multiple environmental and genetic factors without assumptions of independence. It is essential that the research studies are designed in a way that maximizes the potential for meaningful discovery by avoiding the pitfalls of assumptions, omissions, inadequate measurement and statistical power (Figure 3).

Large longitudinal studies of samples that are not selected for a particular diagnosis are needed to enable new discovery. These studies should start in pregnancy, childhood or adolescence to capture the development of psychopathology and allow separation of cases from consequences. Repeated assessments of multiple aspects of environment during the individual's development should cover known environmental risk factors as well as key factors of environment that may be good for some and bad for others. Regular assessments of psychopathology across the life course are needed to establish true age at onset, track the course and record sequential comorbidity.

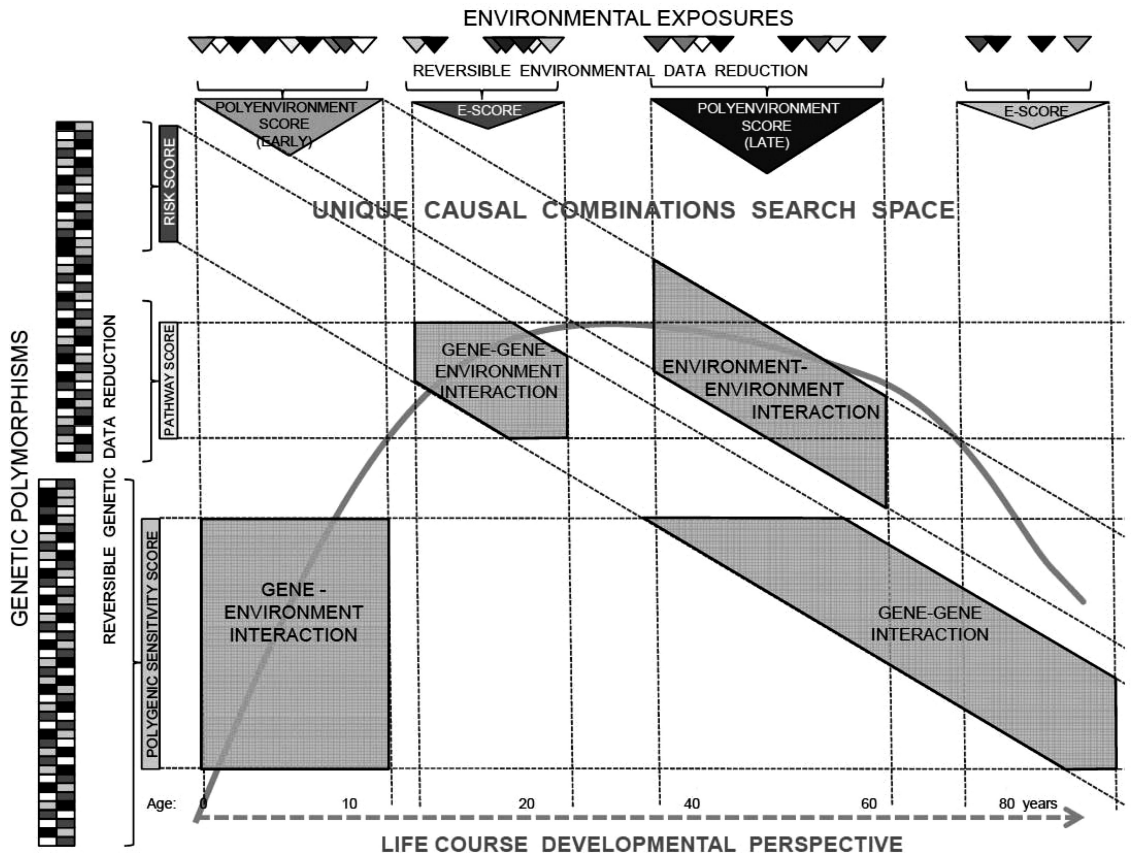

Figure 3 Framework for discovery. Life-course developmental perspective and an open search space for unique combinations of genetic and environmental factors (including gene-gene, gene-environment, and environment-environment interactions) are core elements that will enhance the potential for discovery in etiological research. Genetic and environmental data reduction – polygenic sensitivity scores, polygenic risk scores, genetic pathway scores, poly-environmental scores (E-scores) – may be a necessary intermediate step towards the discovery of broad poly-gene-environmental causal mechanisms, but the reduction process should be reversible to enable fine mapping of specific molecular and behavioral mechanisms.

Measurement of environment and psychopathology should use multiple independent sources of information to maximize objectivity and avoid common source bias (e.g., predictably high but uninformative correlations between questionnaires completed by the same individual at the same time). Instead of case-control studies, genetic measurement should concentrate on samples with high-quality longitudinal data on environment and psychopathology.

With broadly based assumption-free designs, the onus will be on data analysis to make use of the resulting data in a way that can identify complete etiological mechanisms leading to mental illness. The key challenge for data analysts will be to embrace the complexity of causation while retaining the capacity to trace specific causal mechanisms. The data analysis may need to move from theory-driven hypothesis testing focus to a theory-free explanatory framework that aims to explain the causation of a large proportion of cases. It will be important to identify unique combinations of genetic and environmental variables that lead to mental illness, irrespective of whether the biological mechanism corresponds to the constrained concept of statistical interaction. The framework should be open to identify combinations of early and late environmental factors as well as of environmental and genetic factors.

Tools for such analyses are becoming widely available. For example, statistical learning offers a set of tools that are designed to maximize the use of rich datasets in the prediction and explanation of outcomes and at the same time provide understanding of how individual factors contribute to the prediction[63]. Methods are also being developed that make it possible to distinguish between causal heterogeneity and polyfactorial causation[64]. While the available methods potentially offer many ways of analyzing rich datasets, the model complexity will have to be kept proportional to available sample sizes. Given the vast number of potential factors to be considered, data analysis process will require a degree of data reduction in the initial stages. This may take the form of polygenic risk scores of disorder liability or environmental sensitivity[48], genetic pathway scores[47] and poly-environmental risk scores[32].

The degree of data reduction should not be excessive and the process may need to preserve developmental specificity: e.g., with separate procedures for childhood, adolescent and

adulthood exposures. Data reduction also needs to be transparent, so that it is possible to follow a positive result back to the molecules and specific factors that drive the causal mechanisms. Specific constellations of molecular genetic and environmental factors will be needed to inform prevention and treatment[65].

Eventually, the role of each genetic and environmental variable has to be understood in a way that enables independent replication and examination of the underlying biological mechanism. Embracing complexity in a transparent and assumption-free framework will enable researchers to map complete causal mechanisms that explain why large groups of individuals develop mental illness. While this may be a bigger task than what previous generations of psychiatrists had envisioned, knowledge of complete causal mechanisms is necessary to meaningfully transform classification, prevention and treatment.

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The contemporary refugee crisis: an overview of mental health challenges

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There has been an unprecedented upsurge in the number of refugees worldwide, the majority being located in low-income countries with limited resources in mental health care. This paper considers contemporary issues in the refugee mental health field, including developments in research, conceptual models, social and psychological interventions, and policy. Prevalence data yielded by cross-sectional epidemiological studies do not allow a clear distinction to be made between situational forms of distress and frank mental disorder, a shortcoming that may be addressed by longitudinal studies. An evolving ecological model of research focuses on the dynamic inter-relationship of past traumatic experiences, ongoing daily stressors and the background disruptions of core psychosocial systems, the scope extending beyond the individual to the conjugal couple and the family. Although brief, structured psychotherapies administered by lay counsellors have been shown to be effective in the short term for a range of traumatic stress responses, questions remain whether these interventions can be sustained in low-resource settings and whether they meet the needs of complex cases. In the ideal circumstance, a comprehensive array of programs should be provided, including social and psychotherapeutic interventions, generic mental health services, rehabilitation, and special programs for vulnerable groups. Sustainability of services, ensuring best practice, evidence-based approaches, and promoting equity of access must remain the goals of future developments, a daunting challenge given that most refugees reside in settings where skills and resources in mental health care are in shortest supply.

Key words: Refugees, displacement, asylum seekers, ecological models, trauma, stress, mental health, post-traumatic stress disorder, depression, social interventions, brief psychotherapy

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The upsurge in the number of refugees over recent years is unprecedented in the modern world. If current trends continue, one in a hundred persons will be a refugee in the near future[1]. At present, responsibility for mental health support to refugees is shared by a network of agencies, including the United Nations High Commissioner for Refugees (UNHCR) and the World Health Organization (WHO), government and non-for profit organizations, mainstream mental health and specialist refugee services and voluntary organizations. Yet, the ineluctable reality is that most refugees with mental health problems will never receive appropriate services.

The chief reason for this is the scarcity and inequitable distribution of services, but other factors contribute to the situation, including difficulties in coordinating national and international efforts, barriers to accessing care even when services are available, and persisting stigma associated with being both a refugee and mentally ill[2]. Notwithstanding, advances have been made in research, theory, policy and models of treatment. Importantly, there is evidence of growing convergence in these areas, a consensus that is likely to gradually build to the more effective use of scarce resources to achieve better mental health outcomes for this population.

The present paper focuses on issues of general concern amongst adult refugees. The reader is referred to the specialized literature on vulnerable sub-populations (child soldiers, unaccompanied minors, children and youth, single or widowed women) and specific geographical situations around the world[3-7].

THE SCALE OF THE PROBLEM

The United Nations estimate that over 65 million persons worldwide are currently displaced by war, armed conflict or persecution. In total, 16.5 million fall under the mandate of the UNHCR. Although the flow has slowed somewhat, 3.2 million persons were displaced in 2016 alone, the leading source countries being Syria and South Sudan[1]. More than 80% of refugees are displaced internally or have fled across national border to neighbouring countries, the majority being located in low- and lower middle-income countries.

Half of the world's refugees remain in "protracted situations", unstable and insecure locations, most commonly in dense urban areas, but also in refugee camps. For example, 314,000 persons remain displaced from Darfur in Eastern Chad, and more than a million Somalis live as displaced persons in Kenya, Ethiopia, Djibouti and Yemen. Dadaab, a vast refugee camp in Kenya, houses families that have been sequestrated in this remote and insecure location for more than three generations.

In 2016, Europe confronted the largest single inflow of refugees since the World War II, with over a million Syrians and others from the Middle East entering the region[1]. Oscillations in public opinion and government policies resulted at times in chaotic responses in which authorities attempted to halt or divert the influx, indicating the lack of preparedness of even advanced nations to deal with this humanitarian crisis.

To place the European situation in perspective, a total of 13 million Syrians have been displaced by the war, the majority to

neighbouring countries. Lebanon, a small country of 4.5 million persons, now accommodates as many Syrian refugees as the whole of Europe[1,8]. The wars in the Middle East also tend to overshadow lesser known refugee crises around the world, for example in West Papua, Myanmar and Western Sahara[9-14].

OSCILLATIONS IN PUBLIC PERCEPTIONS AND NATIONAL POLICIES

Throughout history, recipient societies have responded in ambivalent ways to refugees, at times greeting them as heroes, and at others as interlopers who threaten the peace, integrity, cultural identity and economic stability of the host country[15].

The policies applied to refugees by host countries are crucial to the mental health of that population. The United Nations Refugee Convention (1951) and later Protocol (1967) ushered in a progressive era in the international response to this problem. The essential principles established by these instruments include: a) that persons with "a well-founded fear of being persecuted for reasons of race, religion, nationality, membership of a particular social group or political opinion" have an inalienable right to seek asylum in signatory countries; b) that refugees are protected from *refoulement* or forced return to places of danger in their homeland; and c) that host countries have a responsibility to provide "favourable" conditions for refugees, including, *inter alia*, the right to work, to freedom of association and movement, and to appropriate services.

The Convention proved effective in the early decades following the World War II, when refugee flows were small, newcomers were mainly of European origin, and recipient societies resonated positively with their reasons for fleeing, usually based on their opposition to the ideology of totalitarian regimes in the countries of origin. The popular campaign against torture in the 1970s further strengthened public compassion for survivors who in most instances were refugees.

The large exodus of Southeast Asian refugees in the 1970s and 1980s created a new challenge for the Convention[16], but after a period of inertia and dissension, leading Western nations finally accepted most of the displaced persons for resettlement. Nevertheless, the crisis underscored a pattern that has been repeated in Europe in contemporary times, that is, that the willingness of recipient countries to accept refugees is inversely related to the rate of influx and ethnic difference of the incoming group[17].

The distinction made in the 1980s onwards between asylum seekers (persons arriving without prior authorization) and "Convention" refugees (those granted residency visas prior to arrival[17]) further put to test the viability of existing international procedures. Australia implemented stringent policies of deterrence to asylum seekers, and other countries of Europe and North America instituted similar policies and practices[18-20]

The spirit of the Convention was further eroded by the phenomenon of terrorism. Several factors, including the ethnic and religious stereotyping of terrorists, increased communal resistance to immigration, the distinction between refugees and voluntary migrants becoming blurred in the process[21-24]. For all these reasons, although the Refugee Convention is still in force, there are unprecedented pressures to dilute if not to dismantle the key provisions for protecting the rights of refugees, irrespective of their backgrounds or countries of origin[25].

EPIDEMIOLOGY OF MENTAL HEALTH PROBLEMS AMONGST REFUGEES

Prior to the 1970s, the field lacked robust scientific data detailing the nature, prevalence and determinants of mental health problems amongst refugees. Pioneering studies undertaken in the US, Canada, Norway and Southeast Asia identified what appeared to be substantial symptom levels of anxiety and depression amongst Indochinese refugees, but the absence of closely matched comparison groups limited interpretation of the findings.

The inclusion of post-traumatic stress disorder (PTSD) in the DSM-III set the stage for the modern era of research in the refugee field, the first studies being conducted amongst Southeast Asian refugees[26-28]. For example, a study conducted in a refugee camp for Cambodian survivors of the Khmer Rouge autogenocide found that half of respondents met threshold criteria for depression and 15% for PTSD[27].

In the following two decades, there was a burgeoning of epidemiological studies in the refugee mental health field, prompting two systematic reviews of the cumulative findings in 2005[30-32]. The first, which was limited to studies of refugees in Western countries, yielded an average prevalence of 9% for PTSD and 5% for depression, noting that lower rates were found amongst the larger, more rigorously conducted studies. These findings provided a corrective to the tendency to regard all refugees as "traumatized" and in need of counselling. The second review, based on studies that included comparison groups, showed that refugees had a modestly elevated risk (effect size of 0.41) of a range of adverse mental health outcomes. Factors associated with poor mental health amongst refugees included socio-demographic characteristics (being older, a woman, from rural background, well educated, and coming from a higher socio-economic status), and stressors in the post-displacement environment (living in institutions, restrictions in economic opportunities, being internally displaced or involuntarily repatriated, and coming from a country that remained in conflict).

The largest review of its kind, published in 2009, identified 181 surveys undertaken amongst 81,866 refugees and other conflict-affected populations from 40 countries[29]. The prevalences of PTSD and depression were similar, approximating 30%, although there was substantial heterogeneity in rates across studies. Exposure to torture and the total number of trauma events experienced emerged as the strongest predictors of PTSD and depression, respectively. Larger, more rigorously designed

studies yielded lower prevalence rates, reducing the estimate for PTSD to 15%, a finding broadly supported by a more recent review[33]. Even so, the PTSD prevalence greatly exceeds the estimate of 1.1% recorded across non-refugee populations in countries participating in the WHO World Mental Health Surveys[34].

The body of research focusing on asylum seekers served to highlight the impact of the post-migration environment on the mental health of displaced populations[35-43]. A growing number of studies in recipient countries found that imposed conditions of adversity, including prolonged detention, insecure residency status, challenging refugee determination procedures, restricted access to services, and lack of opportunities to work or study, combined in a way that compounded the effects of past traumas in exacerbating symptoms of PTSD and depression[29,36,39,44-48]. Yet, in spite of widespread concerns, these practices continue. As a corollary, mental health professionals keep on confronting ethical challenges when working within detention centre hierarchies, and practical questions persist regarding the effectiveness of offering counselling to persons forced to live under such restrictive conditions[49].

TRANSLATING EPIDEMIOLOGICAL DATA INTO POLICY AND PRACTICE

Translating epidemiological data into estimates of service needs requires careful consideration. As indicated, prevalence rates of common mental disorders such as depression and PTSD have shown wide variation across the body of refugee studies reported. Methodological factors are partly responsible, including transcultural measurement error, biases related to non-probabilistic sampling, and the use of screening measures which tend to overestimate the prevalence of disorder[50,51]. In addition, populations from some regions of the world (East Asia, Sub-Saharan Africa and the Pacific) tend to record lower symptom levels compared to high-income countries[52]. Failure to include indigenously derived measures that capture local expressions or idioms of distress also can lead to the under-enumeration of mental health problems[37,53].

Notwithstanding these sources of heterogeneity, substantive issues of a universal nature, such as the extent of exposure to torture, the severity and number of trauma events experienced, the socio-demographic characteristics of the population, the level of ecosocial threat that the community continues to face, and the nature and extent of post-migration stressors, all make a major contribution to the prevalence of disorders across populations. Given the variation in these substantive factors across contexts, it should not be surprising that prevalence rates of common symptoms of mental distress differ from one population to another.

The greatest obstacle in translating epidemiological data into service needs arises from the difficulty in differentiating, in cross-sectional surveys, between reactions which may be commensurate with the level of stress being encountered and frank mental disorder that risks becoming chronic and disabling, in part independent of the context[54]. Longitudinal studies assist to some extent in addressing this problem, in that they are capable of distinguishing between symptom trajectories that indicate recovery as opposed to chronicity, pathways that may be predicted to some extent by the profile of baseline risk and protective factors[55]. Short-term follow-up studies (1-3 years) may not distinguish these trajectories with any accuracy, particularly if the follow-up extends through a period of ongoing instability, for example, in the immediate post-displacement phase[56-59].

Only a small number of studies have followed up refugees for 10 years or longer, in all instances being limited to the measurement of general symptoms of anxiety and depression using screening instruments[57-60]. Broadly interpreted, these studies suggest a common pattern of outcome: most refugees continue to show low or no symptoms; a significant minority show a pattern of gradual recovery; and a small group remain chronic. This picture was supported by a large cross-sectional study using a retrospective quasi-longitudinal analysis[37]. A similar set of trajectories has been found in a six-year follow-up study amongst a post-conflict population in Timor-Leste[61]. This tripartite pattern of low or no symptoms, gradual recovery and chronicity, although tentative, has important implications from a public health perspective in judging which populations will benefit from programs of social reconstruction and which might require more intensive psychotherapeutic interventions, as discussed hereunder.

Estimating service needs also depends on a range of other factors, including help-seeking behaviour. Stigma, mistrust and lack of knowledge of services may limit the extent to which refugees access mental health services, even if available. Taking all factors into account, modelling based on the Global Burden of Disease Study has illustrated how large the gap is between the existing number of mental health professionals and the service needs of low-income countries and regions that have large populations exposed to mass conflict and displacement[62]. There is no realistic prospect, therefore, of formal mental health services, whether generic or specialized, meeting the mental health needs of refugees, noting that the majority reside in low-income countries. Creative solutions are thus necessary, including networking of all agencies to ensure the sharing of responsibility of care for refugees with mental disorder, and task-shifting, i.e., the transfer of skills to primary care and lay workers in order to undertake specific mental health interventions of various types under supervision.

BROADENING KNOWLEDGE OF MENTAL HEALTH OUTCOMES

Recent research in the refugee field has widened the scope of interest to disorders and reactions that extend beyond the conventional focus on PTSD and depression, and to a lesser

extent anxiety and somatic symptoms. There is a resurgence of interest in the construct of prolonged or complicated grief, given the importance of this reaction to refugees, the majority of whom have experienced multiple losses and separations in the context of gross human rights violations[63]. In addition, the long-debated category of complex PTSD, comprising elements of disrupted self-organization (negative self-concept, affective dysregulation, interpersonal difficulties) will be included for the first time in the forthcoming ICD-11[64], early evidence suggesting that the diagnosis can be identified amongst refugees.

There is also a growing body of studies documenting cases in which PTSD is associated with psychotic-like symptoms or frank psychosis amongst refugees and post-conflict populations[65-67]. Recognition of the prevalence and salience of these symptom constellations adds further complexity to the field, particularly in relation to the need to tailor interventions to individual patterns of comorbidity and disability.

TOWARDS AN ECOLOGICAL EPIDEMIOLOGY

The massive disruptions to family and social networks in the context of extreme human rights violations undermines the fundamental sense of coherence of refugees, many becoming isolated and losing trust in authority structures. Chronic anger is one potential outcome that has important social implications. For example, amongst West Papuan refugees, a constellation of mistrust, resentment and anger is embodied in an idiom of distress, *Sakit Hati*, literally meaning "sick heart"[68].

A focus on states of chronic and uncontrollable anger in survivors of extreme trauma creates an important bridge that links individual reactions to the stability of the family and the wider social network. A cycle of violence model posits that, in some instances, aggressive outbursts amongst survivors may be implicated in family conflict, generating a multiplier effect of mental health problems in intimate partners and potentially children, a cycle of violence that may have profound transgenerational effects[69]. Recent applications of multilevel statistical techniques allow examination of these transactional effects both within conjugal couples and families, thereby broadening the scope of epidemiology to increase its ecological and contextual significance[70,71].

CONCEPTUAL FRAMEWORKS

From a theoretical perspective, the formative period of the refugee mental health field (broadly the 1970s to 2000) was marked by spirited and at times divisive debates in relation to theory and models of intervention. Those adopting a critical, transcultural perspective questioned, and in the most extreme case rejected, the tendency by Western mental health professionals to transfer Western diagnostic categories such as PTSD and associated trauma-focused therapies to the culturally distinct environments in which most refugees live[72]. The chief ongoing division in the mainstream was between advocates of individualized, trauma-focused psychotherapeutic approaches and those arguing in favour of psychosocial models that focus on the community as a whole and that aim to promote self-directed recovery and build resilience.

Contemporary models address these issues by providing a comprehensive account of the refugee experience. Most adopt a multisystem, ecosocial framework, drawing on established models in the social sciences[73]. Within these broad frameworks, mental disorder is regarded as the endpoint of an imbalance in the multiplicity of countervailing environmental factors that impact on refugees rather than an expression of innate or intrapsychic problems at an individual level. In that sense, the distinction between normative and pathological responses is somewhat blurred and fluid, the vicissitudes of the ecological context determining the direction and extent to which individuals shift on a continuum of stress.

An example of prevailing models includes Hobfoll's Conservation of Resources theory[74], which gives centrality to the effects of objective losses, and the shared meanings of these deprivations within each culture and context in determining mental health outcomes and resilience. From that perspective, resilience is regarded both as the capacity of the individual to withstand experiences of trauma and stress and as the capacity to remain vigorously engaged with life's tasks, principally, the pursuit of restoring resources that have been lost in times of adversity. The guiding assumption is that all humans have a natural drive to obtain, retain, foster and protect resources, defined widely to include a range of domains including the personal (health, well-being, positive sense of self), familial, and social (preservation of peace, capacity to work, access to facilities and services). Maintaining adequate resources is essential to fulfilling the task of self-regulation and a sense of control. The refugee situation typifies conditions in which there is a sudden and often massive loss of resources, the pattern of deprivation potentially compounding over time. Interventions should focus on providing the supportive environments that allow refugees (and other trauma survivors) to restore their resource base (personal, familial, social, material), a prerequisite for addressing mental health problems. The model offers the potential to make an objective assessment of the resource losses experienced by individuals and the community, the totality of the losses indicating the likely degree of mental distress that will be identified in the populations. Social interventions aimed at creating a supportive environment which facilitates the capacity of refugees to restore their lost resources will advance the overall aim of promoting resilience and mental health.

In their ecological model, Miller et al[75,76] give emphasis to the impact of daily stresses on the mental health of refugees and asylum seekers. The authors draw on data indicating that daily stressors partly or wholly mediate the effects of past war-related trauma in shaping mental health outcomes such as PTSD symptoms[77]. Examples of these stresses include living in unsafe environments, challenges in meeting basic survival needs

(inadequate access to food, water, shelter, health care); inability to pursue income-generating activities; and isolation from family and traditional social supports. Vulnerable groups – such as women exposed to gender-based violence, former child soldiers, unaccompanied and orphaned minors, and persons with physical and mental disabilities – all face exceptional levels of ongoing stress. Based on this conceptualization, the emphasis of interventions is on creating supportive social environments that reduce daily stressors rather than on providing individual psychotherapy focusing on past trauma experiences.

The Adaption and Development After Persecution and Trauma (ADAPT) model[78,79] identifies five core psychosocial pillars disrupted by conflict and displacement, that is, systems of safety and security, interpersonal bonds and networks, justice, roles and identities, and existential meaning and coherence. These pillars form the bedrock on which stable societies are grounded and on which civilians depend for their mental equilibrium. The refugee experience, which involves a sequence of adversity that traverses epochs of conflict, dislocation, flight, transition and resettlement, erodes the integrity of all five psychosocial systems, thereby weakening social structures and institutions and exerting deleterious effects on the mental health of individuals. Although the relationship is indirect, the erosion of each pillar can have broad representations in the symptom patterns identified in refugees. For example, the combination of traumatic loss and extreme injustice may result, via several intermediate pathways, in comorbid symptoms of complicated grief and explosive anger. The ADAPT framework has been used as a conceptual foundation for formulating and implementing a comprehensive refugee mental health program amongst Iraqi refugees in Syria[79]. In support of the model, a recent study showed that a measure of the ADAPT construct moderated the effects of past trauma and ongoing adversity in shaping PTSD symptoms[80]. The ADAPT model alerts clinicians and planners to the importance of understanding the overall social ecology of the refugee experience and contextualizes the array of interventions which may assist in repairing each pillar, thereby creating the context for promoting mental health recovery.

THE GLOBAL MENTAL HEALTH PERSPECTIVE

The refugee mental health field overlaps considerably with the larger movement of Global Mental Health, both focusing on the mental health needs of deprived populations from low-income countries (noting that one of several distinctions is the substantial number of refugees relocated to high-income countries, where they confront special conditions).

There has been a tendency in the refugee field to limit interest in severe mental illnesses such as schizophrenia and related psychoses, bipolar disorder, melancholic forms of depression, drug and alcohol problems, and organic brain disorders. Persons with psychosis in particular are at risk of neglect, exploitation and abuse in acute humanitarian settings and other situations of mass displacement. During these periods, psychiatric hospitals and clinics often close, leaving patients without protection or medication.

The reality for psychiatrists and other mental health professionals working in clinics in Africa and other refugee situations is that a large proportion of the patients they consult manifest one or more of these forms of severe mental disorder. There is now compelling evidence that schizophrenia and other psychotic disorders are more prevalent amongst refugees resettled in high-income countries compared to other immigrants and host populations[81]. Therefore, the field of refugee mental health should include consideration of this subpopulation in mounting comprehensive programs of mental health care, an issue that is now more widely recognized and acknowledged in policy and planning exercises[82].

INTERVENTIONS

Brief psychotherapies

Counselling and psychotherapy remain the mainstay of treatment for common mental disorders – such as PTSD, depression and anxiety or combinations of these symptom profiles – in refugees. Most commonly, workers apply a flexible combination of supportive counselling and cognitive behavioural therapies. In spite of variability in the quality of existing studies, the overall evidence suggests that various forms of psychotherapy are relatively effective in ameliorating symptoms of PTSD, depression and anxiety[83].

Over the past two decades, a series of brief, structured, manualized psychotherapeutic packages have been devised for use amongst refugee and post-conflict populations. Most models draw on evidence from Western contexts supporting trauma-focused cognitive behavioural therapies[84]. The strengths of these newer programs include that: a) they can be adapted to local cultures; b) they allow rapid training of front-line personnel; and c) they facilitate task-shifting, that is, the transfer of skills from professionals such as psychologists to lay or community workers, a vital provision to allow uptake and dissemination in settings where there is a severe lack of mental health specialists. The time-limited nature and low cost of these interventions increase the potential for dissemination (or scalability) and for integrating the procedures within routine public health or community centre settings.

Most approaches use standard cognitive behavioural components including stress management, prolonged exposure, cognitive restructuring, behavioural strategies, and mindfulness or related de-arousal techniques. Increasingly, activation therapies are used for depression. The most widely tested method, narrative exposure therapy, draws on the principles of testimony therapy in tracing the person's chronological life course, embedding imaginal exposure to trauma memories in the natural course of this sequence[85]. A common elements treatment

approach is designed to accommodate common patterns of comorbidity, allowing the therapist flexibility in selecting modules (for example, for traumatic stress, depression, anxiety) to match the particular symptom constellation of each patient. Trials in several settings attest to the efficacy of this method[86]. More recently, the WHO has established a brief intervention, Problem Management Plus (PM+), drawing once again on the core principles and strategies of cognitive behavioural therapy. The first studies examining this method have yielded positive findings[87].

An important next step is to establish that these brief packaged interventions can be embedded in routine primary care services in low-income countries in a manner that is supported by local structures and hence sustainable. Apart from securing resources and the commitment of the hierarchy to these mental health initiatives, there is a major challenge in providing ongoing supervision and mentoring of workers, an essential provision to avert attrition of skills and motivation and to avoid burnout. The increasingly wide reach of the Internet and telecommunication systems improves opportunities to provide supervision from afar to remote locations where many refugee populations are located.

A further concern is whether brief or even extended interventions based on contemporary approaches to psychotherapy are effective for the significant minority of refugees with complex traumatic stress presentations. A controlled trial from Denmark[88] offering a comprehensive array of interventions (medical and psychiatric assessment and consultation, psychopharmacology, social worker assistance, and individualized psychotherapy) found no change in baseline high levels of PTSD symptoms over a one-year course of follow-up, and only modest reductions in symptoms of depression. The most likely reason is that the majority of participants came from the poor prognostic subpopulation provisionally identified in epidemiological studies. Participants had extensive exposure to torture and other forms of abuse; high rates of head injury, chronic pain and physical disability; a chronic pattern of persisting symptoms; and a history of failed response to past treatments. Most were socially isolated, marginalized and unemployed.

Patients with these complex characteristics may not have the motivation, resilience or cognitive capacity to engage in exposure therapies or to implement the techniques of cognitive behavioural therapy which require active practice to be effective. Questions remain, therefore, as to the best strategies to assist these complex cases. It may be that more graduated rehabilitation approaches are needed to encourage what may be a slow recovery trajectory in this subpopulation.

Pharmacotherapies

There is a dearth of research focusing on specific psychopharmacological issues amongst refugee populations. Practitioners apply the same range of psychotropic medications used in routine psychiatric practice, although adjusting dosage according to ethno-pharmacological considerations.

In general, for common patterns of major depressive disorder, PTSD and anxiety disorders, the most commonly used medications are the first generation (tricyclic) drugs and, where available, the newer antidepressants (selective serotonin reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors, and their variants), the latter recommended for PTSD by the WHO's Mental Health Gap Action Programme (mhGAP) guidelines[89]. In many low-income countries, first generation antipsychotic medications (haloperidol, chlorpromazine) are the only ones available for psychoses, although atypical antipsychotics, including clozapine, are becoming more widely available.

Difficulties are frequently encountered in humanitarian and acute refugee settings in ensuring continuity in the supply of medications. A further challenge is the provision of ongoing supervision and in-service training of nurses and other frontline community health workers who commonly oversee the use of psychotropic medications in low-income countries. There is a risk, therefore, that practices will be constrained to standard dosing and that side effects may receive inadequate attention.

Psychosocial interventions

As indicated, research findings are consistent with contemporary ecological models in demonstrating the powerful impact that ongoing social conditions exert on the mental health and psychosocial well-being of refugees. In addition to the effects of past trauma, refugees commonly confront important challenges and stressors in their new environments, including ongoing insecurity, restricted access to essential services (health, mental health, education), lack of opportunities for employment, and more generally, host society attitudes of racism and xenophobia. Death, disappearances and separations result in persisting grief and loss. The ongoing consequence of these losses is that refugees commonly lack the support of nuclear and extended families and other traditional networks, a profound challenge for communities with strong collectivist values. Even in intact families, relationships can be undermined by the cumulative effects of past trauma and ongoing stressors, resulting in conflict and, at worst, intimate partner violence[90].

Social programs for refugees have the potential to revive a sense of connectedness, re-establish social networks, and promote self-help activities. Strategies that foster community initiatives encourage a sense of control and engagement in the task of self-directed recovery, counteracting the inertia, dependency, and inter-group divisions that characterize many transitional refugee settings. There are compelling theoretical, economic, and strategic reasons, therefore, to give priority to social interventions in the array of strategies aimed at relieving distress and promoting well-being amongst refugees.

At the most general level, psychosocial programs focus on the population as a whole, examples being community-wide truth and reconciliation programs, income generation activities, and the development of participatory processes to foster democratic decision-making and self-governance. Practical programs include setting aside child friendly spaces, developing teams of refugee outreach volunteers to assist families confronting a range of economic or social problems, and establishing community centres where individuals can obtain assistance in relation to housing, other basic needs, education, and referral to other services[91-93].

Special populations or vulnerable groups such as former child soldiers and survivors of gender-based violence may require specifically designed programs. In some instances, however, social programs may have paradoxical effects. For example, participation in truth and reconciliation processes can improve community cohesion, but result in worsening of mental health. These findings reinforce the need for rigorous research to test both the benefits and disadvantages of various psychosocial programs.

Sociotherapy is one of the few well researched group psychosocial interventions[94], the primary focus being the fostering of connections between people. The method was developed in the post-genocidal context of Rwanda and has since been applied in other settings including amongst refugees[95]. Groups share and discuss daily problems ranging from interpersonal disputes, feelings of marginalization, and strategies to deal with gender-based violence and poverty at the community level. Trained facilitators create a safe therapeutic environment which nurtures trust, mutual care and community-wide respect. The restorative experience of participating in the group itself may assist in repairing disrupted social relationships, although in all groups of this kind there should be agreed limits to disclosure, for example, discussing and revealing specific instances of intimate partner violence is contraindicated in the group setting. In general, however, the process may foster supportive peer relationships that endure beyond the life of the group program. Preliminary research suggests that sociotherapy has the dual effect of increasing civic participation (and hence social capital) and improving participants' mental health[96,97].

Related models have been trialled, including use of multi-family interventions in which several families share experiences of traumatic stress and chronic adversity. The aim is to reduce isolation, create a sense of shared experiences and solidarity, and foster supportive connections. Preliminary findings indicate that such methods are effective in improving self-confidence, decreasing social isolation and increasing access to mental health services[98,99].

In relation to future developments, a stepped care model in which refugees first attend social programs which address general levels of distress, while at the same time those with more severe mental health problems are identified, offers an integrated approach to maximizing resources and a non-stigmatizing referral pathway to specialist services.

POLICY, LEADERSHIP AND COORDINATION

The pioneering phase of the refugee mental health field was driven by a high level of passion and commitment, in a context where program leaders and clinicians were working from a low knowledge base. The past two decades have witnessed a maturing of the field, an era when lead agencies (the United Nations, international non-governmental organizations, universities, amongst others) have established close working relationships that have allowed the gradual building of an international consensus on issues that previously were divisive.

The fruits of these endeavours include the formulation and wide adoption of influential policies and guidelines that assist the planning and implementation of programs, for example, the Inter-Agency Standing Committee (IASC) Guidelines for Mental Health and Psychosocial Support in Emergency Settings and the SPHERE handbook[100,101]. A further major achievement has been the clinical guidelines produced by the WHO's mhGAP, especially the module focusing on emergencies[102,103]. In addition, United Nations agencies have produced and disseminated a range of assessment and monitoring tools to encourage standardization of assessments across programs around the globe[104]. There also have been important consensus building activities in relation to setting priorities for research[105].

TOWARDS THE FUTURE

As indicated, there are growing points of convergence across activities (research, development of conceptual frameworks and policies) in the refugee field, although tensions remain in some areas. For example, there is clearly a dysjuncture between the breadth and complexity of extant ecological models of mental health and the more limited assumptions underpinning the implementation of brief, symptom-focused packages of intervention that continue to be trialled in a range of refugee settings.

An important direction for research is to distinguish the needs of the various subpopulations of interest: those with distress reactions that are responsive to environmental factors, for whom broader social programs as well as more targeted non-clinical group interventions may be of assistance; those whose traumatic stress reactions are severe, disabling and unlikely to resolve spontaneously and who may benefit from brief structured psychotherapies; more complex trauma-related cases who may benefit from longer-term rehabilitation; the severely mentally ill who need an array of mainstream interventions; persons with drug and alcohol problems requiring specific attention; and special groups such as women exposed to domestic violence who may require a gender-sensitive approach to care.

In relation to advocacy, awareness-raising and embedding mental health programs within the existing institutional structure, the refugee field can learn a great deal from the general

field of Global Mental Health[106,107]. Without establishing a firm foothold for refugee mental health in existing primary care and other public health services, issues of sustainability will persist. Showing that treatments work under controlled research conditions is only the first step in ensuring that effective interventions actually reach the majority of populations in need.

A major challenge that the field confronts at a global level is that most refugee populations reside in locations where the resource base in mental health is extremely low. Theoretical debates aside, the reality is that, in these contexts, no single agency or program can provide for all the inter-related psychosocial and mental health needs of refugees. The success of the overall program will be gauged not by the accomplishments of one component but by the extent to which all contributors coordinate to establish the most comprehensive, inclusive, and integrated response, which includes networking of mental health agencies with social, community, and general health services.

Within the mix, the voice of the refugee communities is vital. Mental health cannot be conferred, it must be regained by the communities that have temporarily lost their equilibrium as a consequence of overwhelming circumstances.

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The clinical relevance of appraisals of psychotic experiences

It is not psychotic experiences in themselves but the way in which we appraise, or make sense of, them that determines their clinical relevance, and provides the key focus of psychological therapy. Psychotic experiences do not inevitably cause distress, impair functioning or result in psychiatric diagnosis. Extensive empirical findings indicate that these experiences can occur in the absence of a "need for care"[1].

What, therefore, determines clinical pathological outcomes? Cognitive models of psychosis[2] outline how the appraisals which people make shape both the content of psychotic experiences and the meaning that is attributed to them, bridging the gap between phenomenological and neurobiological accounts of their occurrence[3]. Characteristic appraisals, for example, of psychotic experiences as betokening threat, and rendering the self as vulnerable or worthless, are associated with need for care. These appraisals in turn are influenced by the psychological (i.e., cognitive, affective and behavioural) processes which have developed in the context of a person's genes, biology and socio-environmental experiences[4].

A case example illustrates our proposition. James grew up in poverty, experienced bullying and was raped during his teenage years. These early experiences led to distressing beliefs that he was weak and others would harm him, and he tended to be alert to potential threats. As adolescence developed into adulthood, jobless, James became increasingly isolated and rarely went outside. James felt very on-edge, and his sleep was disturbed. One day, he heard whispers that sounded critical, which he was sure were people talking about him. He became more anxious and struggled to take care of himself. He started using cannabis. The voices suddenly got more intense, telling him "you are nothing and are going to get it". James just knew this was a sign he would never escape others' persecution, and he became even more guarded and avoidant. James felt completely helpless and had no hope for his future.

James's difficulties highlight how adverse life experiences contribute to negative appraisals about the self and others, which can – in the presence of a range of affective, cognitive, behavioural, social and biological factors – trigger and shape psychotic experiences and the meaning that is attributed to them. James's voices reflect the themes of how he views himself and others; and his appraisals ("I am cursed") and their consequences ("I am helpless") also mirror his negative beliefs.

But note it is not just the content of appraisals that is of clinical relevance, but also the processes by which people reach such conclusions and how they react to them. A certain type of thinking style, *fast thinking*[5], is particularly associated with threatening appraisals in psychosis, and is characterized by a tendency to "jump to conclusions", to have high conviction in one's instincts, and to fail to consider alternative explanations[6]. Worry and ruminative thinking further maintain distressing interpretations, together with threat-focused attention, memory biases and understandable, but unhelpful, avoidant "safety behaviours" which act to prevent disconfirmation of fears[6].

The focus of cognitive-behavioural therapy for psychosis (CBTp) is therefore on understanding and exploring these appraisals of psychotic experiences and the thinking contributing to them, with the goal of supporting people to become less distressed and more able to live a personally meaningful life. The evidence base for CBTp is now consistent in demonstrating benefits for psychotic symptoms[7]. Developing trust and safety in the therapeutic relationship is the foundation of CBTp, as for other therapies, and requires skilful competence, given the nature of people's beliefs and the marked interpersonal difficulties they have often experienced.

An empathic and collaborative approach is essential, conveying a spirit of open enquiry, including the "suspension of disbelief" regarding the veracity of appraisals[8]. Directly challenging these appraisals and presenting contradictory evidence is counter-therapeutic, as it risks invalidating people's subjective experience, and may paradoxically increase their conviction and distress.

However, empathic engagement alone is insufficient to bring about clinically significant improvements in people with psychosis. A key mechanism of change in CBTp, consistent with psychodynamic approaches, is the development of reflective functioning or the ability to make sense of one's own mind and that of others, in order to understand behaviour[9]. Specifically, belief flexibility or s*low thinking* is fundamental to adaptive psychological functioning, and involves reflective curiosity and generation of alternative ideas[5]. There is now evidence that therapy which targets improvements in belief flexibility specifically diminishes paranoia[10].

So, whilst a developmental perspective is valuable in aiding self-understanding, the key therapeutic focus is on identifying and modifying day-to-day cycles which maintain occurrence of distressing appraisals of psychotic experiences. As well as fast thinking processes, these include sensitivity to stress, threat anticipation, negative affect, ruminative worrying and safety behaviours[6].

The synthesis of an individualized narrative provides an account of the range of probable factors that contribute to distressing appraisals, with the goal of increasing people's awareness of the mechanisms by which they attribute meaning to their experiences. CBTp can be seen as a process of "sowing seeds" to support the germination of alternative, less distressing explanations, which over time become more adaptive appraisals of psychotic experiences[11]. This then supports behavioural experimentation in daily life, to explore the impact of modifying these and trying out different ways of managing stressful, but valued activities, with experiential learning gradually reinforcing safer appraisals of experience.

CBTp mirrors the naturalistic process through which we derive meaning from our life experiences to support adaptive functioning. However, sustaining this without support, given heightened vulnerability to stress, is a significant challenge. An important target for future research is the facilitation of enduring generalization of therapy gains to everyday life. To address

this, our research team is trialling a digital therapy called *SlowMo* that targets problematic fast thinking to modify distressing appraisals of psychotic experiences and thereby reduce paranoia[10]. A *SlowMo* mobile app (see www.slowmotherapy.co.uk) assists people to *slow down for a moment* in their daily life to notice new information and develop safer thoughts, thereby aiming to optimize the clinical relevance of adaptive appraisals of psychotic experiences to real life.

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Mating, sexual selection, and the evolution of schizophrenia

For over fifty years, evolutionary theorists have sought to understand the biological roots of our species' vulnerability to schizophrenia – a debilitating disorder that has a relatively high incidence despite being associated with markedly reduced fertility (the so-called "schizophrenia paradox"). While some models treat the entire spectrum of schizophrenia as a manifestation of biological dysfunction, others postulate that psychosis proneness (schizotypy) or even psychotic symptoms may confer adaptive benefits through enhanced survival or reproduction (or they used to do so during our evolutionary history)[1].

Adaptive models of this kind face some formidable challenges. In addition to the low fertility of patients – which is not balanced out by that of their close relatives – and the evidence of reduced IQ and neural integrity in schizophrenia, they need to account for the role played by deleterious *de novo* mutations (including rare copy number variations), which explain a larger share of schizophrenia risk than common genetic variants[1,2].

Schizophrenia is a heterogeneous category, and any comprehensive explanation is likely to require a combination of models. At the same time, theory and evidence increasingly point to mating as a contributing factor in the evolution of psychosis proneness. The sexual selection model (SSM) was first advanced by Nettle[3] and refined by Shaner et al[4]. According to this model, schizophrenia is a maladaptive condition, but schizotypal traits – in particular positive schizotypal traits such as magical thinking, ideas of reference, and unusual perceptual experiences – are associated with enhanced verbal and artistic creativity and, as a result, lead to increased success in courtship and mating. The hypermentalistic cognitive style of schizotypal individuals involves a heightened focus on others' thoughts and emotions, which may also contribute to courtship success[5,6]. Consistent with this hypothesis, several studies have shown that positive schizotypy is associated with artistic creativity, a larger number of sexual partners, and a preference for uncommitted sexual relatioships[7]. Also, a moderate degree of reduction in white matter integrity has been linked to creative thinking and imagination[8].

But how does this model account for the role of rare mutations in schizophrenia? Most sexually selected traits are fitness indicators in that they correlate with the organism's underlying condition, including good nutrition, absence of parasites, low levels of harmful mutations, and so on. Other traits may evolve as amplifiers by further increasing the condition sensitivity of fitness indicators. In a nutshell, the SSM hypothesizes that verbal and artistic creativity are fitness indicators, whereas schizotypy functions at least in part as an amplifier trait[4]. In other words, high schizotypy increases the risk of schizophrenia in people who carry many harmful mutations and/or are exposed to high levels of stress and infections; however, the same traits boost mating success in people with low mutation load and few developmental stressors. Of course, contraception and other evolutionary novel aspects of modern societies may attenuate or break the link between mating success and actual reproduction.

The SSM potentially explains the logic of several risk factors for schizophrenia, from harmful mutations and low IQ (which is also affected by mutation load, especially at the low end of the distribution) to early infections and stressful life events. In addition, specific stressors such as migration into a minority population may partly operate by exacerbating competition for mates in adolescence and early adulthood. Most importantly, the SSM offers a potential solution to the paradox of low fertility in patients and their close relatives. According to the model, the low fertility of patients is not caused by schizotypy alone, but rather by the interaction between schizotypy and fitness-reducing factors such as mutations and adversity. Close relatives of schizophrenics are likely to share some of the same factors, both genetic and environmental. As a result, they can also be expected to show reduced fertility, though less dramatically so than patients[9]. If the model is correct, the crucial comparison would be that between the close relatives of schizophrenics and people with similarly high levels of schizotypy but without a diagnosed relative.

At the genetic level, it is important to appreciate that the SSM postulates the existence of at least two distinct sources of

schizophrenia risk: a) rare and *de novo* mutations, which are overwhelmingly harmful and subject to negative selection; and b) schizotypy-increasing alleles, which should be relatively common and evolve under balancing selection (a regime of alternating positive and negative selection on the same allele)[9]. Common variants that influence IQ may represent a third independent source of risk. The SSM also predicts a unique pattern of genotype-by-genotype interaction – namely, the same deleterious mutations should have a stronger effect on the risk for schizophrenia when they occur on a background of schizotypy-increasing common variants. To my knowledge, this hypothesis has never been tested in genetic research. A recent study found that strong negative selection on rare mutations contributes to maintain variation in other, physically close genes on the same chromosomes[2]. However, the authors did not test whether balancing selection may also contribute to maintain a certain amount of common genetic variation, independent of deleterious mutations.

Mating is only one component of an organism's fitness, and needs to be balanced against other critical tasks. Examples are skills acquisition, feeding, and protection of the offspring. The decisions made in allocating time and energy to these investments determine an individual's life history strategy. Life history strategies have wide-ranging implications for personality, behavior, and physiology. In humans, "fast" strategies are associated with heightened mating effort, precocious sexuality, low investment in stable couple relationships (which are conducive to parenting effort), impulsivity and risk-taking, and broad personality traits such as low agreeableness and conscientiousness. "Slow" strategies are associated with lower mating and higher parenting effort, delayed sexuality, fewer partners, self-control and risk aversion, and high agreeableness and conscientiousness.

Life history concepts can be used to develop a broad-band evolutionary taxonomy of mental disorders[10]. In this framework, schizophrenia spectrum disorders can be classified as fast spectrum conditions, together with borderline personality disorder, antisocial and conduct disorders, and eating disorders marked by behavioral dysregulation. Above and beyond their differences, these disorders share a functional link with fast life history-related traits such as heightened mating effort and impulsivity, and form a comorbidity network with common risk factors and developmental correlates[6,7,10]. They can be contrasted with slow spectrum conditions, such as obsessive-compulsive personality disorder, at least a subtype of autism spectrum disorder (mainly in the high-functioning range), and eating disorders characterized by elevated conscientiousness and self-control.

The taxonomy sketched above is still provisional and open to substantial revisions. Even so, simulations show that the life history model is already capable of reproducing the large-scale empirical structure of mental disorders, including the internalizing-externalizing distinction and the emergence of a general "p factor" of psychopathology[10]. A life history approach recasts the SSM within a broader theoretical framework and integrates its insights with those of other evolutionary models, such as the diametrical model of autism and psychosis advanced by Crespi and Badcock[5]. Together, these developments are starting an exciting new chapter in the evolutionary study of schizophrenia, with novel predictions to test and unexplored implications for epidemiology, prevention, and treatment.

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Validity and utility of the general factor of psychopathology

Psychopathology can be viewed as a variety of symptoms that are organized into first-order dimensions by their correlations. Critically, these first-order dimensions are themselves robustly correlated[1]. These correlations are problematic for categorical taxonomies[2], but provide essential information about the nature of psychopathology[3-5]. Correlations among first-order dimensions vary in magnitude, with stronger correlations among some dimensions yielding second-order factors, particularly internalizing and externalizing factors[6].

These second-order factors do not completely capture the correlations among dimensions of psychopathology, however. Rather, second-order internalizing and externalizing factors are themselves substantially correlated. We provided evidence that the correlations between internalizing and externalizing factors can be explained by a general factor of psychopathology on which every first-order dimension loads[7]. This finding has been replicated many times across the lifespan[4]. Most studies examined only prevalent forms of psychopathology, but several showed that bipolar disorder, schizophrenia and autism are strongly related to the general factor of psychopathology, suggesting that this factor is very general indeed[4].

Before deciding that the general factor of psychopathology is useful, we must know if it is only an artifact of systematic measurement error. The general factor almost certainly partly reflects nuisance correlations due to the same informant reporting on all psychopathology dimensions, but it must also capture something

substantive to have utility. We have addressed this issue rationally[4], but ultimately it reduces to an empirical question of criterion validity. If the general factor is more than a measurement artifact, it will be significantly correlated with variables that are external to its definition but central to its validity. Critically, the general factor is robustly correlated with measures of cognitive ability and the dispositional dimension of negative emotionality. Furthermore, controlling for internalizing and externalizing psychopathology, demographic factors and intelligence, the general factor robustly predicts both concurrent and future adaptive functioning, even when symptoms and functioning are measured by different informants[4].

Can the general factor facilitate studies of the nature of psychopathology and ultimately improve prevention and treatment? We have hypothesized that first-order dimensions of psychopathology are correlated because they have shared causes. Large twin and sibling studies of children, adolescents and adults indicate that the general factor is moderately heritable[8] and that phenotypic correlations among the first-order dimensions are largely attributable to shared genetic influences[9], with less than half of the genetic variance on most first-order dimensions being dimension-specific[5].

These findings support the view that genetic risk factors for psychopathology often function pleiotropically[10], but they suggest a previously unsuspected breadth of pleiotropy, with a significant proportion of genetic factors non-specifically increasing risk for *all* dimensions of psychopathology. This implies that genetic research will be facilitated by letting genetic correlations – rather than ICD and DSM committees – define optimal phenotypes. In concrete terms, if a genetic variant that is robustly related to the general factor were instead tested for association with, say, depression, all cases in which the variant was present but the individual exhibited high levels of any other dimension of psychopathology would erroneously counted as "misses" instead of "hits".

The general factor of psychopathology also implies that first-order dimensions of psychopathology do not each have their own entirely unique pathophysiologies. Dimensions of psychopathology are too highly correlated and there is too much sharing of genetic and environmental influences at the level of higher-order factors not to hypothesize that variations in some neurobiological systems non-specifically underlie multiple dimensions of psychopathology.

We recently proposed a formal causal taxonomy of psychopathology in which the robust correlational structure of first-order dimensions is attributed to a hierarchy of increasingly specific etiologic influences[4]. In this model, some non-specific etiologic factors increase risk for all first-order dimensions of psychopathology to varying degrees through the general factor. Other non-specific etiologic factors increase risk only for all first-order dimensions within the internalizing or the externalizing domains, and each first-order dimension has its own unique causal influences.

This causal taxonomy addresses more than just the sharing of causal influences. It also supports novel hypotheses regarding the equally important heterogeneity of causes and mechanisms underlying each first-order dimension of psychopathology. Each first-order dimension is heterogeneous in its etiologies and mechanisms for the same reasons that different dimensions are correlated. That is, the etiologic influences on each first-order dimension of psychopathology are heterogeneous largely because they arise from (at least) three separate and largely orthogonal sources. Some persons exhibiting high levels of symptoms in any dimension of psychopathology may carry only risk genotypes that pleiotropically increase risk for all dimensions of psychopathology through the general factor. Other persons with the same symptoms may carry only genotypes that increase risk for all externalizing (or all internalizing) dimensions, and others may carry only genotypes that are specific to that dimension of symptoms. Many others will carry varying combinations of genotypes from each of these sources. The result is an intractable degree of heterogeneity in the genetic influences if first-order dimensions are studied individually. It should be far more efficient to identify such diverse etiologic influences and their related mechanisms at their source – by modeling higher-order phenotypes – than by attempting to fractionate each first-order dimension into its diverse etiologies and mechanisms.

This causal taxonomy suggests the need for major changes in how the etiologies and mechanisms of apparently diverse forms of psychopathology are conceptualized and studied. Case-control samples are the current standard for such research. They are optimized for identifying dimension-specific causes, but bias correlations among first-order dimensions of psychopathology, making the modeling of higher-order phenotypes complicated or impossible. In contrast, large representative samples that include sufficient variation in all psychopathology dimensions to model higher-order factors of psychopathology can inform every level of the hierarchy.

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Neuroticism is a fundamental domain of personality with enormous public health implications

Neuroticism is the trait disposition to experience negative affects, including anger, anxiety, self-consciousness, irritability, emotional instability, and depression[1]. Persons with elevated levels of neuroticism respond poorly to environmental stress, interpret ordinary situations as threatening, and can experience minor frustrations as hopelessly overwhelming. Neuroticism is one of the more well established and empirically validated personality trait domains, with a substantial body of research to support its heritability, childhood antecedents, temporal stability across the life span, and universal presence[1,2].

Neuroticism has enormous public health implications[3]. It provides a dispositional vulnerability for a wide array of different forms of psychopathology, including anxiety, mood, substance, somatic symptom, and eating disorders[1,4]. Many instances of maladaptive substance use are efforts to quell or quash the dismay, anxiousness, dysphoria, and emotional instability of neuroticism. Clinically significant episodes of anxiety and depressed mood states will often represent an interaction of the trait or temperament of neuroticism with a life stressor[1].

Neuroticism is comparably associated with a wide array of physical maladies, such as cardiac problems, disrupted immune functioning, asthma, atopic eczema, irritable bowel syndrome, and even increased risk for mortality[2]. The relationship of neuroticism to physical problems is both direct and indirect, in that neuroticism provides a vulnerability for the development of these conditions, as well as a disposition to exaggerate their importance and a failure to respond effectively to their treatment.

Neuroticism is also associated with a diminished quality of life, including feelings of ill-will, excessive worry, occupational failure, and marital dissatisfaction[5]. High levels of neuroticism will contribute to poor work performance due to emotional preoccupation, exhaustion, and distraction. Similar to the duel-edged effect of neuroticism on physical conditions, high levels of neuroticism will result in actual impairment to marital relationships but also subjective feelings of marital dissatisfaction even when there is no objective basis for such feelings, which can though in turn lead to actual spousal frustration and withdrawal.

Given the contribution of neuroticism to so many negative life outcomes, it has been recommended that the general population be screened for clinically significant levels of neuroticism during routine medical visits[1,6]. Screening in the absence of available treatment would be problematic. However, neuroticism is responsive to pharmacologic intervention[1]. Pharmacotherapy can and does effectively lower levels of the personality trait of neuroticism. Barlow et al[7] have also developed an empirically-validated cognitive-behavioral treatment of neuroticism, called the Unified Protocol (UP). They have suggested that current psychological treatments have become overly specialized, focusing on disorder-specific symptoms. The UP was designed to be transdiagnostic. Recognizing the impact of neuroticism across a diverse array of physical and mental health care concerns, the authors of the UP again note that "the public-health implications of directly treating and even preventing the development of neuroticism would be substantial"[7].

Neuroticism has long been recognized since the beginning of basic science personality research and may even be the first domain of personality that was identified within psychology[1]. Given its central importance for so many different forms of mental and physical dysfunction, it is not surprising that neuroticism is evident within the predominant models of personality, personality disorder, and psychopathology.

Neuroticism is one of the fundamental domains of general personality included within the five-factor model or Big Five[2]. It is also within the dimensional trait model included in Section III of the DSM-5 for emerging measures and models[8]. This trait model consists of five broad domains, including negative affectivity (along with detachment, psychoticism, antagonism, and disinhibition). As expressed in the DSM-5, "these five broad domains are maladaptive variants of the five domains of the extensively validated and replicated personality model known as the 'Big Five' or Five Factor Model of personality"[8].

Neuroticism is likewise aligned with the negative affective domain included within the dimensional trait model of personality disorder proposed for the ICD-11[9]. Finally, it is also evident within the transdiagnostic Research Domain Criteria (RDoC) of the National Institute of Mental Health, as RDoC negative valence encapsulates such constructs as fear, distress, frustration, and perceived loss[10]. It would be inaccurate to suggest that RDoC negative valence is equivalent to neuroticism, but it is self-evident that they are closely aligned.

Currently, there is considerable interest in the general factors of psychopathology, personality disorder, and personality. To the extent that degree of impairment and dysfunction (which largely defines the general factors) is associated with level of distress and dismay, which is quite likely to be the case, we would propose that neuroticism will explain a substantial proportion of the variance in those general factors.

In sum, neuroticism is a fundamental domain of personality that has enormous public health implications, impacting a wide array of psychopathological and physical health care concerns. It contributes to the occurrence of many significantly harmful life outcomes, as well as impairing the ability of persons to adequately address them. It has long been recognized as one of the more important and significant domains of personality and is being increasingly recognized as a fundamental domain of personality disorder and psychopathology more generally.

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Implementing shared decision making in routine mental health care

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Shared decision making (SDM) in mental health care involves clinicians and patients working together to make decisions. The key elements of SDM have been identified, decision support tools have been developed, and SDM has been recommended in mental health at policy level. Yet implementation remains limited. Two justifications are typically advanced in support of SDM. The clinical justification is that SDM leads to improved outcome, yet the available empirical evidence base is inconclusive. The ethical justification is that SDM is a right, but clinicians need to balance the biomedical ethical principles of autonomy and justice with beneficence and non-maleficence. It is argued that SDM is "polyvalent", a sociological concept which describes an idea commanding superficial but not deep agreement between disparate stakeholders. Implementing SDM in routine mental health services is as much a cultural as a technical problem. Three challenges are identified: creating widespread access to high-quality decision support tools; integrating SDM with other recovery-supporting interventions; and responding to cultural changes as patients develop the normal expectations of citizenship. Two approaches which may inform responses in the mental health system to these cultural changes – social marketing and the hospitality industry – are identified.

Key words: Shared decision making, mental health care, ethics, implementation, routine outcome monitoring, social marketing

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Decision making is a complex and dynamic social interaction[1]. The balance of involvement between clinician and patient can be conceptualized as lying on a continuum from clinician-led/passive/paternalistic, through shared, to patient-led/informed/active[2]. Clinician-led decision making occurs when the clinician makes the decision for the patient, possibly after consulting with him/her. Patient-led decision making occurs when the patient makes the decision, possibly having received information from the clinician. The intermediate position of shared decision making (SDM) involves collaboration.

A widely used definition of SDM is that it is "a process in which clinicians and patients work together to select tests, treatments, management or support packages, based on clinical evidence and the patient's informed preferences; it involves the provision of evidence-based information about options, outcomes and uncertainties, together with decision support counselling and a system for recording and implementing patients' informed preferences"[3]. This definition focuses, as does the present paper, on interactions between clinicians and patients, but SDM also has relevance to decision making between clinicians and family members, and perhaps also to clinical discussion between different professional groups.

What is a decision? In physical health care, decisions might include whether to complete a diagnostic test, undergo a medical procedure, receive a particular pharmacological or psychological treatment, or attempt a lifestyle change. In mental health, decisions relating to inpatient care are broadly similar. When asked to name recent clinical decisions, inpatients with a diagnosis of schizophrenia (N=60) and their psychiatrists (N=30) consistently mentioned categories such as "medication", "leave from ward/hospital", "non-pharmacological therapies" and "changes in treatment setting"[4]. By contrast, decision making in community mental health settings is more wide-ranging; a principal component analysis of topics discussed in routine consultations between community patients (N=418) and their clinicians found a three-factor solution comprising treatment, social (family, friends, leisure) and financial (work, benefits)[5].

The essential elements of SDM have been identified. A systematic review synthesized 161 conceptual models of SDM to identify eight characteristics of clinician behaviour: define/explain the health care problem, present options, discuss benefits/risks/costs, clarify patient values/preferences, discuss patient ability/self-efficacy, present what is known and make recommendations, clarify the patient's understanding, and make or explicitly defer a decision[6]. This framework underpinned a systematic review of implementation of SDM across different health care settings, identifying five randomized controlled trials of interventions to improve clinicians' adoption of SDM[7]. Training of clinicians and use of decision aids (structured approaches to facilitate SDM) were tentatively recommended, though none of the studies related to mental health populations.

Patients want SDM[8]. A systematic review of 199 analyses from 115 studies of decision-making style preference concluded that patients prefer shared to clinician-led decision making, with the preference proportion higher in studies carried out in patients with cancer or undergoing invasive procedures, compared to those conducted in non-disease specific study populations or patients with other chronic conditions[9].

Overall, there is international consensus across medicine about the importance of SDM[10], and it is widely supported[11]. It is argued that SDM leads to better outcomes, including help-seeking behaviour[12], increased compliance with decisions[13], reduction in errors[14], reduced stigma and increased involvement[15]. In 2010, a gathering of 58 experts from 18 countries produced the Salzburg Statement on Shared Decision Making[16]. This included a call for clinicians to recognize SDM as an ethical imperative, stimulate two-way flow of accurate and tailored information, and give patients and their families resources and help to reach decisions. The statement

also exhorted action by researchers, editors, journalists, patients (to speak up, to expect to be an equal partner, to seek and use high-quality information) and policy makers.

SHARED DECISION MAKING IS RECOMMENDED IN MENTAL HEALTH

SDM is promoted in mental health systems[17]. It is advocated as an important approach in the mental health policy of many countries internationally[10]. For example, in England it is recommended that "a shared decision making approach should be facilitated" across all adult mental health services[18].

Why is SDM in mental health so widely recommended? The standard argument made to support SDM is that clinicians have expertise in diagnosis, etiology, prognosis, treatment options and outcome probabilities, whereas patients have expertise in illness experience, social circumstances, attitudes to risk, values and preferences[3]. Bringing these two types of expertise together can, when informed by research evidence, produce better decisions. However, this standard argument conflates two overlapping but separate justifications: the clinical and the ethical.

The clinical justification

The clinical justification put forward for SDM is that patients who are active participants in managing their care have better outcomes. Increased involvement will lead to better engagement, higher-quality decision making, and increased treatment adherence – all of which will improve outcome. There is some evidence supporting this justification. For example, a trial in the Netherlands involving 220 psychiatric inpatients showed that SDM led to reduced substance use and improved quality of life[19]. A follow-up study found that SDM was also associated with increases in patient autonomy[20].

However, critical appraisal of all available evidence is less positive. A Cochrane review of SDM in mental health[21] identified only two randomized controlled trials. Both studies took place in Germany, one involving 107 patients with a schizophrenia diagnosis[22] and the other 405 patients with depression[23]. The Cochrane review concluded that there was no evidence for harm, but the weak evidence base meant that no firm conclusions could be drawn. Since that review, one randomized controlled trial involving 80 community patients[24], also showing advantages for decision aids, has been published.

Other reviews have reached similar conclusions. A systematic review[25] identified eleven randomized controlled trials, including two in mental health, one focussing on schizophrenia[26] and the other on depression[27]. Five trials, including the two mental health trials, showed positive outcomes associated with SDM, but the reviewers concluded that the overall evidence is encouraging but inconclusive.

It should be noted that this conclusion is not unique to mental health. The most recent systematic review of trials (N=22) testing the impact of SDM on outcome in physical health concluded: "The trials performed to date to address the effect of SDM on patient-relevant, disease-related endpoints are insufficient in both quantity and quality. Although just under half of the trials reviewed here indicated a positive effect, no final conclusion can be drawn"[28]. But available evidence does suggest that SDM in mental health is particularly challenging. For example, SDM leads to a greater increase in treatment adherence in general medicine than in mental health[29].

Overall, the totality of evidence is inconclusive about the impact of SDM on patient outcomes in mental health.

The ethical justification

The ethical justification put forward for SDM is that it is a human right. Sometimes expressed as "No decision about me without me"[3], the right to self-determination implies full involvement in decisions affecting the person. This seems to be a view increasingly taken by patients: the above-mentioned 2012 systematic review of 115 studies investigating decision-making preferences[9] identified a patient preference for SDM in 63% of studies, but a time trend was evident, with 50% of studies before 2000 and 71% after 2000 showing this preference.

Reviews of SDM in persons with schizophrenia[30] and depression[31] showed that patients and clinicians found SDM acceptable and did in fact engage in SDM, which resulted in improvements in patients' knowledge about their illness and a higher level of perceived involvement in decision making.

The ethical justification is often positioned as a solution to the suggested problem of an assumption that the clinician is the only competent decision maker, who will make decisions *for* rather than *with* the patient. Ethical justifications emphasize that "clinicians and patients bring different but equally important forms of expertise to the decision-making process"[3]. Arguments made from this perspective often focus on values and power relationships, for example by linking SDM with values-based practice[32]. SDM is understood primarily as a process involving the expert-by-training (the clinician) and the expert-by-experience (the patient) both contributing their expertise, committing to decision-making responsibility, and being respectful of the other's perspective. This transactional focus contrasts with the clinical justification emphasis on producing better outcomes.

Shared decision making is a polyvalent concept

SDM is thus supported both by those who prioritize clinical expertise and expertise-by-experience. In this sense, the term is what sociologists call a polyvalent concept[33] – one which commands superficial agreement and apparent consensus between disparate stakeholders, but which conceals incompatible assumptions and expectations. Put concretely, does the clinician still support SDM if it leads to empowered patients who are less adherent to treatment recommendations? Does the patient still support SDM if apparently involving conversations that seem somehow always to end up with the clinician's view prevailing[34]?

There are particular challenges in mental health care[35]. Is SDM still the best approach to decision making with non-capacitous adults, such as those with advanced dementia or acute psychosis[36]? Is it appropriate in a forensic context, where the decisions that the person makes may fall slightly or greatly outside social norms?

These tensions between different justifications for shared decision making also occur in other initiatives in mental health. The same features of apparent universal agreement occur in relation to the service agenda and rights agenda which both provide support for anti-stigma initiatives[37]. Other polyvalent constructs include self-management, advance directives and social inclusion.

For example, recovery has emerged as a guiding vision for mental health systems[38]. Like the ethical justification for SDM, a recovery orientation involves a refocussing on subjectively-defined process rather than clinician-defined outcome. The relevance of recovery to dementia[39], forensic[40] and mental health inpatient services[41], however, has been questioned. A focus on recovery creates challenges for clinicians and patients. Clinicians have the uncomfortable experience of competing priorities[42] leading to role tensions[43], yet advocates raise concerns that recovery is being "commandeered"[44] to individualize social problems, to de-politicize individual experience and to remain focussed on deficit amelioration[45]. The recommendation that sociological research is needed to understand the socio-cultural meaning and implications of recovery[46] is probably equally applicable to SDM.

HOW IS SHARED DECISION MAKING IMPLEMENTED IN MENTAL HEALTH?

SDM is not yet widely implemented across mental health systems. For example, in the National Health Service (NHS) Community Mental Health Survey 2015 in England[47], only 42% – a reduction with respect to 2014[48] – fully agreed with the statement "Have you agreed with someone from NHS mental health services what care you will receive?" (N=12,695). Only 50% fully agreed with the statement "Were you involved as much as you wanted to be in decisions about which medicines you receive?" (N=9,775), and among patients who received non-pharmacological treatments, only 55% fully agreed with "Were you involved as much as you wanted to be in deciding what treatments or therapies to use?".

Is there a difference between SDM in mental versus physical health? A study in the Canary Islands compared experience of decision making between patients attending psychiatric outpatient clinics and primary care (N=1,477)[49]. It found no difference in overall score, but differences at the item level. Participants using psychiatric outpatient services said that they were helped to understand the information, but were more likely to say that they were not asked about which treatment option they preferred, that there was no negotiation, and that the selection of treatment was not a consensus decision. There may be challenges specific to SDM in mental health.

A qualitative investigation of the views of experienced psychiatrists (N=26) identified barriers to its use in relation to prescribing[50]. The most frequently identified barrier was beliefs about the insight of the patient, which in some cases was seen as an absolute barrier. Other challenges were societal expectations about mental disorder (so statutory powers are held by the psychiatrist), beliefs about the primacy and the tranquillizing effects of antipsychotic medication, and financial pressures limiting options.

These barriers may lead to SDM conversations in mental health being more factual than values-based. An exploration using factor analysis of decision making in psychiatric visits in the US (N=191) found that discussions about the science (pros and cons, clinical issues and uncertainties, consumers' goals and understanding) were more common than about preferences (the consumer's role in decision making, consideration of alternatives, exploration of preferences)[51].

Other implementation challenges have been identified in physical health[10] and mental health[52] settings, such as hierarchical doctor-patient relationships[53], differing understandings of, and low commitment to, SDM[54], lack of a "rights discourse" in the culture[55], and challenges of avoiding inequities when access to support tools is through insurance-funded health systems[56].

RESEARCH IN ROUTINE CLINICAL SETTINGS

Given these implementation challenges, research in routine mental health services is needed. The European Union-funded "Clinical decision making and outcome in routine care for people with severe mental illness" (CEDAR) study took place in six European countries (Denmark, Germany, Hungary, Italy, Switzerland and UK) from 2009 until 2014[57]. The study had two aims.

The first aim was to establish a methodology to assess clinical decision making in people with severe mental illness. This aim was met by the development and cross-cultural validation of three new measures. All of them comprised parallel clinician and patient versions, and were developed in English followed by rigorous translation and cultural adaptation using good practice guidelines[58] into Danish, German, Hungarian and Italian. The Clinical Decision Making in Routine Care (CDRC) measure assesses the content and implementation of decisions[59]. The Clinical Decision Making Style (CDMS) measure assesses preference for different styles of decision making[60]. The Clinical Decision-making Involvement and Satisfaction (CDIS) measure assesses involvement and satisfaction in a specific decision. All measures are available at www.cedar-net.eu/instruments.html.

The second aim was to investigate decision making in routine adult community-based mental health services, using a six-country prospective observational design. A total of 588 patients met inclusion criteria, primarily aged 18-60, with a diagnosis of a mental disorder (established using research criteria[61]) severe[62] and enduring for two years. After giving consent, patients identified a clinician, and these clinician-patient dyads were then asked to complete bimonthly assessments for one year.

The main study investigated the relationship between decision making style

and outcome[63]. A preference for shared, rather than patient-led or clinician-led, decision making was reported by both patients (χ^2=135.08, p<0.001) and clinicians (χ^2=368.17, p<0.001). SDM was also the dominant experience, with a 10% increase in the proportion of both groups reporting SDM over the one-year study period. Hierarchical linear modelling found that the decision-making style of clinicians significantly affected patient-rated unmet needs over time, with unmet needs decreasing more in patients whose clinicians preferred patient-led to clinician-led (−0.406 unmet needs per two months, p=0.007) or shared (−0.303 unmet needs per two months, p=0.015) decision making. In other words, outcomes were best when clinicians supported patient-led decision making.

A second study investigated the relationship between decision-making involvement and satisfaction[64]. Patients (N=445) were partitioned based on involvement preferences (assessed using CDMS) and experiences (assessed using CDIS). The preference hypothesis was that satisfaction with a specific decision will be higher if it is made using the patient's preferred decision-making style (patient-led, shared or clinician-led). This was not confirmed. Overall, 90 patients (20%) had less involvement than preferred ("disempowered"), 190 (43%) were "matched" and 162 (37%) were "empowered". Empowered patients, who experienced more involvement in decision making than they desired, rated highest satisfaction (OR=2.47, p=0.005, 95% CI: 1.32-4.63). The agreement hypothesis was that satisfaction will be higher when decisions are made with a clinician with the same preferred decision-making style. This was also not confirmed, since ordinal logistic regression modelling showed that decisions made with clinicians whose decision-making style preference was for more active involvement than the patient preference were rated with highest satisfaction (OR=3.17, p=0.003, 95% CI: 1.48-6.82). So, higher satisfaction was experienced following more active involvement in decision making than the patient stated as desired, and with a clinical orientation towards empowering, rather than shared, decision making. This is consistent with findings from other health sectors. For example, a primary care study (N=1,913) in Germany found that high experienced involvement predicted higher patient satisfaction[65].

The CEDAR study has two implications for routine practice. First, if the intention is to reduce patient-rated unmet needs and to maximize satisfaction, then the empirical findings indicate that long-term efforts should be oriented towards developing patient-led rather than shared decision making. This is challenging to the current culture of health services. Patient-led decision making is not always valued by the system; a patient preference for involvement has been found to be negatively associated with experienced involvement[65]. Socio-political debate would be needed about the purpose of the mental health system – to what extent is the "core business" of the system keeping people (patients and others) safe, which may necessarily involve some clinician-led decision making, versus supporting them to live as well as possible? Can and should we socialize clinicians into a professional role which gives primacy to patient-led decision making? Clinical practice would need to be oriented towards supporting this type of patient empowerment, with a recovery-oriented culture in mental health systems which promotes the normal entitlements of citizenship[66]. We know that the desire to participate in decision making is higher in some groups of patients, e.g., inpatients with experiences of involuntary treatment, with negative attitudes toward medication, with a higher level of education, with lower treatment satisfaction, with better perceived decision-making skills, in patients of female gender and in younger patients[30]. Should efforts to support patient-led decision making be targeted at these patient subgroups, or at all patients?

Also, patients may bring expectations about being looked after whilst unwell. When is this expectation helpful, and when is it ultimately harmful? Recovery is far more common than often understood in mental health systems[67,68], and access to peer workers can powerfully transform these role expectations[69]. How do we minimize harm, balancing the reality that being allowed to disengage from services leads to the best outcome for some people[70] and to avoidable tragedies for others?

The second implication is that an orientation towards SDM is an empirically defensible goal in mental health systems which have traditionally used clinician-led decision making. An SDM orientation will improve both patient experiences and outcomes, indicating an alignment between the clinical and ethical justifications for SDM as a more beneficial style than clinician-led decision making. If it is accepted that SDM is a necessary component of a modern mental health system, then three challenges can be identified: the technical problems of access to appropriate tools and integration with other innovations, and addressing the implications of changing culture.

DECISION SUPPORT TOOLS

Changing practice often involves the use of formal decision support tools, and resources exist to support SDM. For example, online decisions support systems are available which are both generic (e.g., optiongrid.org) and condition-specific (e.g., sdm.rightcare.nhs.uk/pda for depression).

These tools may target behaviour change in either clinicians or patients. Clinician-focussed approaches typically involve training and support for practice change. These approaches have been evaluated in depression, and (when augmented with patient information leaflets giving information and encouragement towards involvement) they lead to improved patient participation and satisfaction without adding to consultation time[23].

A good example of a patient-focussed approach is the Common Ground system, which is an online peer-delivered system to support patient involvement and empowerment in psychopharmacology consultations[71].

Widespread access to generic and condition-specific decision support tools is needed. Tools need to be of a high quality: a systematic review of decision aids

across medicine found a tendency to under-specify the procedure, to emphasize benefits more than harms, and to focus more on false positives than on false negatives in screening tools[72]. Development of reporting guidelines for decision aid studies would be one approach to improving quality[73].

Decision support tools also need to be small in number: the same systematic review identified 68 tools relating to treatment and 30 relating to screening. This variation makes benchmarking and comparison between services and systems more difficult[28]. Finally, there needs to be a focus on tailoring and testing tools in different clinical groups and geographical locations. The extent to which patients expect to be actively involved in treatment decisions varies according to the prevailing culture[74]. In paternalistic cultures, both clinicians and patients are likely to assume that decisions are the responsibility of the clinician only, whereas in more egalitarian cultures a partnership or SDM approach may be jointly preferred[75]. Translation processes therefore need to address these cultural factors in ensuring both linguistic and conceptual equivalence[58].

INTEGRATION WITH OTHER RECOVERY-SUPPORTING INNOVATIONS

Implementation of SDM will involve the integration of the relevant technologies with wider innovations, and the application of improvement science to support evaluation and sustainable implementation. A number of measures of SDM now exist: a structured review identified 19 measures, and a move towards measuring processes from both patient and clinician perspectives[76]. These provide standardized approaches to evaluate complex interventions which integrate SDM with other established innovations.

Advanced directives and joint crisis plans are examples of established innovations[77]. Advance directives involve the patients pre-specifying their preferences for what should occur if they lose capacity due to mental illness. An emergent problem with this patient-led approach was that the clinician might not be involved in, or even aware of, the directive in advance, leading to low implementation[78]. A variant involving SDM has emerged, called joint crisis plans. These are developed through facilitated meetings between the patient and involved clinicians[79]. A randomized controlled trial involving 569 patients in 64 community mental health teams in England found that implementation by clinicians was the main challenge, with no significant treatment effect for the primary outcome of compulsory admissions, or any secondary outcome with the exception of improved therapeutic relationships[80]. Qualitative investigation identified four barriers to clinician engagement: ambivalence about care planning; perceptions that they were "already doing SDM"; concerns regarding the clinical "appropriateness of service users' choices"; and limited "availability of service users' choices"[81].

Another example of integration is with the emergent field of routine outcome monitoring[82], which involves the longitudinal collection of patient-level outcome information to inform individualized care. There is strong evidence of short-term benefit and moderate evidence of longer-term benefit from routine outcome monitoring[83]. A study is now underway which integrates SDM and that monitoring[84]. Routinely collected outcome data are fed into the SDM process, with the intervention supported by a quality improvement collaborative programme involving a national and local implementation strategy.

ETHICAL AND CULTURAL CHALLENGES OF IMPLEMENTATION

Although most clinicians believe that they are using the SDM approach, there is evidence to the contrary[85]. Perceptions about level of involvement differ, with patients identifying more clinician-led and clinicians identifying more shared approaches[86]. Patients report inhibiting factors including the patient-clinician relationship, fear of being judged, perceived inadequacy, and a history of substance abuse[87]. The use of clinician-led decision making is most pronounced in treatment-related decisions[5].

One reason for low implementation is represented by ethical tensions. A widely-used biomedical ethical framework identifies four principles: respect for autonomy, justice, beneficence and non-maleficence[88]. Skilled clinicians attempt to integrate these principles, for example supporting patient participation not just for reasons of autonomy but also justified by beneficence (as well as other influences, such as avoiding legal liability)[89]. However, engagement remains challenging[90]. The potential conflict between these principles has been characterized in relation to antipsychotic prescribing for a patient who lacks insight; the psychiatrist may think: "If I leave it up to the patient, he would certainly choose not to initiate treatment. Symptoms would persist or even worsen, and thus I would harm the patient. If I apply pressure and he accepts antipsychotics, he may respond to treatment and likely gain insight. Then he will later be thankful that I proceeded in the way I did"[91]. This reflects the tension between deontological (duty-based) ethical frameworks emphasized in the training of many professional groups and teleological (rights-based) frameworks emphasized by citizens.

A second reason for low implementation is cultural. An asylum-based system creates a micro-culture (a "total institution"[92]) which can be out of step with wider cultural values. Institutional structures can powerfully socialize a patient into a moral duty to be treatment-adherent (a "good" patient) and respectful of the clinician's sapiential expertise and professional authority. When the dominant discourse is clinician-led, a primary flow of information from clinician to patient means that the patient's values and treatment preferences are given less importance[93]. Overall, it is difficult to avoid clinician-led decision making being the default choice in institution-based

mental health services, because SDM involves a shift in power arrangements[94].

TRANSFORMATION IN THE MENTAL HEALTH SYSTEMS

The world is changing. Mental health systems internationally are transitioning towards community-based services[95-101], which involve interactions with patients who are more influenced by citizenship expectations relating to consumerism, self-determination and empowerment[102]. Patients increasingly expect as a right to be active participants in decisions about their lives, with a greater emphasis on the biomedical ethical principles of autonomy and justice.

The implications of this shift for mental health systems are profound, and extend well beyond discussion of approaches to decision making. Organizational transformation may be needed if the mental health systems are to survive this transition to engaging with patients holding citizenship expectations. A readiness to draw in insights and use language and constructs from other sectors will be needed to inform this transformation. This can be illustrated by two examples, both of which are potentially relevant but currently almost unused in planning and developing mental health systems.

The first example is given by the academic discipline of social marketing[103], which could be used as an approach to fostering culture change in mental health systems. Social marketing involves the application of marketing principles and practices to advance social good, in this case participation in decision making. It takes a citizen-centred approach in which insights developed with citizens and stakeholders inform the process[104]. An orientation towards mutuality, exchange and reciprocity differentiates social marketing from other social intervention approaches, particularly in traditional expert-driven, top-down public health approaches. So, social marketing provides an approach to developing citizen-centred mental health systems oriented around the preferences of participants (patients), and in which partnership working (shown for example by SDM) is the foundation rather than a feature to be added on.

Participatory approaches to service development already exist in mental health services. Peer support theories such as intentional mutuality emphasize relationships in which both people have value and reciprocity is possible[105]. Recovery Colleges are based on principles of collaboration, co-production, inclusiveness and a community focus[106]. Similarly, "a majority of participants in user-run programmes value role equity, the mutuality and reciprocity of relationships and the non-hierarchical organization"[107].

Market segmentation is a well-established business technique used to identify and manage diverse customer needs and to target marketing resources[108]. Positioning similar groups of people into market segments, and then focusing marketing efforts at these different segments as appropriate can manage heterogeneity in preferences. By developing marketing strategies and behaviour change strategies for distinct groups of patients who have specific needs or values, it becomes possible to influence culture and create demand for SDM in clinicians working with, and patients coming from, different clinical populations.

The second example is given by the expertise held by the hospitality industry in working with disparate customers: "Key values, such as the importance of welcome, the customer always being right and the job being to provide help to meet the customer's needs, underpin the best interactions in this service industry. Hospitality workers are skilled in recognizing how customers like to be engaged with – from face-to-face to elbow-to-elbow. Workers are not doing their job if customer care is poor"[109]. If patients achieve similar levels of emancipation and agency as other citizens, then patient choices and preferences become central. If clinicians don't work in partnership with patients to ensure they have a positive experience, then patients will – and should – choose to go elsewhere for support.

CONCLUSION

In this paper, the case has been made that SDM is part of a broader movement of change in the mental health system[110]. There are implementation challenges, but these are ethical and cultural as well as technical.

It is worth addressing these complex issues relating to power, control, expertise and valued knowledge, because SDM has the potential to contribute to supporting people to live as well as possible in communities of their own choosing.

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Shared decision making: a consideration of historical and political contexts

M. Slade[1] provides a thought-provoking and helpful review of ways in which shared decision making (SDM) may be understood, its justifications generally and the application of SDM principles in mental health. He suggests adoption of cross-sectoral practices, such as from marketing and hospitality, in promoting SDM. This commentary takes a more medically oriented perspective and further explores some political implications raised by the challenges of SDM.

SDM in mental health care may be formally a relatively recent arrival, but SDM does not exist in historical isolation either within medicine or mental health care. Through the history of medicine, shifts in the power balance have occurred in decision making between physician and patient[2], and recent decades may have seen some shifting of this locus of control towards the patient.

Related concepts within modern medicine and medical sociology can be seen as dating back at least half a century. Szasz and Hollander[3] and Balint[4], in the mid-20th century, advocated for a shift in management of chronic diseases from activity-passivity and guidance-cooperation models towards a model of "mutual participation" in doctor-patient relationships. This approach shares features with what may now be termed SDM.

The chronic disease model elaborated by Wagner and others in the US[5] emphasizes an activated and informed patient as a critical component. Sharing of decisions may also be seen as critical to evidence-based medicine best practice, which involves "integrating individual clinical expertise with the best available external clinical evidence... reflected in many ways, but especially in more effective and efficient diagnosis and in the more thoughtful identification and compassionate use of individual patients' predicaments, rights, and preferences in making clinical decisions about their care"[6].

An influential model in medical training and practice, including in psychiatry, is the CanMEDS framework. Here medical training at all levels is seen as leading towards development of connected competencies: that of "medical expert" is described as an integrating role for the work of a doctor as communicator, collaborator, leader, health advocate and scholar[7], which can be seen as equipping practitioners potentially to work in alignment with the chronic disease model, evidence-based medicine or SDM.

Work cited by Slade demonstrates that people appreciate being invited to take more autonomy than they may directly ask for. Often the health care consultation starts from a point in which the patient is situationally disadvantaged by power dynamics, cultural expectations, and the potentially disabling nature of interacting with an "expert"[8]. So, patients or clients appreciate efforts to promote their empowerment even if they don't ask for it. In mental health care, there are also other important convergences: firstly with the challenge of practice in the context of the application or availability of compulsory treatment; then with the politics of the recovery movement and with working towards recovery oriented practice.

While there are multiple convergences across the medical and mental health care literature with the key propositions of SDM, implementation often still faces great challenges. Promoting SDM can challenge clinicians in terms of the depth and breadth of their professional skills and invite commitment through other roles as citizens that may intertwine with those of professional practice.

Slade helpfully makes the point that transitions towards SDM require changes in prevailing service culture. Here we enter a realm that in a broad sense is political, in that it involves processes whereby power is assigned. For instance, by virtue of income, specific legal powers and societal status, not uncommonly psychiatrists can assert influence in many service systems that is not necessarily commensurate with the potency of the interventions they control[9]. For many psychiatric conditions, medications or other physical treatments that are the special purview of doctors are not particularly more powerful than psychological or social interventions, yet delivery systems and power dynamics can serve to support prioritization of those interventions over others.

A set of issues related to allocative and distributional justice bring into the frame more formal kinds of politics. The breadth of existing services influences the options available to service providers and so conditions what may be considered within the SDM reasoning space. For instance, in Australia at least, there are dramatic differences in what is available in terms of psychological treatments in different parts of the country[10], so what is a primary care physician for instance to do where psychological treatments that could substantially improve the lot of someone with a mental health problem are not actually available? Is it within the scope of SDM to advise patients with a current major depressive disorder that, if they lived in a more affluent area or personally were better financially resourced than they are, then they should augment their antidepressants with some well conducted cognitive behaviour therapy but, because of their location and personal circumstance, this isn't an available option? Often this discussion will not occur and the reasoning space of SDM will be constrained by what is practically available, even where that does not conform to evidence-based practice or to principles of justice. Here we encounter a connection between SDM and what in the CanMEDS model[7] is described broadly as the health advocacy role and in practice may involve formal political engagement.

Implementation of SDM, as Slade suggests, may benefit from ideas from marketing and hospitality. These can be seen as just two examples among possible strategies that stretch across all the CanMEDS competencies and can present clinicians with political challenges. Even if we succeed in addressing many of the personal

politics that allow our practice to move towards more effective use of the range of enablers to SDM that Slade has identified, other critical factors may block progress. Key impediments to SDM may arise because informal politics in institutions constrain exploration of what is possible and because government formal politics constrains the range of possible decisions in ways that may be palpably unjust.

Full engagement with SDM may challenge practitioners with the prospect of participation in processes that may radically shift existing power balances in services systems, and with the challenge of perhaps engaging in formal political activism where there are critical constraints to implementation of SDM that relate to political policies on social justice.

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Involvement in decision making: the devil is in the detail

M. Slade[1] highlights that there is superficial, not deep agreement between stakeholders about the idea of shared decision making (SDM) in mental health care. To begin to unpack why this may be so, it is important to reflect on decision making about what, when and with whom.

Firstly, what kinds of decisions are made in mental health care? They range from life-changing decisions, sometimes when the person is deemed to no longer have capacity or to have reduced capacity to make decisions (e.g., involuntary admission to hospital, medical treatment in dementia, starting psychotropic medication) to more routine decisions relating to, for example, changing medication, addressing physical health, consent to share information, and referral to other services (e.g., drug and alcohol, day opportunities).

Some decisions require explicitly overriding the patient's preferences in his/her best interest. The danger is that this practice "leaks" into other decisions, due to a cognitive bias that people with mental health problems are perceived to be less worthy or capable of being involved in decisions when capacity is intact. Hence, it is important to question and safeguard our practice against these assumptions. Specific interventions may be required when decisional capacity is reduced, e.g., preparing patients in an acute ward for planning talks with their psychiatrist to increase their ability to participate in decision making[2].

Secondly, different types of decisions are taken at specific junctures in an illness trajectory, e.g. starting a psychotropic medication is a much bigger decision than changing the dose of an existing medication. Mental health problems tend to be episodic, so that the ability to process information and motivation to participate varies over time. For example, the presence of negative symptoms has been found to be associated with less involvement in decision making[3].

Thirdly, who is involved in decision making in mental health care? In addition to the patient and clinician, carers are frequently involved. Decision making in three-way communication, i.e., patient-doctor-carer, is undoubtedly more nuanced and delicate than two-way communication. With three people, there is the potential for two people to become aligned in support of a particular course of action. This could be the patient and carer (e.g., in a bid to reduce or stop medication), or the doctor and carer (e.g., in a bid to increase medication or admit the patient), or the doctor and patient (e.g., in a bid to keep the patient out of hospital). Sometimes, patients feel that carers are acting as advocates. At other times, they feel that carers are working against them with clinicians to make decisions that they do not agree with. At all times, clinicians need to gauge the expectations, needs and preferences of both parties in a fine balancing act.

Understanding the extent to which SDM is implemented is intricately linked to how it is measured. As Slade points out, "decision making is a complex and dynamic social interaction"[1]. Most research to date, with some notable exceptions[4-7], is based on what people *say* about SDM. Perhaps the most informative means of researching decision making is to record and analyse what people do rather than what they say they do. This approach facilitates an understanding of the dilemmas faced by both clinicians and patients *in situ* and the resources they deploy to deal with them. It offers a window on how clinicians and patients *jointly* construct the clinical encounter[8].

In an observational study of decision making in outpatient clinics in the UK, involving people with a diagnosis of schizophrenia or depression, there was striking variation in the extent to which different psychiatrists involved patients in decision making across their consultations. Out of a total possible score of 48 using the Observing Patient Involvement (OPTION) scale, scores ranged from 0 to 38. The differences in how psychiatrists communicated were overwhelmingly explained more by their individual style than by

socio-demographic, structural or clinical factors[3].

This shows that there is a widely varying practice but also some good practice, which can be identified and disseminated. It would be interesting to explore what attitudes are associated with communication practices that involve patients more in decision making.

Decision aids are helpful in drawing attention to and focusing discussion on various aspects that need to be considered in making a decision. However, they should not detract from the clinician-patient interaction, as *how* decision aids are actually used in interactions is important in determining whether they are effective. For example, subtle differences in how clinicians ask questions have consequences for what patients say[9]. This is critical for decision making. For example, asking a patient if he/she has questions with the commonly deployed "Any questions?" is designed not to elicit any further information, whereas asking "Do you have some questions?" is more likely to elicit further discussion. Asking about medication with questions such as "No problems with the medication?" invites the patient to confirm that there are no problems, making it very difficult for the patient to discuss concerns he/she may have and influence subsequent treatment proposals. Clinicians need to be aware of how question design shapes patient responses, in order to involve patients in a meaningful rather than a superficial way.

Training clinicians so that they are aware of the subtle differences in how they communicate with patients generally, and in decision making specifically, was found to improve clinician-patient communication and the therapeutic relationship[10]. Eliciting the patient's experiences and listening are fundamental: they are the starting point for identifying what decisions are to be made and whether these reflect the patient's concerns. Working with patients to reach a shared understanding of concerns is the first step in identifying *what* needs to be addressed. This step is likely to circumvent some of the difficulties that currently undermine SDM in mental health care.

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Psychiatric practice: caring for patients, collaborating with partners, or marketing to consumers?

Slade's paper[1] usefully articulates the clinical and ethical arguments in support of shared decision making (SDM); emphasizes that, despite widespread superficial agreement that SDM is important, there is significant potential for contradiction between these arguments; and puts forward a number of approaches which may inform responses to the shift in the mental health system brought about by more empowered patients.

Here I briefly comment on each of these components of Slade's review. While I admire his elegant synthesis of the literature and concur with the thrust of many of his arguments, I do also wish to express some cautions.

First, Slade notes that – while there is a clinical argument that patients who are active decision makers will be more engaged, with consequent improved decision making, increased adherence, and superior outcomes – there are in fact limited data to support this view. One potentially important consideration is that, in psychiatry, the link between scientific knowledge and patient outcomes is not always as tight as we would ideally like; so that clinical decision making, whether shared or not, is unable to predict fully which individual will respond to which intervention.

Furthermore, the data included in the Cochrane review of the clinical value of SDM for people with psychiatric disorders[2] are from work done in Germany. It is theoretically possible that in other settings, where patients may have different expectations of the clinical encounter, the data may be even less supportive of the clinical argument for SDM.

Second, Slade notes that, despite the ethical argument that SDM is a human right, clinical practice occurs in a range of different contexts, and it is less clear that SDM is the best approach to decision making in non-capacitous patients. Indeed, a potentially important issue is that, in medical and psychiatric practice, disorders range from more typical conditions (where, say, the disorder can be conceptualized as caused by an external agent that both clinician and patient are committed to eradicating) to more atypical ones (where, for example, it is harder to differentiate the self from the illness, which may itself impact negatively on decision making)[3].

It is also noteworthy that the desire to participate in SDM appears higher in some patient groups. Good ethical arguments can be put forward to support different sorts of decision-making models for different sorts of patients and different sorts of disorders.

Third, Slade emphasizes that, although SDM is widely endorsed in official policies and by active clinicians, in theory it entails potential contradictions (for example, there is a potential for empowered patients to

choose to be less adherent to treatment recommendations), and that in practice SDM is in fact often not implemented.

Slade argues that data from the "Clinical decision making and outcome in routine care for people with severe mental illness" (CEDAR) study[4] show that both patient outcomes and experiences are improved by SDM, so that there is an alignment between clinical and ethical justifications. However, although the CEDAR study is multi-national, it is based on a relatively restricted population (outpatients in Europe), and the statistical analysis cited by Slade does not focus on clinical symptoms (but rather on patient-rated unmet needs).

Finally, Slade suggests that social marketing and the hospital industry provide potentially useful approaches for addressing the shift in the mental health system that will be brought about by more empowered patients. Metaphors play a crucial role in framing our views of physical and mental disorders, and of the clinician-patient relationship[5]. A collaborative model of the clinician-patient relationship has been particularly useful in cognitive behavioural therapy, for example. And viewing the patient as a consumer does have some advantages, perhaps particularly in the context of empowerment or activism[6].

However, we should be careful not to entirely jettison metaphors of the doctor-patient relationship that emphasize caring (rather than only collaborating or consuming). Caring is a core aspect of the work of mental health professionals, and one that is deserving of particular emphasis and pride.

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Common sense alone is not enough

Slade's paper[1] suggests implementing shared decision making (SDM) in mental health care. This sounds desirable. SDM is characterized by collaboration, and who would disagree with a call for more collaboration between psychiatrists and patients? A more detailed look, however, raises at least two major concerns.

Firstly, what exactly is SDM? According to Slade, SDM is an intermediate position between two extremes, one in which the clinician decides, having consulted the patient, and one in which the patient decides, having received information from the clinician. SDM is in between those two and involves collaboration. Consulting a patient and providing information, however, also require collaboration, possibly with extensive questions, explanations and clarifications. So, the unique characteristic of what would need to be implemented as SDM becomes unclear.

Unless the decision is about coercive treatment, clinicians are not entitled to make decisions that patients do not agree to. Obtaining informed consent to any treatment is a professional duty. Patients must explicitly agree to whatever is being decided in a consultation. Beyond this formal requirement, patients' agreement is needed anyway for making a treatment happen. Decisions about taking medication or attending a group therapy need to be implemented by the patient, and, if the patient is not happy with the decision, the treatment is unlikely to materialize. Reaching an explicit agreement with patients about any decision is, therefore, a matter of both professional obligation and clinical necessity. No new concept of SDM is needed to reflect this.

So, is there anything more specific? The referenced review of conceptual models of SDM identifies several types of clinician behaviour that characterize SDM. They include: explaining the problem and options; discussing benefits and risks, patient preferences and abilities; presenting evidence; making recommendations; clarifying patient's understanding; and making decisions explicit. All this has been part of good clinical practice for decades and may be regarded as common sense. It remains unclear how a basic understanding of good communication benefits from being relabelled as SDM[2].

Secondly, there is a claim that "patients want SDM". Patients are not one homogenous block of people who would all want the same thing and all of the time. Patients have different preferences for the communication style of their clinicians. Preferences differ associated with their personality, background and experiences, and may vary even for the same patient depending on the given health problem, the context, the specific content of the consultation, and the mood on the day.

Slade cites a patient survey in the UK National Health Service, seemingly suggesting that patients in mental health care in the UK are not involved in treatment decisions although they would like to be[3]. A closer look at the data shows, however, that the question "Were you involved as much as you wanted to be in agreeing what care you will receive?" was answered with "no" by only 7% of patients. Although it should be a challenge to reduce this figure even further, it is hardly a reason to call for a radical change in the current approach.

Furthermore, it should be noted that this survey was conducted in patients with severe mental illness in community mental health care in the UK, who cannot easily go to a different clinician in case they are unhappy with their current one. In other systems and other patient groups, e.g. when patients pay for their services directly or through insurance, SDM is presumably even less of a prob-

lem, as patients can simply go to a different psychiatrist, if they do not like the communication style or the treatment suggestions of their psychiatrists.

Do these concerns suggest that there is no problem in how clinicians and patients communicate in mental health care? Far from it! On the contrary, I would argue that the communication between patients and clinicians is at the heart of mental health care, and that improving this communication is the single most important and promising route to more effective treatment. For achieving this, however, general and vague terms such as SDM are not very helpful. Research on patient-clinician communication requires precise theories, specified models and detailed analyses.

Examples from our own group to illustrate such research on different aspects of patient-clinician communication include: in-depth analyses of the difficulty of psychiatrists to address patients' concerns about their delusions[4,5]; a non-clinical experiment about how psychiatrists should introduce themselves in the first encounter[6]; and randomized controlled trials on how to improve communication and, through that, treatment outcomes.

One trial showed that a new intervention structuring and focusing the routine communication between patients and clinicians in community mental health care (DIALOG+) leads to substantially more favourable clinical and social outcomes[7]. Another trial demonstrated that clinicians can learn and successfully apply new skills in addressing psychotic symptoms of their patients[8]. Such research still faces a range of significant conceptual and methodological challenges, and the results are hardly conclusive. Yet, the findings may be seen as encouraging to pursue and advance both rigorous research in patient-clinician communication and teaching of relevant skills.

The call for SDM may reflect a wider and fundamental problem of current psychiatry. The last decades have seen the rise of appealing terms that arose in the public arena and with lay audiences, where the absence of a precise definition is often an advantage. Recent examples include SDM, but also recovery and co-production. Such terms are intuitively appealing to various stakeholders, who are free to understand them in any way they like. These terms may have their value in a political debate, but less so in a professional discourse.

One might argue that, for psychiatry as a scientific discipline, these terms are even harmful. All scientific progress requires intellectual honesty as the starting point. One needs an unbiased account of what a discipline has already discovered and achieved, but also of what the limitations are. If there has been limited progress in treatment concepts in psychiatry over the last three decades, then this is no disgrace. It has to be considered appropriately, so that as a discipline we can learn from failure and hopefully move on.

Terms like recovery, SDM and co-production give the illusion of novelty, of new ideas and new insights, when in fact there have been none. I wish such terms would be recognized as what they are, a combination of common sense, simplification and fashionable jargon, without much new substance that would help mental health care move forward. They resemble the "the emperor's new clothes" in Andersen's tale[9]. Facing a lack of novelty may be uncomfortable, but it is likely to be a necessary step towards real innovation.

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Shared decision making in mental health care settings: perspective, purpose and practice

Rates of chronic illness are growing rapidly, as are health care costs. These phenomena and the burdens that they present demand not only biomedical and care-delivery advancements but also innovations in patient engagement, defined as the process of "engaging patients and their caregivers in effective self-care, behavior change, and chronic disease management; and [addressing] the need to better align treatment choices with patients' well-informed preferences and values through shared decision making"[1]. In his review on shared decision making (SDM) in mental health care, M. Slade[2] provides an excellent examination of existing research on the topic and offers innovative recommendations – such as involving social marketing and the hospitality industry – to move the field forward. While I agree with what Slade has written about SDM tools, I would like to go one step back in this commentary, (re)examining theoretical perspectives on SDM and proposing a fidelity framework to support the practice of SDM at the service level. Without the commitment of practitioners and the transformation of the entire workplace[3], SDM is rhetoric, not a reality.

Examining the theoretical perspective that underpins SDM is not purposeless. It helps us better understand the essence and values behind the practices. The closure of

asylums and psychiatric institutions across the globe beginning in the 1970s, along with the introduction of community care, brought about a paradigm shift in mental health care, moving the field from one that was traditional and professionally-led to one that is service-centered and in which patients participate (patient-led care remains rare in practice). The authors of a seminal work explain that "at present, there are broadly three strands to the project of critical psychiatry: the development of a critique of the influence of the pharmaceutical industry on the theory and practice of psychiatry, the establishment of a medical discourse about mental suffering that is sensitive to the issue of meaning, and the promotion of a partnership with the emerging user/survivor movement"[4]. In other words, the traditional medical paradigm has been challenged, and an alternative discourse has been offered, one that acknowledges the existence of both professional knowledge and lived-experience knowledge that lay the often forgotten foundation for SDM.

The sociological analysis of medical versus lived-experience knowledge dates back to the early 1970s, with Freidson's landmark publication[5]. Knowledge is created by people working individually or interdependently, and it is often bounded by what society believes to be legitimate[3,6]. Knowledge is "never a neutral or objective phenomenon but a matter of positionality, that is, of the place from which one speaks, to whom and for what purpose"[7]. Knowledge construction (e.g., recovery-oriented use of medication, illness management strategies) and communication – the essence of SDM – are human activities and therefore subject to human vices and virtues. There is a difference in power between professional and service user in an SDM session, and that difference is only exaggerated by time pressure and by the meaning and suffering associated with a mental health condition.

Combining professional and lived-experience knowledge in the search for personal recovery is not always a straightforward process. The two forms of knowledge sometimes work in a complementary manner, but at other times their interaction causes more tension and raises questions. It is of paramount importance that health knowledge construction moves from a process that is hierarchical to one that is horizontal, or defined by consensus[3,8]. Such a shift would allow all parties, if willing, to participate in the construction of knowledge that forms the basis for decision-making in the search for personal recovery from mental illness. The proposed fidelity framework consists of the following elements[9,10]:

External environment. Health care services would deliver systematic and specific programs to promote social inclusion and equality and to reduce the stigma and discrimination associated with mental illness (e.g., targeting people recovering from psychosis whose employment is at risk). These programs would form a solid base from which to implement SDM.

Leadership commitment. Organizations would adopt a recovery approach in their overarching philosophies and put that concept into practice (e.g., interactions with service users would be directed toward nurturing the service user's autonomy and choices). The position adopted in SDM is that both professional and lived-experience knowledge are valid and that knowledge is most powerful when professional and service user collaborate on terms of mutual understanding, respect and equality. There should be clear publicity in the form of brochures, posters and web resources about using SDM as a tool to support service users in achieving their recovery goals. Senior personnel of a given organization would join forces with everyday practitioners to ensure that SDM be implemented in a multidisciplinary manner across different clinical services (from acute inpatient facilities to community-based services) throughout the entire organization. Similarly, the practice of SDM would be incorporated into the day-to-day operation of organizations. Finally, a hallmark of leadership commitment to SDM would be the employment of people with personal experiences of mental illness in positions of senior management, in committees monitoring SDM execution, and as peer support specialists to assist SDM programs.

Implementation of SDM. Organizations would establish SDM implementation teams to provide for the ongoing and regular supervision of practitioners. The five essential steps of SDM stipulated in the SHARE approach form part of the proposed fidelity framework[9]. These steps are: a) to seek the participation of service users in the SDM process; b) to help service users explore and compare intervention options based on their recovery goals; c) to assess service users' values and preferences; d) to reach decisions jointly with service users; and e) to evaluate the outcomes of SDM. Services would provide physical settings that assist service users in participating in the SDM process, with features such as SDM corners and gadgets (e.g., tablets, laptops). Moreover, senior management would invest in building up reference resources (e.g., evaluation instruments, SDM aids) and evaluating SDM implementation.

The current body of literature on SDM has three major limitations. First, although the outcome measures used by the majority of trial studies are fairly comprehensive in terms of covering clinical status, service satisfaction and intervention adherence, no studies have assessed the innovation and creativity of service users in problem solving, service users' decision making, or service users' insight into and understanding about their conditions. Second, we should not undermine the increasingly sophisticated capability of smartphones in the era of Web 3.0[11]. It provides new options and groundbreaking social media interfaces that could support the application of SDM. Third, there is a void in the existing literature on the application of SDM in non-Western, non-Nordic jurisdictions.

SDM is largely a psycholinguistic process. The use of words, metaphors and non-verbal communication; the art of involving families and caregivers in the intervention process; and the level of service users' participation in mental health services more broadly are crucial factors that need to be considered when it comes to delivering SDM in mental health care.

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Incorporating shared decision making in mental health care requires translating knowledge from implementation science

M. Slade[1] provides a broad overview of the literature on shared decision making (SDM) with a focus on mental health care. The overview is timely and pertinent, as SDM is considered a central component of the widely accepted recovery model of mental health services[2]. We are encouraged by Slade's focus on implementation, which is the current challenge facing SDM practice across all settings and countries.

Slade highlights significant challenges to decision aid uptake, including quality control and the overwhelming number of those aids. The movement toward quality control of decision aids is over ten years old. The International Patient Decision Aids Standards Collaboration (http://ipdas.ohri.ca) has provided criteria to judge the quality of patient decision aids. Certification is also underway and has the potential to improve the quality of the growing number of those aids.

However, we agree that the current model of decision aid development and maintenance is unsustainable. The use of technology is being harnessed to address this challenge. For example, the SHARing Evidence to Inform Treatment decisions (SHARE-IT) project is an initiative designed to automate decision aid production based on guideline updates[3].

While decision aids are useful adjuncts to SDM, it is important to clarify that the practice of SDM does not require a decision aid. Informing patients of their options, eliciting their preferences and integrating these patient preferences into the health care decision is a practice that requires communication skills, not just tools. Only a clinician who has the necessary communication skills can appropriately use a decision aid during the consultation. The use of decision aids can indeed promote the engagement of patients in the decision making process, but there are also other ways of fostering SDM, including patient-mediated interventions that prompt patients to ask questions[4].

We agree with Slade's second challenge that SDM implementation endeavors could potentially be more successful if better integrated into other innovations in mental health care. This argument is especially compelling from a clinician's perspective. By branding SDM as the most important singular new intervention that clinicians must adhere to in their portfolio of skills and interventions, we undermine its potential and may cause resistance. More work is needed to integrate SDM with other health care innovations in particular fields of health care. Thus, the mental health field has the potential to take the lead, for example, through the integration of SDM and advance directives and joint crisis plans[5].

Slade highlights the important ethical tension between beneficence and patient autonomy to make decisions. An overemphasis on beneficence-focused treatment at the expense of patient autonomy can result in treatment decisions that represent the clinician's values imposed on the patient. This is particularly concerning in mental health care, where the effectiveness of treatments is often overstated, despite only modest gains and significant potential side effects.

As Slade indicates, the question most often raised in mental health care relates to an individual's decision making capacity. While individuals with mental illness may have impaired cognitive abilities, most desire and have the capacity to be involved in treatment decision making, including those with severe conditions such as schizophrenia and major depression[6]. Similar to patients with other cognitive disabilities, strategies are available to increase participation in decision making among individuals with severe mental illness, such as the use of multiple display formats when communicating treatment options and risks.

Of course, these individuals are not always capable of becoming involved in a decision making process; this ability may vary over the course of their illness. In such cases, joint crisis plans may be useful. For example, when a patient's decision making capacity is reduced, a clinician or family member can draw on the patient's stated preferences that were gathered when the patient was capable of making a decision. Such plans could be beneficial in institutional settings where patient autonomy is even more restricted.

Nevertheless, research has shown that most people diagnosed with a mental illness have a similar level of decision making capacity as a healthy comparison group from the general population[6]. Increased awareness of this ability would be an important step toward increasing patient engagement in SDM.

This appeal for reducing the stigma towards mentally ill patients by not denying them their decision making capacities is related to the prominent and broader call for a culture change in health care

practice. In order to achieve this culture change in the clinical world and move away from paternalism, we need to do more than just change attitudes and norms of individual health care professionals. Change is needed at all levels, from individual to organizational and institutional.

Slade correctly points out that when considering how to transform mental health care systems – both regarding SDM and other possible upcoming changes – it could be helpful to "use language and constructs from other sectors to inform this transformation"[1]. When discussing the implementation of SDM, whether in mental health care or in other clinical areas, we should carefully consider translating knowledge from the field of implementation science to influence clinical care. For successful implementation we need to take a range of basic sciences (e.g., behavioral science, psychology, communication, economics) into account; thus, social marketing can only be one piece of the jigsaw.

We recommend the Consolidated Framework for Implementation Research[7] to develop a theoretically based implementation strategy. This stresses the need to foster implementation at different levels (e.g., individual, organizational, policy) and describes social marketing as one among a range of other activities (e.g., education, role modeling, training) to engage stakeholders at the individual level. Another seminal model is the Behavior Change Wheel[8], which can be used to design behavior change interventions to foster routine implementation of SDM.

In summary, we applaud Slade for his effort to push forward the SDM agenda in the mental health field. We agree with his conclusion that implementation challenges are the key concern. Social marketing and insights from the hospitality industry are unique and helpful, but they must be combined with implementation science to effectively amplify the voice of those with mental illness in making treatment decisions through an SDM process.

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Mental health shared decision making in the US

M. Slade's paper[1] presents the most accurate, balanced and up-to-date summary of shared decision making in mental health care that is currently available. Because his review takes a decidedly UK perspective, I will address some of the related issues in the US.

The US health care system (more accurately, the US health care non-system) continues to be extraordinarily expensive and ineffective. Health care services in the US have been created by vested interest groups: private hospitals, pharmaceutical companies, insurance agencies, device makers, professional guilds, specialty care groups, large health conglomerates, for-profit nursing homes, and so on. All of these entities prosper in the US by providing services that maximize profits rather than patient outcomes.

Although patient-centered care is widely endorsed as a principle in the US[2], it is more honored in the breach than the observance. In mental health, the call for patient-centered care and shared decision making seems unlikely to shift care away from hospitals, expensive medications, specialists, facility-based rehabilitation, and other profit-generating services, even though studies show that patients would prefer other services such as safe housing, employment, peer supports, and help with general functioning[3,4]. People with mental illness recognize the need to address the social issues that cause and exacerbate mental disorders. But shared decision making may not include the services they want and need.

Medical solutions to social problems are very expensive and ineffective. Yet social factors often determine exacerbations of mental illness and cause excessive, unnecessary mental health treatment. Consider the current trends to increase mental hospital beds and to incarcerate people with mental illness. The erosion of low-cost housing and the absence of employment opportunities, rather than true increases in the prevalence or severity of mental illness, underlie these misguided initiatives. In fact, hospitals and prisons often harm people with mental illness by decreasing self-esteem and opportunities, harm society by increasing stigma and segregation, and harm government by wasteful spending.

The crux of the US problem is that prevention and social safety net services, though preferred by people with mental health challenges, do not generate profits. Effective interventions for primary, secondary and tertiary prevention in mental health exist, but in the US we spend minimally in these areas. Northern European countries, by contrast, spend less on health care but more on the social safety net: prenatal services, early childhood care, maternal leave, family support, early education, nutrition, early behavioral health interventions, safe housing, and psychosocial supports for people with disabilities[5].

Consider the examples of supported housing[6], supported employment[7], and supported medication management[8]. These interventions are highly effective, strongly desired by people with mental illness, and clearly helpful for recovery. But they are rarely available because social services

are not considered medical necessities. Shared decision making cannot address unavailable services.

As health care costs in the US spiral out of control, policy makers and health care leaders have pursued economic outcomes such as lower hospital and emergency use rather than increased involvement or satisfaction with the health encounter. Adoption of decision aids and shared decision making has been largely ignored. Instead, policy makers continue to try to change incentives and risk adjustments within the health care system in order to reduce costs. Thus far, managed care, accountable care organizations, paying for performance, behavioral health integration, and other popular approaches to reform have not succeeded – as though we do not quite have the incentives and adjustments right! But what if the solutions are outside of the traditional health care system? What if they do not generate profits for medical industries? What if they involve listening to patients rather than to vested interest groups?[9] More money, more clinical trials, and more professionalization may not solve problems that are related to social, educational, economic and health inequities[10].

Thus, shared decision making, to drive effective change in the US, must address more than traditional medical interventions. People with mental health problems need and want safe neighborhoods, decent housing, and opportunities for education, employment and community integration. Yet they are getting more and more medicines, forced treatments, hospitals and psychiatric specialists. As inequality, prejudice and health disparities expand in the US, we must listen to people in a broader sense – let people choose the services and outcomes that matter to them. People with mental health disabilities deserve access to housing, schools, jobs, family supports and safety[11]. But will they be allowed to share in these decisions?

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Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls

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People with severe mental illness (SMI) – schizophrenia, bipolar disorder and major depressive disorder – appear at risk for cardiovascular disease (CVD), but a comprehensive meta-analysis is lacking. We conducted a large-scale meta-analysis assessing the prevalence and incidence of CVD; coronary heart disease; stroke, transient ischemic attack or cerebrovascular disease; congestive heart failure; peripheral vascular disease; and CVD-related death in SMI patients (N=3,211,768) versus controls (N=113,383,368) (92 studies). The pooled CVD prevalence in SMI patients (mean age 50 years) was 9.9% (95% CI: 7.4-13.3). Adjusting for a median of seven confounders, patients had significantly higher odds of CVD versus controls in cross-sectional studies (odds ratio, OR=1.53, 95% CI: 1.27-1.83; 11 studies), and higher odds of coronary heart disease (OR=1.51, 95% CI: 1.47-1.55) and cerebrovascular disease (OR=1.42, 95% CI: 1.21-1.66). People with major depressive disorder were at increased risk for coronary heart disease, while those with schizophrenia were at increased risk for coronary heart disease, cerebrovascular disease and congestive heart failure. Cumulative CVD incidence in SMI patients was 3.6% (95% CI: 2.7-5.3) during a median follow-up of 8.4 years (range 1.8-30.0). Adjusting for a median of six confounders, SMI patients had significantly higher CVD incidence than controls in longitudinal studies (hazard ratio, HR=1.78, 95% CI: 1.60-1.98; 31 studies). The incidence was also higher for coronary heart disease (HR=1.54, 95% CI: 1.30-1.82), cerebrovascular disease (HR=1.64, 95% CI: 1.26-2.14), congestive heart failure (HR=2.10, 95% CI: 1.64-2.70), and CVD-related death (HR=1.85, 95% CI: 1.53-2.24). People with major depressive disorder, bipolar disorder and schizophrenia were all at increased risk of CVD-related death versus controls. CVD incidence increased with antipsychotic use (p=0.008), higher body mass index (p=0.008) and higher baseline CVD prevalence (p=0.03) in patients vs. controls. Moreover, CVD prevalence (p=0.007), but not CVD incidence (p=0.21), increased in more recently conducted studies. This large-scale meta-analysis confirms that SMI patients have significantly increased risk of CVD and CVD-related mortality, and that elevated body mass index, antipsychotic use, and CVD screening and management require urgent clinical attention.

Key words: Cardiovascular disease, severe mental illness, schizophrenia, bipolar disorder, major depression, coronary heart disease, cerebrovascular disease, congestive heart failure, premature mortality

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People with severe mental illness (SMI) – including schizophrenia, bipolar disorder, major depressive disorder, and their related spectrum disorders – have a life expectancy shortened of 10-17.5 years compared to the general population[1,2]. While suicide explains some of this reduced life expectancy[3], it is now established that physical diseases account for the overwhelming majority of premature mortality[4,5]. Among physical conditions, cardiovascular disease (CVD) is the main potentially avoidable contributor to early deaths in patients with SMI[4].

Given the importance of understanding the magnitude, contributors to and relative distribution of CVD risk in people with SMI, a number of disease-specific meta-analyses investigated if people with major depressive disorder, bipolar disorder or schizophrenia are at an increased risk of CVD compared to controls. These meta-analyses reported that people with depression (defined by the presence of depressive symptoms or a diagnosis of major depressive disorder) are at increased CVD risk[6,7], including stroke (risk ratio, RR=1.34, 95% CI: 1.17-1.54), myocardial infarction (hazard ratio, HR=1.31, 95% CI: 1.09-1.57), coronary heart disease (RR=1.36, 95% CI: 1.24-1.49) and coronary heart disease-related death (HR=1.36, 95% CI: 1.14-1.63)[6-8]. While clearly informative, results concerning CVD were not specific for major depressive disorder defined according to established diagnostic criteria, possibly biasing such observed association towards a lower risk[9]. Another meta-analysis of longitudinal studies, which utilized standardized criteria to define bipolar disorder, reported mixed results, since people with that disorder were actually not at increased risk of myocardial infarction (RR=1.09, 95% CI: 0.96-1.24), whereas the risk of stroke was higher compared to controls (RR=1.74, 95% CI: 1.29-2.35)[10]. Among individuals with schizophrenia, previous meta-analyses[11,12] reported an overall increased risk of CVD compared to controls (RR=1.53, 95% CI: 1.27-1.86). This risk increase included stroke (up to RR=1.71,

95% CI: 1.19-2.46) and heart failure (RR=1.81, 95% CI: 1.42-2.29), but not coronary heart disease (RR=1.20, 95% CI: 0.93-1.53).

While the existing literature has provided relevant insights, several limitations are to be highlighted and important questions remain unanswered. First, some of the previous meta-analyses did not use standardized clinical assessments to identify and categorize SMI and/or cardiovascular events. Second, the exact prevalence and incidence of each type of CVD among people with SMI, both within and across major diagnostic SMI subgroups, remains unclear. Third, the magnitude of premature CVD-related mortality risk in people with SMI versus controls is to be specified. Fourth, potential risk factors for increased CVD and related mortality risk across the SMI groups have not been elucidated via meta-analytic techniques, which could help identify targets for treatment guidelines, clinical standards and development of preventive and therapeutic programs. In this regard, large-scale pooled analyses in the SMI population can provide relevant information, allowing the investigation of potentially shared risk factors across many studies and participants, thus dissecting CVD risk factors associated with SMI and/or treatments for these disorders from factors which are non-specific or shared with the general population[13]. Additionally, pooling of data allows for the investigation of demographic, regional and treatment variables, both within and across major diagnostic categories.

Given the caveats mentioned above, the current gaps within the literature and the need to better understand CVD risk among people with SMI, we conducted a large scale meta-analysis investigating the prevalence, incidence and mortality attributed to CVD and their correlates among people with SMI, both within and across major diagnostic groups.

METHODS

This systematic review and meta-analysis adhered to the PRISMA statement[14], following a predetermined, but unpublished protocol.

Search strategy

An electronic literature search was conducted in PubMed, Embase and Scopus from database inception until August 2, 2016 by two independent reviewers, using the search terms ("bipolar disorder" OR mania OR schizophrenia OR schizoaffective OR psychosis OR "major depression" OR "serious mental illness") AND (cardiovascular OR stroke OR cerebrovascular OR "transient ischemic attack" OR "transient ischaemic attack" OR "peripheral vascular" OR "myocardial infarction" OR "coronary heart disease" OR" coronary artery disease" OR "ischemic heart disease" OR "ischaemic heart disease" OR "hypertensive heart disease" OR angina OR "cardiac failure" OR "heart failure" OR "congestive heart failure" OR "atrial fibrillation" OR "pulmonary embolism" OR "cardiovascular mortality"). Furthermore, bibliographies of included papers were reviewed.

Inclusion and exclusion criteria

We included studies with the following characteristics: a) reporting on patients with schizophrenia, schizophrenia spectrum or schizoaffective disorder, bipolar disorder or bipolar spectrum disorders, major depressive disorder or depressive episodes, or SMI (defined as at least two among major depressive spectrum, bipolar spectrum and schizophrenia spectrum disorders) according to DSM-III, DSM-IV, DSM-5, ICD-8, ICD-9 or ICD-10, or a medical record diagnosis based on a clinical interview; b) having a cross-sectional or a retrospective/prospective longitudinal design, either with or without a control group; c) using a standardized definition of CVD; d) reporting RR, HR or odds ratio (OR) comparing patients with region-specific controls, percentage or number of events at baseline (data used for cross-sectional analysis = prevalence) and/or follow-up (data used for longitudinal analysis = cumulative incidence).

We excluded studies that investigated cardiovascular risk estimates and/or factors, subclinical CVD, or SMI rates in populations with CVD. In case of multiple publications from the same study, only the most recent paper or the article with the longest follow-up was included. When required, we contacted the primary/corresponding authors of potential studies to confirm eligibility or acquire unpublished variables of interest.

Data extraction

Seven authors divided in four pairs independently extracted data in a standardized Microsoft Excel sheet, with reciprocal validation of data extraction results. The extracted data included: authors, year and country; geographic region; study design; data source; period of data collection; SMI diagnostic criteria; CVD diagnostic criteria; specific SMI and CVD diagnosis; case and control inclusion criteria; number of cases and controls; percentage or number with CVD, coronary heart disease, cerebrovascular disease and congestive heart failure at baseline; number of events at follow-up; follow-up duration; number and type of covariates considered in the analyses; OR, RR, rate ratio and HR with their respective 95% upper and lower CIs; mean age with standard deviation; mean body mass index with standard deviation; proportion of males; co-occurring obesity, alcohol and substance related disorders, diabetes, hypertension, and hyperlipidemia; married status; employment status; percentage of patients with poorest income and least urbanized; and percentage of patients taking antipsychotics. Rate ratios calculated with Cox regression models were included in HR analyses. When authors did not specify whether or not a rate ratio had been calculated with Cox regression models, we contacted them seeking clarification.

Outcomes

Primary outcomes were CVD prevalence and cumulative incidence plus CVD-related mortality in people with SMI, as

well as adjusted OR for prevalence and HR for incidence rates in SMI versus controls. Secondary outcomes were the same measures for specific CVDs (i.e., coronary heart disease, cerebrovascular disease, congestive heart failure) in SMI patients, as well as adjusted OR and HR versus controls.

Prevalence and OR were calculated from cross-sectional studies and from baseline results of longitudinal studies. Where available, incidence, RR and HR were calculated from longitudinal studies.

Quality assessment

For the purpose of this meta-analysis, a checklist (yes versus no) was used to assess the methodological quality of included studies. The evaluation of methodological quality across studies was based on the following factors: clear diagnostic criteria, presence of a control group, matching of the control group, covariate-adjusted outcomes, reported cardiovascular risk factors at baseline, and follow-up $\geq$5 years.

Data analysis

This meta-analysis was performed using Comprehensive Meta-Analysis V3[15]. All outcomes were meta-analyzed when at least two studies provided data. A random effects model[16,17] was used to account for between-study heterogeneity. We calculated pooled CVD prevalences and pooled CVD cumulative incidences, each with SMI subgrouping. For dichotomous primary and secondary outcomes comparing pooled SMI and SMI subgroups with controls, we calculated unadjusted as well as adjusted pooled OR for cross-sectional data, and unadjusted pooled RR, as well as adjusted pooled HR, for longitudinal data. Funnel plots were visually inspected, and Egger's test[18] and Begg-Mazumdar Kendall's tau[19] were used to determine if publication bias was likely. When publication bias was present, the trim and fill[20] procedure was run to evaluate if the results changed after imputing potentially missing studies.

Between-study heterogeneity was measured using the chi-squared and I-squared statistics, with chi-squared $p<0.05$ and I-squared $\geq$50% indicating significant heterogeneity[21]. To identify potential moderators, meta-regression was run with Comprehensive Meta-Analysis V3 for unadjusted outcomes where heterogeneity was significant.

Since CVD rates in the general population vary across the world, we also performed a stratified analysis across geographic regions (Asia, Europe, North America, Oceania) regarding raw CVD prevalence and incidence in SMI populations, and compared patients to their respective region-specific general population controls (calculating RRs as well as adjusted ORs and HRs for the four regional strata and comparing them across the different regions whenever at least two studies provided data per each region).

The following study and patient characteristics were explored as potential moderators and mediators in addition to SMI status: geographical region of the sample; time of data collection; percentage of patients taking antipsychotics; and the difference between patient and control samples regarding age, body mass index, proportion of males and of those with married status, unemployed, with poorest income, least urbanized, and having co-occurring obesity, alcohol and substance-related disorders, diabetes, hypertension or hyperlipidemia.

RESULTS

Search results

Out of 18,064 initial hits across the searched electronic databases, 11,878 unduplicated hits were screened, and 11,576 were excluded through title/abstract reading. Altogether, 302 full texts were reviewed, and 210 were excluded with specific reasons. Among 92 studies meeting inclusion criteria, 27 had a cross-sectional design[22-48] and 65 studies had a retrospective or prospective longitudinal design[49-113] (Figure 1).

Characteristics of included studies

We included 92 studies, with a total population of 3,211,768 patients (mean age 50 years, 49% male) with SMI and 113,383,368 controls (mean age 51 years, 49% male), with a total of 116,595,136 subjects when summing those studies where patient and control sample sizes were not separately reported. Altogether, 27 studies (N=27,037,943) were cross-sectional and 65 studies (N=89,557,193) were longitudinal. Overall, 38 studies included patients with schizophrenia (of which 29 were longitudinal), 30 with bipolar disorder (21 longitudinal), 30 with major depressive disorder (22 longitudinal), and 14 with SMI (8 longitudinal). Taken together, six studies included only patients with SMI (N=884,412), 16 studies included only patients with bipolar disorder (N=71,832), 20 studies included only patients with major depressive disorder (N=111,360), and 29 studies included only patients with schizophrenia (N=1,591,106), while 19 studies included different subgroups of SMI, providing data for each of them separately (some studies included more than one diagnostic group, see Tables 1 and 2 for details).

Meta-analysis: cross-sectional results

The pooled CVD prevalence in SMI was 9.9% (95% CI: 7.4-13.3; 38 studies). Individual rates were 8.4% for people with bipolar disorder (95% CI: 5.4-12.6, 12 studies, N=66,911); 11.7% for those with major depressive disorder (95% CI: 3.6-32.2, 7 studies, N=83,965); 11.8% for those with schizophrenia (95% CI: 7.1-19.0, 13 studies, N=191,982), and 11.8% for those with SMI (95% CI: 4.1-29.4, 6 studies, N=17,286) ($p<0.001$ for SMI diagnostic subgroup comparisons).

Adjusting for a median of seven potential confounders, the adjusted pooled OR for CVD in SMI compared to controls was

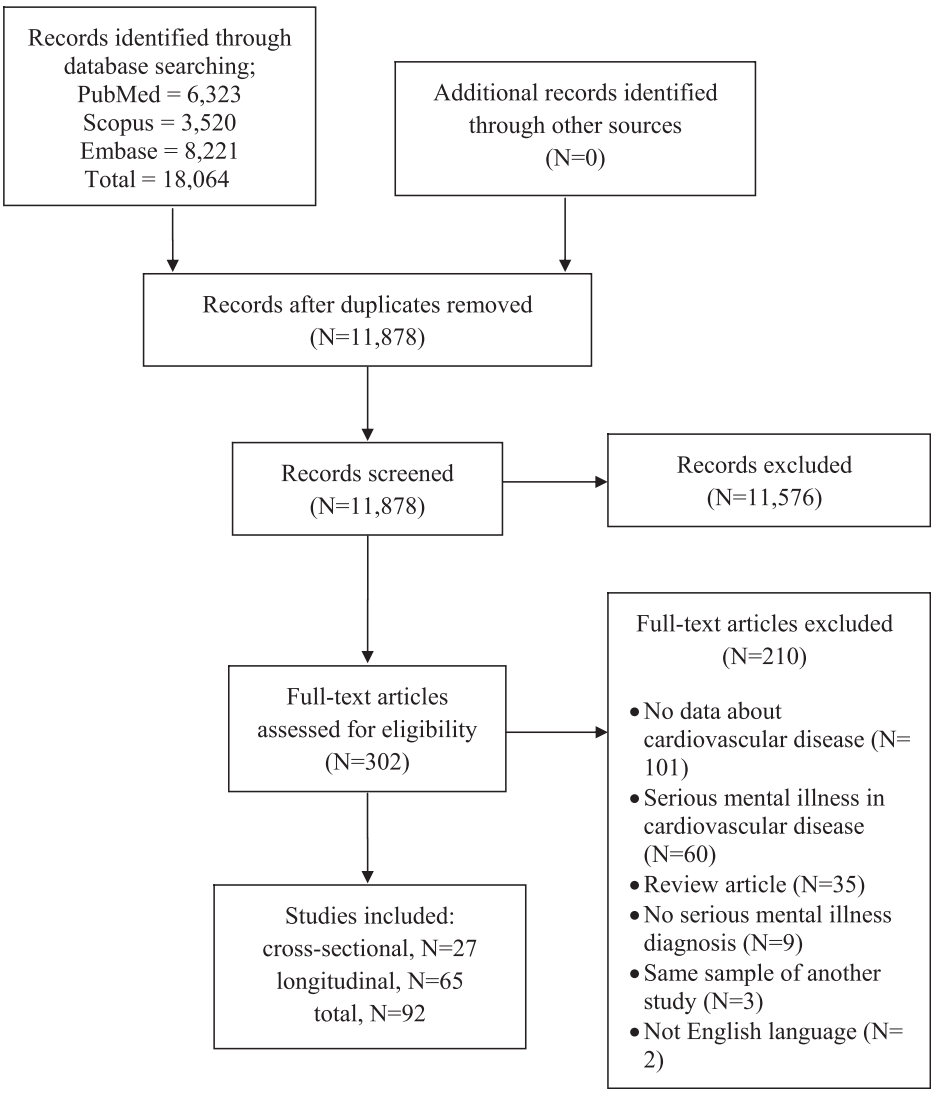

Figure 1 PRISMA flow chart

1.53 (95% CI: 1.27-1.83, p<0.001, 11 studies). For specific CVDs, pooled together, people with SMI had an increased risk of coronary heart disease (OR=1.51, 95% CI: 1.47-1.55, p<0.001, 5 studies) and cerebrovascular disease (OR=1.42, 95% CI: 1.21-1.66, p<0.001, 6 studies), with a strong statistical trend for congestive heart failure (OR=1.28, 95% CI: 0.99-1.65, p=0.06, 4 studies). Considering separately single types of SMI and CVD, in adjusted OR analyses, bipolar disorder was not significantly associated with CVD or its subtypes; major depressive disorder was significantly associated with CVD and coronary heart disease; and schizophrenia was significantly associated with coronary heart disease, cerebrovascular disease and congestive heart failure (Table 3). No adjusted ORs were available for mixed SMI groups.

All significant results were significantly heterogeneous. After adjusting for publication bias with the trim-and-fill method, all pooled previously significant ORs remained statistically significant, confirming the association of CVD, coronary heart disease and cerebrovascular disease with SMI, while the OR for congestive heart failure became marginally significant (p=0.05).

Meta-analysis: longitudinal adjusted results

Among patients with SMI, 3.6% (95% CI: 2.7-5.3%) experienced a CVD event during a median follow-up period of 8.4 years (range 1.8-30.0) (65 studies). After adjusting for a median of six potential confounders, people with SMI were at significantly increased risk across longitudinal studies for CVD (HR=1.78, 95% CI: 1.60-1.98) (31 studies, N=671,384 cases vs. N=14,335,203 controls) as well as for specific CVDs, including coronary heart disease (HR=1.54, 95% CI: 1.30-1.82, 18 studies, N=194,017 cases vs. N=13,530,858 controls), cerebrovascular

Table 1 Cross-sectional studies: characteristics of included studies and samples

Study	Country	No. cases	No. controls	Period of data collection	SMI definition	Inclusion criteria for cases	No. covariates
Beyer et al[22]	USA	1,379	-	2001-2002	Medical records	Bipolar disorder	-
Bresee et al[23]	Canada	28,775	2,281,636	1995-2006	ICD-9,10	Schizophrenia	4
Bresee et al[24]	Canada	399	120,044	2005	Medical records	Schizophrenia	11
Chen et al[25]	Taiwan	80	-	2015	DSM-IV	Bipolar disorder, >60 years	-
Curkendall et al[26]	Canada	3,022	12,088	1994-1999	ICD-9	Schizophrenia	7
Devantier et al[27]	Denmark	28	27	2009-2011	ICD-10	Major depressive disorder, late onset	-
Hagg et al[28]	Sweden	269	-	2000-2003	DSM-IV	Schizophrenia, 20-69 years	-
Herbst et al[29]	USA	10,573 total population		2001-2002	DSM-IV	Major depressive disorder, >60 years	11
Huang et al[30]	Taiwan	117,987	21,356,304	2000-2003	ICD-9	Bipolar disorder or major depressive disorder	1
Hyde et al[31]	Australia	355	-	2008-2012	Medical records	Severe mental illness, prescribed clozapine	-
Kilbourne et al[32]	USA	8,083	-	2001	ICD-9	Severe mental illness, >60 years	-
Kilbourne et al[33]	USA	9,705	5,353	2000-2001	ICD-9	Bipolar disorder or severe mental illness, male	3
Lindegard[34]	Sweden	368	87,176	1966-1979	ICD-9, DSM-III	Major depressive disorder or bipolar disorder	-
Maina et al[35]	Italy	185	-	2006-2008	DSM-IV	Severe mental illness	-
Morden et al[36]	Canada	65,362	65,362	2000-2007	ICD-9	Schizophrenia	4
Munoli et al[37]	India	120	-	2011	ICD-10	Bipolar disorder	-
Nielsen et al[38]	Denmark	937	-	1969-2014	ICD-10	Schizophrenia	-
Niranjan et al[39]	USA	5,695	34,979	2007	DSM-IV	Major depressive disorder	6
Oreski et al[40]	Croatia	289	192	2011	ICD-10	Bipolar disorder or schizophrenia	-
Prieto et al[41]	USA	988	-	2009-2013	DSM-IV	Severe mental illness	-
Scherrer et al[42]	USA	628	6,903	1990-1992	DSM-III	Major depressive disorder, male twins	-
Scott et al[43]	Multicenter	52,095 total population		2001-2011	DSM-IV	Bipolar disorder or major depressive disorder	6
Shen et al[44]	Taiwan	203	2,036	2005-2007	ICD-9	Schizophrenia, in intensive care unit	6
Smith et al[45]	UK	9,677	1,414,701	2007	Medical records	Schizophrenia	3
Smith et al[46]	UK	2,582	1,421,796	2007	Medical records	Bipolar disorder	2
Swain et al[47]	Multicenter	45,288 total population		2001-2011	DSM-IV	Bipolar disorder or major depressive disorder	7
Zilkens et al[48]	Australia	656	349	2000-2009	ICD-8,9,10	Major depressive disorder, 65-84 years, developing dementia	-

SMI – severe mental illness

disease (HR=1.64, 95% CI: 1.26-2.14, 11 studies, N=188,841 cases vs. N=13,113,564 controls), congestive heart failure (HR=2.10, 95% CI: 1.64-2.70, 2 studies, N=409 cases vs. N=41,678 controls), peripheral vascular disease (only unadjusted RR=3.11, 95% CI: 2.46-3.91, three studies), and CVD-related death (HR=1.85, 95% CI: 1.53-2.24, 16 studies, N=353,407 cases vs. N=7,317,053 controls).

According to adjusted HRs, schizophrenia was significantly associated with CVD in longitudinal studies (HR=1.95, 95% CI: 1.41-2.70, 14 studies), as well as with coronary heart disease (HR=1.59, 95% CI: 1.08-2.35, 5 studies), cerebrovascular disease (HR=1.57, 95% CI: 1.09-2.25, 5 studies), and CVD-related death (HR=2.45, 95% CI: 1.64-3.65, 9 studies).

According to adjusted HRs, bipolar disorder was significantly associated with CVD in longitudinal studies (HR=1.57, 95% CI: 1.28-1.93, 10 studies) as well as with CVD-related death (HR=1.65, 95% CI: 1.10-2.47, 3 studies), with a trend toward a significant association with cerebrovascular disease (HR=1.60, 95% CI: 0.99-2.57, 4 studies), but no significant association with coronary heart disease (HR=1.16, 95% CI: 0.76-1.78, 4 studies). One study reported a significant association with congestive heart failure (HR = 2.27, 95% CI: 1.49-3.45).

According to adjusted HRs, major depressive disorder was significantly associated with CVD in longitudinal studies (HR=1.72, 95% CI: 1.48-2.00, 18 studies) as well as with coronary heart disease (HR=1.63, 95% CI: 1.33-2.00, 9 studies), cerebrovascular disease (HR=2.04, 95% CI: 1.05-3.96, 3 studies), congestive heart failure (HR=2.02, 95% CI: 1.48-2.75, 2 studies), and CVD-related death (HR=1.63, 95% CI: 1.25-2.13, 7 studies).

According to adjusted HRs, mixed SMIs were significantly associated with CVD in longitudinal studies (HR=3.24, 95%

Table 2 Longitudinal studies: characteristics of included studies and samples

Study	Country	No. cases	No. controls	Period of data collection	SMI definition	Inclusion criteria for cases	No. covariates
Almeida et al[49]	Australia	1,503	35,691	1996-2010	ICD-9	Schizophrenia, bipolar disorder or major depressive disorder, 65-85 years, male	8
Bremmer et al[50]	The Netherlands	41	2,080	1992-2000	DSM-III	Major depressive disorder, >55 years	13
Butnoriene et al[51]	Lithuania	184	369	2003-2004	DSM-IV	Major depressive disorder, >45 years	4
Callaghan et al[52]	Canada	5,999	5,999	2002-2006	Medical records	Bipolar disorder	6
Callaghan et al[53]	Canada	9,815	9,815	2002-2006	ICD-10	Bipolar disorder	8
Carney et al[54]	USA	1,074	726,262	1996-2001	ICD-9	Schizophrenia or schizoaffective disorder	4
Chen et al[55]	Taiwan	63,913	63,913	2002-2008	ICD-9	Schizophrenia	8
Clouse et al[56]	USA	16	60	1982-1992	DSM-III	Major depressive disorder with diabetes	7
Coryell et al[57]	USA	903	-	1998-1999	RDC	Severe mental illness	-
Crump et al[58]	Sweden	6,618	6,580,418	2003-2009	ICD-10	Bipolar disorder	6
Crump et al[59]	Sweden	8,277	6,097,834	2003-2009	ICD-10	Schizophrenia, >25 years	6
Davis et al[60]	Hawaii	280	39,000	1999-2005	Medical records	Major depressive disorder	5
Davydow et al[61]	Denmark	68,137	5,912,158	1999-2013	ICD-9	Schizophrenia, schizoaffective disorder or bipolar disorder	5
Enger et al[62]	USA	1,920	9,600	1995-1999	ICD-9	Schizophrenia, on antipsychotic treatment, 15-64 years	-
Fiedorowicz et al[63]	USA	288	147	1978-1981	RDC	Bipolar disorder	8
Filik et al[64]	UK	482	1,998	1999-2002	DSM-IV	Schizophrenia, schizophreniform or schizoaffective disorder	6
Fors et al[65]	Sweden	255	1,275	1981-1991	DSM-II	Schizophrenia	3
Gasse et al[66]	Denmark	873,898	52,693,301	1995-2009	ICD-8,10	Severe mental illness (affective psychoses)	22
Goldstein et al[67]	USA	5,835	26,266	2001-2005	DSM-IV	Bipolar disorder or major depressive disorder	8
Healy et al[68]	UK	1,429	-	1875-1924; 1994-2010	Medical records	Schizophrenia	-
Hendrie et al[69]	USA	757	30,831	1999-2008	ICD-9	Schizophrenia, >65 years	-
Hou et al[70]	Taiwan	8,264	-	1985-2008	DSM-III or IV, ICD-9	Schizophrenia	-
Hsieh et al[71]	Taiwan	9,715	-	2001-2009	ICD-9	Schizophrenia	10
Huang et al[72]	Taiwan	7,937	31,748	1996-2006	ICD-9	Major depressive disorder	9
Ifteni et al[73]	Romania	7,189	-	1989-2011	DSM-IV	Schizophrenia, inpatients	-
Jakobsen et al[74]	Denmark	74,759	338,747	1977-2000	ICD-8,10	Schizophrenia or major depressive disorder	2
Janszky et al[75]	Sweden	646	48,675	1969-2007	ICD-8	Major depressive disorder, 18-20 years	7
Jokinen & Nordstrom[76]	Sweden	346	-	1980-2005	DSM-IV	Major depressive disorder or bipolar disorder	-
Joukamaa et al[77]	Finland	606	8,000	1977-1994	Medical records	Schizophrenia, mood disorder or severe mental illness	1
Kendler et al[78]	Sweden	5,647	24,727	1998-2003	ICD-10	Major depressive disorder, twins	-
Kiviniemi et al[79]	Finland	6,987	-	1998-2003	ICD-9	Schizophrenia, first onset	-
Lahti et al[80]	Finland	204	11,880	1969-2004	ICD-8,9,10	Schizophrenia	5
Lan et al[81]	Taiwan	3,681	-	2001-2006	ICD-9	Bipolar disorder	-
Laursen et al[82]	Denmark	22,294	2,411,852	1995-2007	ICD-8,10	Schizophrenia or bipolar disorder, 15-52 years	3
Laursen et al[83]	Denmark	1,454	59,256	1995-2006	ICD-8,10	Schizophrenia or bipolar disorder	4

Table 2 Longitudinal studies: characteristics of included studies and samples *(continued)*

Study	Country	No. cases	No. controls	Period of data collection	SMI definition	Inclusion criteria for cases	No. covariates
Lemogne et al[84]	France	4,336	16,621	1990-2010	ICD-9,10	Depression or severe mental illness (bipolar disorder, psychosis)	6
Li et al[85]	Taiwan	1,003	4,012	1996-2009	ICD-9	Major depressive disorder	6
Lin et al[86]	Taiwan	7,353	22,059	2000-2006	ICD-9	Schizophrenia	8
Lin et al[87]	Taiwan	2,289	16,413	1998-2003	ICD-9	Bipolar disorder	10
Lin et al[88]	Taiwan	5,001	10,002	1998-2003	ICD-9	Schizophrenia, <45 years	9
Maina et al[89]	Italy	309	-	2003-2011	DSM-IV	Bipolar disorder	-
McDermott et al[90]	USA	503	2,083	1990-2003	ICD-9	Schizophrenia or severe mental illness	9
Murray-Thomas et al[91]	UK	232,132	193,920	1997-2001	ICD-10	Schizophrenia, bipolar disorder or major depressive disorder	2
Olfson et al[92]	USA	1,138,853	-	2001-2007	ICD-10	Schizophrenia, 20-64 years	4
Osborn et al[93]	UK	38,824	-	1995-2010	Medical records	Bipolar disorder or severe mental illness, 30-90 years	-
Pratt et al[94]	USA	73	1,107	1981-1994	DSM-III	Major depressive disorder	11
Prieto et al[95]	USA	334	334	1966-1996	DSM-IV	Bipolar disorder	4
Rahman et al[96]	Sweden	6,822	29,832	1998-2002	ICD-7,8,9,10	Major depressive disorder, twin population study	7
Ramsey et al[97]	USA	129	1,339	1981-1982	DSM-III	Bipolar disorder or major depressive disorder	6
Saint Onge et al[98]	USA	548	10,821	1999-2006	ICD	Major depressive disorder	11
Scherrer et al[99]	USA	77,568	214,749	1999-2007	ICD-9	Major depressive disorder, 25-80 years	4
Schoepf & Heun[100]	UK	1,418	14,180	2000-2012	ICD-10	Schizophrenia, inpatients	-
Schoepf et al[101]	UK	621	6,210	2000-2012	ICD-10	Bipolar disorder	-
Shah et al[102]	USA	538	7,103	1988-2006	DSM-III	Major depressive disorder or bipolar disorder, 17-39 years	14
Stewart et al[103]	USA	235	-	NA	ICD-9	Major depressive disorder	-
Surtees et al[104]	UK	3,057	16,592	1996-2008	DSM-IV	Major depressive disorder, 45-80 years	11
Ting et al[105]	China	153	7,682	1996-2008	DSM-IV	Major depressive disorder with diabetes	18
Torniainen et al[106]	Sweden	21,492	214,920	2006-2015	ICD-10	Schizophrenia, 17-65 years	2
Tsai et al[107]	Taiwan	80,569	241,707	1999-2003	ICD-9	Schizophrenia	8
Tsan et al[108]	USA	49,173	-	2002-2009	ICD-9	Schizophrenia	-
van Marwijk et al[109]	The Netherlands	143	139	2002-2003	DSM-IV	Major depressive disorder, >55 years	-
Weeke et al[110]	Denmark	3,795	-	1950-1957; 1969-1977	ICD-8	Bipolar disorder	-
Westman et al[111]	Sweden	17,101	10,631,208	1987-2006	ICD-10	Bipolar disorder	3
Wu et al[112]	Taiwan	16,821	67,284	1999-2010	ICD-9	Bipolar disorder	9
Wu et al[113]	Taiwan	70,225	207,592	1996-2007	ICD-9	Schizophrenia or bipolar disorder	8

SMI – severe mental illness, RDC – Research Diagnostic Criteria

CI: 2.15-4.88, 3 studies) as well as with CVD-related death (HR=2.75, 95% CI: 1.32-5.73, 3 studies).

All significant results were significantly heterogeneous, except for mixed SMI and CVD risk, as well as all the congestive heart failure results. After trim and fill procedure, all results remained unchanged, and Egger test did not show any evidence of publication bias influencing the results (see Table 4 for details).

Quality assessment of included studies

Quality ratings of single studies are presented in Table 5. All studies used clear diagnostic criteria, by design. Among the 27 cross-sectional studies, all except 9 studies had a control group, 5 studies used a matched control sample, 13 studies adjusted analyses for relevant covariates, and all except 6 studies reported cardiovascular risk factors. Among the 65 longitudinal studies, all

Table 3 Meta-analysis of cross-sectional studies: unadjusted and adjusted odds ratios

	Meta-analysis of unadjusted odds ratios								Meta-analysis of covariate adjusted odds ratios							
	No.	No. participants		Unadjusted odds ratios				Hetero-geneity	No.	No. participants		Adjusted odds ratios				Hetero-geneity
Disorder	studies	Patients	Controls	OR	95% CI		p	I^2	studies	Patients	Controls	OR	95% CI		p	I^2
Cardiovascular disease																
Bipolar disorder	4	19,562	1,526,110	**1.73**	**1.11**	**2.71**	**0.02**	91	4	2,640	1,423,135	1.28	0.90	1.80	0.17	52
Major depressive disorder	3	1,577	47,851	**2.08**	**1.51**	**2.88**	**<0.001**	58	7	7,050	43,570	**1.75**	**1.36**	**2.26**	**<0.001**	69
Schizophrenia	10	190,584	4,100,315	1.23	0.92	1.65	0.16	99	5	42,076	3,860,505	1.38	0.93	2.05	0.11	96
Severe mental illnesses	1	146	2,083	1.59	0.87	2.88	0.13	-	-	-	-	-	-	-	-	-
Pooled	14	211,869	7,808,603	**1.59**[a]	**1.32**	**1.91**	**<0.001**	99	11	51,766	5,325,871	**1.53**[e]	**1.27**	**1.83**	**<0.001**	94
Coronary heart disease																
Bipolar disorder	3	19,504	1,524,771	**1.75**	**1.11**	**2.77**	**0.02**	94	1	2,582	1,421,796	0.94	0.79	1.11	0.49	-
Major depressive disorder	1	958	35,691	**2.44**	**2.13**	**2.79**	**<0.0001**	-	3	6,323	41,882	**2.52**	**1.81**	**3.52**	**<0.001**	93
Schizophrenia	8	187,359	4,086,191	1.03	0.85	1.25	0.76	98	1	399	120,044	**1.52**	**1.48**	**1.56**	**<0.001**	-
Severe mental illnesses	1	146	2,083	1.02	0.56	1.83	0.96	-	-		-	-	-	-	-	-
Pooled	8	207,967	4,160,030	**1.80**[b]	**1.62**	**2.00**	**<0.001**	98	5	9,304	1,583,722	**1.51**[f]	**1.47**	**1.55**	**<0.001**	90
Cerebrovascular disease																
Bipolar disorder	3	2,741	1,458,826	**1.68**	**1.07**	**2.63**	**0.03**	47	2	2,582	1,421,796	1.06	0.85	1.31	0.62	0
Major depressive disorder	3	1,577	47,851	**2.24**	**1.33**	**3.79**	**0.003**	81	2	656	349	1.64	0.96	2.78	0.07	72
Schizophrenia	5	41,071	37,77,039	**1.63**	**1.19**	**2.24**	**0.003**	96	3	32,196	2,413,768	**2.05**	**1.59**	**2.64**	**<0.001**	61
Severe mental illnesses	1	146	2,083	1.02	0.56	1.83	0.96	-	-	-	-	-	–	-	-	-
Pooled	10	45,535	5,454,785	**1.63**[c]	**1.31**	**2.02**	**<0.0001**	93	6	35,434	3,835,913	**1.42**[g]	**1.21**	**1.66**	**<0.001**	90
Congestive heart failure																
Bipolar disorder	1	2,582	1,421,796	**1.38**	**1.03**	**1.84**	**0.03**	-	1	2,582	1,421,796	1.11	0.80	1.54	0.53	0
Major depressive disorder	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Schizophrenia	5	40,984	3,743,431	**1.71**	**1.36**	**2.15**	**<0.001**	92	3	41,474	5,708,425	**1.60**	**1.06**	**2.40**	**0.02**	97
Severe mental illnesses	1	146	2,083	1.59	0.87	2.88	0.13	-	-	-	-	-	-	-	-	-
Pooled	6	43,712	5,167,189	**1.57**[d]	**1.32**	**1.87**	**<0.001**	88	4	44,056	7,130,221	1.28[h]	0.99	1.65	0.06	96

Bold values represent significant results

Egger test for bias: [a]2.24, p=0.53; [b]6.41, p=0.03 (Duval & Tweedie trim-and-fill procedure adjusted OR: 1.35, 95% CI: 0.98-1.83); [c]−1.69, p=0.24; [d]−2.39, p=0.15; [e]−1.73, p=0.18; [f]0.17, p=0.93; [g]−2.59, p=0.07; [h]−5.26, p=0.20

Table 4 Meta-analysis of longitudinal studies with publication bias assessment

	Meta-analysis of unadjusted relative risk								Meta-analysis of covariate adjusted hazard ratio							
	No.	No. participants		Unadjusted relative risk				Hetero-geneity	No.	No. participants		Adjusted hazard ratio				Hetero-geneity
Disorder	studies	Patients	Controls	RR	95% CI		p	I^2	studies	Patients	Controls	HR	95% CI		p	I^2
Cardiovascular disease																
Bipolar disorder	12	66,549	9,606,575	**1.50**	**1.28**	**1.75**	**<0.0001**	76	10	91,187	6,967,728	**1.57**	**1.28**	**1.93**	**<0.0001**	91
Major depressive disorder	13	328,431	800,718	1.29	0.92	1.81	0.14	99	18	282,621	682,045	**1.72**	**1.48**	**2.00**	**<0.0001**	67
Schizophrenia	16	361294	16,096,125	**1.21**	**1.006**	**1.45**	**0.04**	98	14	296,778	7,176,374	**1.95**	**1.41**	**2.70**	**<0.0001**	99
Severe mental illnesses	2	874022	52,709,922	**2.44**	**1.13**	**5.25**	**0.02**	74	3	798	31,724	**3.24**	**2.15**	**4.88**	**<0.0001**	0
Pooled	33	1,630,296	76,031,192	**1.38**[a]	**1.23**	**1.54**	**<0.0001**	98	31	671,384	14,335,203	**1.78**[g]	**1.60**	**1.98**	**<0.0001**	95
Coronary heart disease																
Bipolar disorder	4	25,286	9,200,196	**1.95**	**1.20**	**3.17**	**0.007**	96	4	19,129	6,789,683	1.16	0.76	1.78	0.49	87
Major depressive disorder	6	14,3671	515,187	1.15	0.71	1.85	0.57	98	9	99,028	392,210	**1.63**	**1.33**	**2.00**	**<0.0001**	80
Schizophrenia	8	169,507	15,446,625	0.93	0.81	1.08	0.33	87	5	75,860	6,348,965	**1.59**	**1.08**	**2.35**	**0.02**	95
Severe mental illnesses	1	873,898	52,693,301	**1.80**	**1.74**	**1.86**	**<0.0001**	-	-	-	-	**-**	**-**	**-**	**-**	-
Pooled	17	1,212,362	75,235,865	**1.75**[b]	**1.69**	**1.80**	**<0.0001**	99	18	194,017	13,530,858	**1.54**[h]	**1.30**	**1.82**	**<0.0001**	92
Cerebrovascular disease																
Bipolar disorder	6	32,898	9,082,511	**1.92**	**1.13**	**3.26**	**0.02**	97	4	23,831	6,649,375	1.60	0.99	2.57	0.05	85
Major depressive disorder	4	8,121	41,665	**1.55**	**1.02**	**2.35**	**0.04**	77	3	7,046	38,853	**2.04**	**1.05**	**3.96**	**0.04**	74
Schizophrenia	8	243,254	15,475,608	**1.48**	**1.21**	**1.81**	**<0.0001**	96	5	157,964	6,425,336	**1.57**	**1.09**	**2.25**	**0.02**	95
Severe mental illnesses	-	-	-	**-**	**-**	**-**	**-**	-	-	-	-	**-**	**-**	**-**	**-**	-
Pooled	17	284,273	22,187,932	**1.53**[c]	**1.29**	**1.82**	**<0.0001**	96	11	188,841	13,113,564	**1.64**[i]	**1.26**	**2.14**	**<0.0001**	90

Table 4 Meta-analysis of longitudinal studies with publication bias assessment *(continued)*

	Meta-analysis of unadjusted relative risk								Meta-analysis of covariate adjusted hazard ratio							
	No.	No. participants		Unadjusted relative risk				Hetero-geneity	No.	No. participants		Adjusted hazard ratio				Hetero-geneity
Disorder	studies	Patients	Controls	RR	95% CI		p	I^2	studies	Patients	Controls	HR	95% CI		p	I^2
Congestive heart failure																
Bipolar disorder	1	6,215	2,411,852	**11.52**	**9.37**	**23.14**	**<0.0001**	-	1	58	1,339	**2.27**	**1.49**	**3.45**	**<0.0001**	0
Major depressive disorder	-	-	-	-	-	-	-	-	2	351	40,339	**2.02**	**1.48**	**2.75**	**<0.0001**	0
Schizophrenia	3	85,290	9,050,272	**1.80**	**1.15**	**2.79**	**0.009**	84	-	-	-	-	-	-	-	-
Severe mental illnesses	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pooled	4	91,505	11,459,059	**8.24**[d]	**6.84**	**9.94**	**<0.0001**	99	2	409	41,678	**2.10**	**1.64**	**2.70**	**<0.0001**	0
Peripheral vascular disease																
Bipolar disorder	1	6,215	2,411,852	**3.44**	**2.70**	**4.38**	**<0.0001**	-	-	-	-	-	-	-	-	-
Major depressive disorder	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Schizophrenia	3	85,290	9,050,272	0.96	0.43	2.17	0.92	93	-	-	-	-	-	-	-	-
Severe mental illnesses	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pooled	3	91,505	11,402,868	**3.11**[e]	**2.46**	**3.91**	**<0.0001**	98	-	-	-	-	-	-	-	-
Death due to cardiovascular disease																
Bipolar disorder	5	37,144	356,298	1.31	0.94	1.83	0.11	75	3	17,420	162,231	**1.65**	**1.10**	**2.47**	**0.02**	88
Major depressive disorder	5	18,112	283,746	1.30	0.59	2.86	0.51	99	7	183,297	282,014	**1.63**	**1.25**	**2.13**	**<0.0001**	81
Schizophrenia	9	53,779	7,179,454	1.26	0.84	1.90	0.27	96	9	152,690	6,872,808	**2.45**	**1.64**	**3.65**	**<0.0001**	96
Severe mental illnesses	3	874,146	52,714,134	**2.99**	**2.84**	**3.13**	**<0.0001**	0	3	798	31,724	**2.75**	**1.32**	**5.73**	**0.007**	75
Pooled	18	1,151,181	60,287,400	**2.89**[f]	**2.75**	**3.03**	**<0.0001**	99	16	353,407	7,317,053	**1.85**[j]	**1.53**	**2.24**	**<0.0001**	95

Egger test for bias: [a] −0.44, p=0.80; [b] −1.24, p=0.71; [c] 0.03, p=0.96; [d] 8.07, p=0.37; [e] 3.08, p=0.60; [f] −3.66, p=0.20; [g] 1.16, p=0.31; [h] −0.13, p=0.92; [i] 2.57, p=0.07; [j] −1.19, p=0.43

Table 5 Quality assessment of included studies

Study	Clear diagnostic criteria	Control group	Matched controls	Coavariate adjusted analyses	Reported cardiovascular risk factors at baseline	Follow-up at least 5 years
Cross-sectional studies						
Beyer et al[22]	Y	N	N	N	Y	N
Bresee et al[23]	Y	Y	N	Y	Y	N
Bresee et al[24]	Y	Y	N	Y	Y	N
Chen et al[25]	Y	N	N	N	Y	N
Curkendall et al[26]	Y	Y	Y	Y	Y	N
Devantier et al[27]	Y	Y	Y	N	Y	N
Hagg et al[28]	Y	N	N	N	Y	N
Herbst et al[29]	Y	Y	N	Y	N	N
Huang et al[30]	Y	Y	N	Y	Y	N
Hyde et al[31]	Y	N	N	N	Y	N
Kilbourne et al[32]	Y	N	N	N	Y	N
Kilbourne et al[33]	Y	Y	N	Y	Y	N
Lindegard[34]	Y	Y	N	N	N	N
Maina et al[35]	Y	N	N	N	Y	N
Morden et al[36]	Y	Y	Y	Y	Y	N
Munoli et al[37]	Y	N	N	N	Y	N
Nielsen et al[38]	Y	N	N	N	Y	N
Niranjan et al[39]	Y	Y	N	Y	Y	N
Oreski et al[40]	Y	Y	N	N	Y	N
Prieto et al[41]	Y	N	N	N	Y	N
Scherrer et al[42]	Y	Y	N	N	N	N
Scott et al[43]	Y	Y	N	Y	N	N
Shen et al[44]	Y	Y	Y	Y	Y	N
Smith et al[45]	Y	Y	N	Y	Y	N
Smith et al[46]	Y	Y	N	Y	Y	N
Swain et al[47]	Y	Y	N	Y	N	N
Zilkens et al[48]	Y	Y	Y	N	N	N
Longitudinal studies						
Almeida et al[49]	Y	Y	Y	N	Y	Y
Bremmer et al[50]	Y	Y	Y	N	Y	Y
Butnoriene et al[51]	Y	Y	Y	N	N	Y
Callaghan et al[52]	Y	Y	Y	Y	Y	N
Callaghan et al[53]	Y	Y	Y	Y	Y	N
Carney et al[54]	Y	Y	Y	N	Y	N
Chen et al[55]	Y	Y	Y	Y	Y	Y
Clouse et al[56]	Y	Y	Y	N	Y	Y
Coryell et al[57]	Y	Y	N	N	N	Y
Crump et al[58]	Y	Y	Y	N	N	Y
Crump et al[59]	Y	Y	Y	N	Y	Y
Davis et al[60]	Y	Y	Y	N	Y	N
Davydow et al[61]	Y	Y	Y	N	N	Y

Table 5 Quality assessment of included studies *(continued)*

Study	Clear diagnostic criteria	Control group	Matched controls	Coavariate adjusted analyses	Reported cardiovascular risk factors at baseline	Follow-up at least 5 years
Enger et al[62]	Y	Y	Y	Y	Y	N
Fiedorowicz et al[63]	Y	Y	Y	N	Y	Y
Filik et al[64]	Y	Y	Y	N	Y	N
Fors et al[65]	Y	Y	Y	Y	N	Y
Gasse et al[66]	Y	Y	Y	N	N	Y
Goldstein et al[67]	Y	Y	Y	N	Y	N
Healy et al[68]	Y	Y	N	N	N	Y
Hendrie et al[69]	Y	Y	Y	N	Y	Y
Hou et al[70]	Y	Y	N	N	N	Y
Hsieh et al[71]	Y	Y	N	N	N	N
Huang et al[72]	Y	Y	Y	Y	Y	Y
Ifteni et al[73]	Y	Y	N	N	N	Y
Jakobsen et al[74]	Y	Y	Y	Y	N	Y
Janszky et al[75]	Y	Y	Y	N	Y	Y
Jokinen & Nordstrom et al[76]	Y	Y	N	N	N	Y
Joukamaa et al[77]	Y	Y	Y	N	N	Y
Kendler et al[78]	Y	Y	Y	N	N	Y
Kiviniemi et al[79]	Y	Y	N	N	N	Y
Lahti et al[80]	Y	Y	Y	N	Y	Y
Lan et al[81]	Y	Y	N	N	Y	Y
Laursen et al[82]	Y	Y	Y	N	N	Y
Laursen et al[83]	Y	Y	Y	N	N	Y
Lemogne et al[84]	Y	Y	Y	N	Y	Y
Li et al[85]	Y	Y	Y	Y	Y	Y
Lin et al[86]	Y	Y	Y	Y	Y	Y
Lin et al[87]	Y	Y	Y	Y	Y	Y
Lin et al[88]	Y	Y	Y	Y	Y	Y
Maina et al[89]	Y	Y	N	N	N	Y
McDermott et al[90]	Y	Y	Y	N	N	Y
Murray-Thomas et al[91]	Y	Y	Y	N	N	N
Olfson et al[92]	Y	Y	N	N	N	Y
Osborn et al[93]	Y	Y	Y	N	Y	Y
Pratt et al[94]	Y	Y	Y	N	Y	Y
Prieto et al[95]	Y	Y	Y	Y	Y	Y
Rahman et al[96]	Y	Y	Y	Y	Y	N
Ramsey et al[97]	Y	Y	Y	N	Y	Y
Saint Onge et al[98]	Y	Y	Y	N	Y	Y
Scherrer et al[99]	Y	Y	Y	N	Y	Y
Schoepf & Heun[100]	Y	Y	Y	Y	N	Y
Schoepf et al[101]	Y	Y	Y	Y	Y	Y
Shah et al[102]	Y	Y	Y	N	Y	Y
Stewart et al[103]	Y	Y	N	N	N	Y
Surtees et al[104]	Y	Y	Y	N	N	Y

Table 5 Quality assessment of included studies *(continued)*

Study	Clear diagnostic criteria	Control group	Matched controls	Coavariate adjusted analyses	Reported cardiovascular risk factors at baseline	Follow-up at least 5 years
Ting et al[105]	Y	Y	Y	N	Y	Y
Torniainen et al[106]	Y	Y	Y	Y	N	Y
Tsai et al[107]	Y	Y	Y	Y	Y	Y
Tsan et al[108]	Y	Y	N	N	Y	Y
van Marwijk et al[109]	Y	Y	Y	Y	Y	N
Weeke et al[110]	Y	Y	N	N	N	N
Westman et al[111]	Y	Y	Y	N	N	Y
Wu et al[112]	Y	Y	Y	Y	Y	Y
Wu et al[113]	Y	Y	Y	N	Y	Y

N – no, Y – yes

Table 6 Prevalence and incidence of cardiovascular disease (CVD) in severe mental illness stratified by region

Regional strata	Analysis details	Prevalence of CVD	Incidence of CVD	Risk ratios for incident CVD	Adjusted hazard ratios for incident CVD
Asia	Pooled estimate, % (95% CI)	5.4 (4.3-6.7)	2.6 (1.9-3.6)	1.63 (1.31-2.04)	1.75 (1.38-2.22)
	p value	<0.0001	<0.0001	<0.0001	<0.0001
	Heterogeneity, I^2 (p value)	98 (<0.0001)	100 (<0.0001)	99 (<0.0001)	96 (<0.0001)
	No. comparisons	8	12	9	10
Europe	Pooled estimate, % (95% CI)	9.7 (6.5-14.2)	3.4 (2.2-5.3)	1.17 (0.96-1.42)	1.88 (1.44-2.46)
	p value	<0.0001	<0.0001	0.11	<0.0001
	Heterogeneity, I^2 (p value)	97 (<0.0001)	100 (<0.0001)	97 (<0.0001)	96 (<0.0001)
	No. comparisons	9	35	20	22
North America	Pooled estimate, % (95% CI)	14.6 (12.0-17.7)	4.6 (3.4-6.2)	1.39 (0.91-2.12)	1.88 (1.62-2.19)
	p value	<0.0001	<0.0001	0.13	<0.0001
	Heterogeneity, I^2 (p value)	97 (<0.0001)	100 (<0.0001)	97 (<0.0001)	62 (0.003)
	No. comparisons	17	15	11	11
Oceania	Pooled estimate, % (95% CI)	20.6 (10.9-35.4)	26.3 (24.1-28.6)	1.52 (1.40-1.66)	1.58 (1.41-1.78)
	p value	<0.0001	<0.0001	<0.0001	<0.0001
	Heterogeneity, I^2 (p value)	97 (<0.0001)	100 (<0.0001)	0 (0.72)	0 (0.84)
	No. comparisons	4	3	3	3
	p (difference between regions)	<0.0001	<0.0001	0.08	0.29

had a control group, which was matched in all but 12 studies, only 19 studies adjusted for covariates, 38 studies reported on cardiovascular risk factors, and all except 12 studies had a follow-up of at least 5 years.

Regional CVD prevalence, incidence and longitudinal risk

Raw CVD prevalence and incidence rates consistently increased from Asia, through Europe and North America, to Oceania (Asia: 5.4% and 2.6%; Europe: 9.7% and 3.4%; North America: 14.6% and 4.6%; Oceania: 20.6% and 26.3%; p<0.0001 for both prevalence and incidence). However, when comparing CVD risk in SMI patients in each region with their respective control groups, there was no statistically significant difference anymore across regions, with both RRs and adjusted HRs showing comparably increased CVD incidence risk in the SMI population (RRs ranging from 1.17 in Europe to 1.63 in Asia, p=0.08; and HRs ranging from 1.58 in Oceania to 1.88 in both Europe and North America, p=0.29) (Table 6). There were insufficient numbers of studies to perform this analysis for adjusted ORs

regarding prevalence rates across regions, or for adjusted ORs, RRs or HRs pertaining to specific CVD subgroups.

Meta-regression

Due to heterogeneous or partial reporting of possible moderator variables in the included studies, all meta-regression analyses were based on a much reduced number of studies. Hence, all analyses were less powered in comparison with the large sets of data used for cross-sectional prevalence and longitudinal incidence analyses. Nonetheless, CVD incidence increased significantly with a higher percentage of patients using antipsychotics (12 studies; β=0.04, 95% CI: 0.01-0.08, p=0.008), higher baseline body mass index in patients vs. controls (6 studies; β=0.24, 95% CI: 0.06-0.42, p=0.008), and higher CVD prevalence at baseline in patients vs. controls (7 studies; β=0.07, 95% CI: 0.01-0.14, p=0.03). CVD prevalence increased in more recent studies (38 studies; β=0.07, 95% CI: 0.02-0.12, p=0.007), whereas the same was not true for CVD incidence (65 studies; β=–0.02, 95% CI=–0.07 to 0.01, p=0.21).

DISCUSSION

To our knowledge, this is the first large scale meta-analysis providing comprehensive quantitative data on the prevalence and incidence of CVD in people with SMI, including both pooled data and comparisons across CVD and SMI diagnostic subgroups. Our results establish that approximately 10% of people with SMI with a mean age of 50 years have at least one comorbid CVD. Moreover, our longitudinal analysis documents a 3.6% incidence rate of CVD during a median of 8.4 years of follow-up. Patients with SMI show a 53% higher risk for having CVD, a 78% higher risk for developing CVD, and an 85% higher risk of death from CVD compared to the regionally matched general population.

This study provides a worldwide epidemiologic representation of CVD prevalence and incidence rates in SMI, reporting the lowest absolute prevalence and incidence in Asia, increasing through Europe and North America, and reaching the highest levels in Oceania. However, in analyses with sufficient numbers of available studies, neither RRs nor adjusted HRs indicated significantly different CVD incidence risk across regions, meaning that SMI patients are at an increased risk across the world and that CVD risk-reducing interventions in SMI are needed with the same urgency across all regions of the world. Moreover, while the prevalence and incidence of each CVD in people with SMI show some minor variations, people with major depressive disorder, bipolar disorder and schizophrenia are clearly all at an increased risk of CVD-related deaths compared to population-stratified controls, calling for urgent action.

We were able to identify some important and actionable moderators of increased CVD risk, including antipsychotic use, elevated body mass index and elevated baseline CVD. Based on these results, it is imperative that clinicians: a) only utilize antipsychotics, particularly for non-psychotic conditions, when alternative treatment options with lower CVD risk potential have been tried sufficiently; and b) screen for and manage emerging and existing CVDs as well as their risk factors, including weight gain and elevated body mass index. Our data, adding to research demonstrating a significantly higher prevalence of metabolic syndrome in people with SMI compared to controls[114], clearly suggest there is an urgent need to prevent and manage CVD risk in this population.

Our results demonstrating a higher CVD prevalence in SMI populations versus controls in more recent studies are also concerning, as they support accumulating data indicating that secondary prevention has been much less successful in the SMI population that in the general population, leading to a widening of the mortality gap in recent years[49,115,116]. Our findings confirm prior reports that antipsychotic medication use is associated with higher CVD risk[13,117,118]. However, due to limitations in the published data, we were unable to explore variations in CVD risk profiles between different antipsychotic medications[13,117-120]. Previous research has suggested that the highest cardio-metabolic risks are associated with clozapine and olanzapine, whilst the lowest risk is with aripiprazole, ziprasidone, lurasidone, amisulpride and high potency typical antipsychotics[13,117-122]. However, in this context it is also important to note that antipsychotic medications can decrease CVD-related mortality, as reported for example in Finnish[79] and Swedish[123] national database studies, that are highly generalizable. These data underscore that symptom control and functional improvement benefit both psychiatric and overall health, as severe psychiatric illness negatively affects lifestyle behaviors, medical care seeking and adherence to medical treatments. Thus, benefits of improved psychiatric status with antipsychotics and other psychotropic agents need to be carefully weighed against their potential for elevated cardiometabolic risk, which differs across available agents[13,117].

Since antipsychotic medication use moderates CVD risk and since antipsychotics are increasingly used as first line treatments for much more prevalent non-psychotic conditions, including bipolar disorder[124] and major depressive disorder with suboptimal response to antidepressant treatment[125], the pool of people at an increased CVD risk is greatly enlarged. Therefore, research on the underlying mechanisms for the increased CVD risk after pharmacotherapy initiation is even more urgently needed to develop more effective and targeted preventive and interventional treatments. Studies should also examine whether different clinical subtypes of depression (i.e., melancholic, psychotic, atypical or undifferentiated) and bipolar disorder (e.g., type 1 or 2, cyclothymic disorder), certain mood states (manic, depressive, mixed or euthymic), or different antipsychotics, antidepressants or mood stabilizers[13] significantly moderate CVD risk.

Furthermore, the pathophysiology underlying the association between SMI and CVD risk is complex and not well understood, clearly requiring further investigation. Emerging

evidence suggests that SMI and CVD share pathophysiological features, including hypothalamic-pituitary-adrenal and mitochondrial dysfunction, peripheral immune activation, neuroinflammation, oxidative and nitrosative stress, as well as common genetic links and epigenetic interactions[126]. However, since these different mechanisms probably interact, research that integrates these pathways is urgently needed. Beyond mechanistic evaluations, such studies also need to investigate the general and specific effects of physical health improvements on SMI outcomes.

Future research should also investigate optimal monitoring regimens across stratified patient subgroups as well as the most effective timing and efficacy of primary, secondary and tertiary preventive interventions[120,127]. In this regard, studies should comprehensively assess relevant moderator and mediator variables of CVD risk, including type and duration of specific psychotropic medications use, physical activity (including using passive monitoring via actimetry or mobile phone technology), diet, smoking, body mass index, personal and family history of CVD, in order to identify subgroups of patients who may require different monitoring and or interventions schemes. Long-term follow-up studies are also required to accurately document the emergence of more distal physical and mental health as well as health economic outcomes in relationship to the early identification and management of CVD risk factors and manifest CVD conditions in people with SMI.

Finally, since people with SMI engage in unhealthy lifestyle and often take psychotropic medication for extensive periods, long-term follow-up studies are needed that assess whether current predictor models based on the magnitude of traditional CVD risk factor effects observed in the general population apply or need to be adjusted for the SMI population[93], in whom CVD risk factors also emerge at a far earlier age[117,128].

While this is the most comprehensive meta-analysis of CVD risk in people with SMI conducted to date, we acknowledge several limitations that are largely related to factors in the primary data. First, lifestyle behavior information (e.g., physical activity) was inadequately reported, precluding meta-analytic assessment of these important factors as moderating or mediating variables. People with SMI are less likely than the general population to engage in physical activity and have higher levels of sedentary behaviour[129], smoke more[130], consume diets that are high in saturated fats and refined sugars, while being low in fruit and vegetables[131], all factors relevant for CVD risk. Second, variables such as clinical subtypes of major depressive disorder and bipolar disorder, negative symptom severity in people with schizophrenia, and concomitant or previous use of specific antipsychotics, antidepressants and mood stabilizers were not reported or were insufficiently reported or controlled for in most available studies. Third, as expected when combining observational data[132], many of the results were moderately to highly heterogeneous. However, in accordance with the MOOSE guidelines[133], we conducted meta-regression analyses and were able to explain some of the observed heterogeneity. In addition, all of our results remained robust after adjustment for potential publication bias with the trim and fill analysis.

In conclusion, SMIs pooled together were significantly associated in cross-sectional studies with CVD, coronary heart disease, cerebrovascular disease and CVD-related death. Additionally, in longitudinal studies, each specific diagnostic SMI group was significantly associated with CVD and CVD-related death. Furthermore, schizophrenia was associated with coronary heart disease and cerebrovascular disease, while bipolar disorder was associated with congestive heart failure, and major depressive disorder was associated with coronary heart disease, cerebrovascular disease, and congestive heart failure.

Importantly, our data confirm that CVDs are associated with an increased risk of mortality in people with SMI, which to a large part explains the shortened life expectancy of people with SMI compared to the general population[2,4,5]. Furthermore, we showed geographical variations in raw CVD prevalence and incidence risk in SMI populations, but no significant regional variance in the difference in CVD risk compared to the region-specific general population. Finally, the fact that antipsychotic use, higher body mass index and baseline CVD significantly increased the risk for CVD morbidity and mortality underscores the urgent need to limit antipsychotic use to those populations truly requiring them, choosing the lowest risk antipsychotic agents first in the treatment algorithm, screening all SMI patients regularly for CVD risk factors and conditions, and addressing any identified abnormalities aggressively.

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Has the rising placebo response impacted antidepressant clinical trial outcome? Data from the US Food and Drug Administration 1987-2013

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More than fifteen years ago, it was noted that the failure rate of antidepressant clinical trials was high, and such negative outcomes were thought to be related to the increasing magnitude of placebo response. However, there is considerable debate regarding this phenomenon and its relationship to outcomes in more recent antidepressant clinical trials. To investigate this, we accessed the US Food and Drug Administration (FDA) reviews for sixteen antidepressants (85 trials, 115 trial arms, 23,109 patients) approved between 1987 and 2013. We calculated the magnitude of placebo and antidepressant responses, antidepressant-placebo differences, as well as the effect sizes and success rates, and compared these measures over time. Exploratory analysis investigated potential changes in trial design and conduct over time. As expected, the magnitude of placebo response has steadily grown in the past 30 years, increasing since 2000 by 6.4% ($r=0.46$, $p<0.001$). Contrary to expectations, a similar increase has occurred in the magnitude of antidepressant response (6.0%, $r=0.37$, $p<0.001$). Thus, the effect sizes (0.30 vs. 0.29, $p=0.42$) and the magnitude of antidepressant-placebo differences (10.5% vs. 10.3%, $p=0.37$) have remained statistically equivalent. Furthermore, the frequency of positive trial arms has gone up in the past 15 years (from 47.8% to 63.8%), but this difference in frequency has not reached statistical significance. Trial design features that were previously associated with a possible lower magnitude of placebo response were not implemented, and their relationship to the magnitude of placebo response could not be replicated. Of the 34 recent trials, two implemented enhanced interview techniques, but both of them were unsuccessful. The results of this study suggest that the relationship between the magnitude of placebo response and the outcome of antidepressant clinical trials is weak at best. These data further indicate that antidepressant-placebo differences are about the same for all of the sixteen antidepressants approved by the FDA in the past thirty years.

Key words: Antidepressants, clinical trials, placebo response, antidepressant-placebo difference, effect size, success rate, enhanced interview techniques

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Fifteen years following the advent of several new antidepressants in the mid-1980s, it became evident that the "success" rate of antidepressant clinical trials was low; less than 50% of trials demonstrated statistical superiority for antidepressants over placebo[1,2]. Following Walsh et al's finding[3] of a rising placebo response, it was assumed that the clinical trial failure rate was related to this phenomenon[4].

Investigators have attempted to determine if the increasing placebo response in antidepressant clinical trials observed by Walsh et al[3] continues to this day. Meta-analytic reviews of antidepressant clinical trials[5,6], or psychotropic trials in general[7], as well as patient-level data in trials for major depression[8] have converged in showing that the placebo response has continued to grow over the past 15 years. Furthermore, Khin et al[9] conducted an internal review for the US Food and Drug Administration (FDA), which seemed to confirm that the magnitude of placebo response was continuing to increase. Although this group of investigators had access to specific data, they did not identify the antidepressant trials that they reviewed.

One discordant voice is a study published by Furukawa et al[10], which contradicts the observation of an increase in placebo response rate in more recent trials. These investigators conducted a review of 252 depression studies, examining the rate of therapeutic response to placebo using various dependent measures. They surmised that the proportion of placebo responders, defined as patients with 50% or greater reduction in depressive symptoms, had remained the same after 1991. However, no mechanism was offered to explain this shift from a growing placebo response to a steady one[11], nor did the authors evaluate the effect of such a phenomenon on the outcome of antidepressant clinical trials.

Concern over the impact of increasing placebo response on antidepressant clinical trials has fueled a line of inquiry looking for variables predicting higher rates of placebo response, based on *post-hoc* analyses[12,13]. Several hypotheses, such as the idea that more severely depressed patients might be relatively non-responsive to placebo, have been proposed on the basis of associative observations from these analyses[14,15]. However, prospectively selecting more severely depressed patients for antidepressant clinical trials has neither resulted in a reduction in magnitude of the placebo response nor in enhanced antidepressant-placebo differences[16].

Research has illuminated other possible variables, such as the flexible dosing of the investigational antidepressant, potentially showing a relationship to reduction of placebo response[17]. This flexible dosing schedule has been suggested for use in antidepressant clinical trials but, as of now, not fully implemented. Furthermore, retrospective analysis of earlier trials has found that placebo response is higher in trials of longer duration[18] compared to shorter ones, although this phenomenon has not been tested prospectively.

Another hypothesis has been that the magnitude of placebo response and its variability was related to the low reliability among clinicians assessing depressed patients[19-21]. It was then recommended that patient sessions should be audio- or video-taped and audited by a centralized group of specifically trained raters to increase reliability. This type of enhanced interviewing technique has been implemented, although its effects on the outcome of more recent antidepressant trials remain questionable[22,23].

What stands out from these studies aiming to elucidate factors possibly mitigating placebo response in antidepressant clinical trials is that such factors are elusive and complex, and that their predictive ability varies across different contexts[24]. This lack of fruitfulness in pinpointing what may moderate placebo response in antidepressant clinical trials has led to a form of therapeutic nihilism.

In fact, following the observation that antidepressant efficacy in clinical trials appears more robust when severely depressed patients are included, and that antidepressants do not reliably perform better than placebo, criticism has been raised regarding antidepressant's overall therapeutic efficacy and ability to treat the more mildly depressed population[25-28]. However, other investigators do not agree with this view, contending that the magnitude of the antidepressant-placebo response in clinical trials does not reflect the actual therapeutic efficacy of antidepressants in ordinary clinical practice[29-32].

However, in the midst of this investigative history, it has become obvious that expectations for antidepressant effect have changed as use of psychiatric medications has increased exponentially in the past 30 years[33]. For example, currently one in six adults in the US are reported to have taken a psychiatric medication (primarily antidepressants) in the past year[34], potentially indicating high regards for antidepressant efficacy.

This observation of a potential increase in expectations for antidepressants has given credence to the theory that placebo response has increased due to the heightened expectations of clinicians and patients. Specifically, studies investigating this theory[35-37] showed that the higher the risk of receiving placebo in an antidepressant clinical trial, the lower was the magnitude of placebo response. The caveat is that this theory has not been fully tested prospectively.

Given the possibility that the magnitude of placebo response continued to increase in recent antidepressant clinical trials and may have impacted the outcome of these trials, we conducted the present study. We evaluated data from the medical and statistical reviews of sixteen antidepressant programs approved by the FDA from 1987 to 2013, comparing the earlier antidepressant clinical trials to more recent ones.

We decided to conduct this analysis using the FDA clinical trial database[38] for several reasons. First, these data are not influenced by publication/investigator/analysis bias, while these selectivity biases are common in the published literature[39,40]. Second, findings are verified at the source by the FDA staff in order to authenticate them. Third, reviews conducted by the FDA more often provide an analysis that includes the magnitude of antidepressant response as well as the magnitude of placebo response, and clearly report the statistical analysis used for efficacy approval of the antidepressant. Last, this database is very large, with patient numbers in the tens of thousands, allowing to observe patterns with more confidence.

We hypothesized that the magnitude of placebo response has continued to increase in more recent antidepressant clinical trials, and that such an increase in placebo response may have reduced the frequency of successful trials. Also, we theorized that an increase in placebo response would correspond to a decrease in the antidepressant-placebo differences and observed effect sizes of more recent antidepressant clinical trials. Lastly, we explored if any of the research design features or enhanced interview techniques proposed to help contain placebo response have been implemented, and if so, with what results.

METHODS

Selection of trials

For the purpose of determining if the pattern of increasing placebo response continued in antidepressant clinical trials following Walsh et al's observation[3], we formulated groups based on this point in time. We assigned each trial for an investigational antidepressant to the year that the antidepressant was approved, and grouped trials into pre-2000 and post-2000 ones.

We included only acute, parallel-group, double-blind, placebo-controlled trials for investigational antidepressants approved after registering a new drug application (NDA) program with the FDA. Trials were included if they enrolled adult patients with a primary diagnosis of major depressive disorder.

Data from treatment arms evaluating active comparator antidepressants (approved antidepressants not under investigation) were excluded from this analysis, due to the fact that the focus of this examination was to characterize new antidepressants in the process of gaining approval, not performance of established antidepressants.

In addition, we excluded data from treatment arms of investigational antidepressants at dosing levels not approved by the FDA, as shown in product labeling. Therefore, we examined only the clinical trial data from arms with doses expected to guide approved use of the investigational antidepressant.

We excluded depression trials enrolling only geriatric (>65 years old) patients, children (<18 years old) and inpatients, as well as relapse prevention or maintenance studies, as it is not possible to draw comparisons between trials studying unique populations or with confounding differences in experimental design.

Trials included and excluded in this analysis

After review of the FDA database for NDA registrations approved between 1987 and 2013, we identified a total of

sixteen adult depression programs for inclusion in the analysis. The investigational antidepressants (with year of approval) were: fluoxetine hydrochloride (1987), sertraline hydrochloride (1991), paroxetine hydrochloride (1992), venlafaxine hydrochloride (1993), nefazodone hydrochloride (1994), mirtazapine (1996), bupropion hydrochloride SR (1996), venlafaxine hydrochloride ER (1997), citalopram (1998), escitalopram oxalate (2002), duloxetine hydrochloride (2002), desvenlafaxine succinate (2008), trazodone hydrochloride ER (2010), vilazodone hydrochloride (2011), levomilnacipran hydrochloride (2013) and vortioxetine hydrobromide (2013).

These programs comprised a total of 125 efficacy evaluation trials. We excluded 40 trials after applying our selection criteria: six were conducted in a geriatric population, 22 were uncontrolled, four were carried out in inpatients, four had a relapse prevention design, and four used doses not approved by the FDA. Thus, 85 registration trials were included in this analysis.

These 85 trials had 172 treatment arms: 33 were active comparators and 24 utilized a dose of the investigational antidepressant not approved by the FDA. After excluding these 57 arms, 115 active treatment arms of investigational antidepressants at approved doses remained for analysis.

Data analysis

The medical and statistical reviews conducted by the FDA contain the published results of efficacy analysis along with the treatment group raw baseline and change scores on the primary efficacy measure when available. We encountered alternative statistical methods for handling missing data from patient dropout in the reporting and analysis of these efficacy data. These methods included observed cases analysis, analysis of covariance, and last observation carried forward (LOCF). Since data from LOCF analysis were available for all of the trials, we decided to use data (primary efficacy measure scores, p values, and patient numbers) from these LOCF statistical computation tables.

We decided to calculate percent symptom reduction as our measure of response magnitude. We divided the mean change score reported in the FDA reviews by the mean baseline score and multiplied by −100 to get a percent symptom reduction that takes into account variation in baseline and different measurement scales. This measure was calculated for placebo and antidepressant treatment groups separately.

We calculated the average antidepressant-placebo difference, taken by subtracting the placebo percent symptom reduction from the antidepressant percent symptom reduction for each trial arm. In instances where placebo had a greater percent symptom reduction than antidepressant, this measure would be negative.

Success of a treatment arm was defined as it is in the FDA reviews, with a p value threshold of 0.05 for endpoint analysis of the primary efficacy measure.

We calculated effect sizes for individual treatment arm comparisons using Hedges' g formula. This procedure has been used in previous analyses of antidepressant clinical trials[39,41]. As noted in Turner et al's paper[39], the formula for calculation of Hedges' g requires baseline scores, change scores and confidence intervals, as well as number of patients to generate t scores. NDA packets do not reliably report these data in full, and therefore we followed the statistical workaround method outlined in the supplement to Turner's paper[42], using the inverse t score function in Microsoft Excel. Precise p values and degrees of freedom are imputed into the function to calculate a t score, which can be transformed to Hedges' g using a specific equation. Hedges' g effect size relies on number of patients and therefore is susceptible to sample size error. We used an appropriate correction to mitigate this risk.

Corrected Hedges' g scores were calculated for each trial arm. We examined effect sizes for trial arms as opposed to means for the trial overall, because the FDA evaluates efficacy for trial arms separately and uses these individual comparisons to support efficacy claims. Since the FDA approval process considers these individual comparisons, we wanted to examine individual treatment arm effects sizes both to retain the variability of signal detection among differing dose levels as well as to replicate the data handling of the FDA approval process. To generate a mean effect size for the two groups of pre-2000 and post-2000, we weighted the corrected effect size by the degrees of freedom to further account for sample size error.

All statistics were performed with IBM Statistical Package for Social Sciences (SPSS). Independent sample t tests were used to compare means from older antidepressant trial arms to the more recent ones, to evaluate if any significant changes had occurred in the distribution of scores from outcome measures. Correlations between year of new drug approval and percent symptom reduction, and between year of new drug approval and mean program effect size, were calculated using Pearson's coefficient.

We calculated frequency of trial design characteristics, including duration ($\geq$8 weeks and $<$8 weeks), number of trial arms (2 arms or $\geq$3 arms), and dosing schedule (fixed or flexible). We computed percentages of trials using either category of design feature and used chi-square analysis of proportions to explore any evidence of systematic implementation.

Statistical analysis of the results of trials using enhanced interview assessment techniques was not possible because only two (vortioxetine 317 and levomilnacipran MD-02) recent trials out of 34 used such techniques.

RESULTS

Tables 1 and 2 report the program/trial essential characteristics. Prior to 2000, there were nine antidepressant NDA programs, contributing 51 trials and 67 active treatment arms from efficacy tables that met our inclusion/exclusion criteria. The seven programs approved after 2000 supplied 34 trials and 48 active treatment arms for analysis. Four (6.0%) of the treatment arms in pre-2000 trials and 13 (27.1%) of the treatment

Table 1 Characteristics of 51 clinical trials for the approval of nine antidepressants from 1987 to 2000

				Placebo			Investigational antidepressant				
Protocol number	Dosing schedule	Duration (weeks)	Primary efficacy measure	No. patients	Baseline/change score on primary efficacy measure	Percent response	No. patients	Baseline/change score on primary efficacy measure	Percent response	p value for efficacy calculation	Effect size (Hedges' g)
Fluoxetine (1987)											
19	Flexible	4	HAM-D	24	28.2/−5.5	19.5	22	**28.6/−12.5**	**43.7**	0.011	0.77
27	Flexible	6	HAM-D	163	28.2/−8.4	29.8	181	**27.5/−11.0**	**40.0**	0.012	0.27
25	Flexible	4	HAM-D	24	25.8/−8.8	34.1	18	26.2/−7.2	27.5	0.50	0.21
62-A	Fixed	6	HAM-D	56	4.0/−1.21	30.2	105	3.9/−1.33	34.1	0.46	0.12
							103	3.9/−1.38	35.4	0.34	0.16
							100	3.9/−1.19	30.5	0.50	0.11
62-B	Fixed	6	HAM-D	48	24.3/−5.7	23.4	97	**24.7/−9.8**	**39.6**	0.007	0.48
							97	**24.1/−9.6**	**39.8**	0.01	0.46
							103	24.2/−7.2	29.8	0.34	0.17
Sertraline (1991)											
103	Fixed	6	HAM-D	86	25.3/−7.6	30.0	90	**24.8/−10.6**	**42.7**	0.34	0.32
							89	**24.9/−9.8**	**39.4**	0.102	0.25
							82	**25.7/−9.9**	**38.5**	0.252	0.23
104	Flexible	8	HAM-D	141	23.4/−8.2	35.0	142	**23.3/−11.7**	**50.2**	0.001	0.40
315	Flexible	8	HAM-D	73	22.2/−6.7	29.6	76	23.1/−8.8	38.1	0.46	0.12
Paroxetine (1992)											
01-001	Flexible	6	HAM-D	24	27.4/−10.5	38.3	24	28.0/−13.5	48.2	0.204	0.37
02-001	Flexible	6	HAM-D	53	25.9/−6.8	26.3	51	**26.6/−12.3**	**46.2**	0.0042	0.57
02/002	Flexible	6	HAM-D	34	24.9/−5.8	23.3	36	**25.0/−10.9**	**43.6**	0.0146	0.60
02/003	Flexible	6	HAM-D	33	28.9/−7.2	24.9	33	28.6/−9.7	33.9	0.3092	0.25
02-004	Flexible	4	HAM-D	38	27.3/−7.2	26.4	36	**28.9/−12.2**	**42.2**	0.0018	0.75
03-005	Flexible	6	HAM-D	42	26.8/−4.0	14.9	40	**26.1/−10.0**	**38.3**	0.0076	0.60
03-006	Flexible	6	HAM-D	38	28.7/−3.0	10.5	39	**29.7/−9.1**	**30.6**	0.0014	0.75
03-001	Flexible	4	HAM-D	38	24.8/−4.7	19.0	40	**24.9/−10.8**	**42.4**	0.006	0.63
03-002	Flexible	4	HAM-D	40	25.6/−6.2	24.2	40	24.9/−8.0	32.1	0.0004	0.61
03-003	Flexible	4	HAM-D	42	27.0/−9.2	34.1	39	25.7/−9.3	36.2	0.98	0.01
03-004	Flexible	4	HAM-D	37	27.0/−6.7	24.8	37	27.6/−10.4	37.7	0.04	0.48
09	Fixed	12	HAM-D	51	NR/−8.2	NR	104	NR/−10.6	NR	0.34	0.16
							99	NR/−9.0	NR	0.34	0.16
							100	NR/−9.4	NR	0.34	0.16

Table 1 Characteristics of 51 clinical trials for the approval of nine antidepressants from 1987 to 2000 *(continued)*

				Placebo			Investigational antidepressant				
Protocol number	Dosing schedule	Duration (weeks)	Primary efficacy measure	No. patients	Baseline/change score on primary efficacy measure	Percent response	No. patients	Baseline/change score on primary efficacy measure	Percent response	p value for efficacy calculation	Effect size (Hedges' g)
Venlafaxine (1993)											
600A-206	Flexible	4	HAM-D	47	28.6/−4.8	16.8	46	**28.2/−14.2**	**50.4**	0.006	0.58
600A-301	Flexible	6	HAM-D	78	24.6/−9.5	38.6	64	**25.4/−13.9**	**54.7**	0.0004	0.61
600A-302	Flexible	6	HAM-D	75	24.4/−8.9	36.5	65	**25.0/−11.9**	**47.6**	0.008	0.45
600A-303	Flexible	6	HAM-D	79	24.6/−9.9	40.2	70	23.6/−10.1	42.8	0.493	0.11
600A-203	Fixed	6	HAM-D	92	25.3/−6.7	26.5	77	**26.0/−11.1**	**42.7**	0.004	0.45
							79	**26.0/−11.9**	**45.8**	0.001	0.51
							75	**24.9/−10.5**	**42.2**	0.003	0.47
600A-313	Fixed	6	HAM-D	75	25.4/−9.5	37.4	72	25.6/−10.9	42.6	0.193	0.21
							77	25.6/−11.8	46.1	0.142	0.24
Nefazodone (1994)											
030A2-0007	Fixed	6	HAM-D	47	26.4/−9.8	37.1	47	25.4/−10.7	42.1	0.60	0.11
03A0A-003	Fixed	6	HAM-D	45	25.9/−6.8	26.3	44	**25.4/−11.0**	**43.3**	0.03	0.46
03A0A-004A	Fixed	6	HAM-D	77	23.5/−8.5	36.2	76	23.6/−9.0	38.1	0.66	0.71
03A0A-004B	Fixed	6	HAM-D	80	25.0/−9.4	37.6	78	**25.4/−12.4**	**48.8**	0.02	0.37
CN104-005	Flexible	8	HAM-D	90	23.5/−8.0	34.0	86	**24.4/−12.0**	**49.2**	0.01	0.39
CN104-006	Flexible	8	HAM-D	78	23.8/−8.9	37.4	80	23.5/−10.0	42.6	0.35	0.15
Mirtazapine (1996)											
003-002	Flexible	6	HAM-D	44	24.7/−5.4	21.9	44	**24.2/−11.7**	**48.3**	0.0008	0.73
003-003	Flexible	6	HAM-D	45	25.5/−8.8	34.5	45	25.4/−10.4	40.9	0.49	0.14
003-008	Fixed	6	HAM-D	28	25.8/−9.6	37.2	30	26.0/−7.6	29.2	0.293	−0.28
							28	25.5/−7.3	28.6	0.282	−0.29
							30	25.3/−8.1	32.0	0.346	−0.25
003-020/3220	Flexible	6	HAM-D	39	29.5/−4.8	16.3	40	**27.8/−10.3**	**37.1**	0.004	0.66
003-021/3220	Flexible	6	HAM-D	48	24.4/−9.5	38.9	45	24.2/−11.7	48.3	0.223	0.25
003-022/3220	Flexible	6	HAM-D	50	31.2/−9.0	28.8	49	**33.0/−16.1**	**48.8**	0.003	0.61
003-024/3220	Flexible	6	HAM-D	48	27.7/−7.7	27.8	50	**27.5/−12.1**	**44.0**	0.01	0.53
85027	Flexible	4	HAM-D	61	26.2/−10.9	41.6	64	26.4/−13.4	50.8	0.189	0.23

Table 1 Characteristics of 51 clinical trials for the approval of nine antidepressants from 1987 to 2000 *(continued)*

				Placebo			Investigational antidepressant				
Protocol number	**Dosing schedule**	**Duration (weeks)**	**Primary efficacy measure**	**No. patients**	**Baseline/change score on primary efficacy measure**	**Percent response**	**No. patients**	**Baseline/change score on primary efficacy measure**	**Percent response**	**p value for efficacy calculation**	**Effect size (Hedges' g)**
Bupropion SR (1996)											
203	Fixed	8	HAM-D	117	23.2/−8.1	34.9	113	23.4/−10.2	43.6	0.04	0.27
205	Fixed	8	HAM-D	116	23.4/−8.3	35.5	111	23.6/−9.0	38.1	0.53	0.8
							111	24.2/−9.3	38.4	0.30	0.14
212	Fixed	8	HAM-D	148	23.9/−9.8	41.0	144	24.4/−11.1	45.5	0.16	0.16
Venlafaxine ER (1997)											
208	Flexible	12	HAM-D	91	24.6/−8.7	35.4	85	**24.4/−14.9**	**61.1**	0.001	0.50
209	Flexible	8	HAM-D	100	23.6/−6.8	28.8	91	**24.5/−11.7**	**47.8**	0.0003	0.53
367	Flexible	8	HAM-D	81	26.6/−13.1	49.2	83	26.5/−15.6	58.9	0.37	0.14
							85	NR/NR	NR	0.14	0.23
Citalopram (1998)											
85A	Flexible	4	HAM-D	78	33.7/−9.6	28.5	82	**33.5/−12.9**	**38.5**	0.0344	0.33
86141	Flexible	6	HAM-D	50	21.0/−4.9	23.3	97	22.2/−6.3	28.4	0.316	0.17
89303	Fixed	6	HAM-D	64	23.7/−10.6	44.7	61	23.0/−13.3	57.8	0.12	0.28
91206	Fixed	6	HAM-D	124	24.6/−9.3	37.8	120	**24.4/−12.2**	**50.0**	0.0025	0.39
							110	**24.5/−12.1**	**49.4**	0.0053	0.37
89306	Fixed	6	MADRS	88	33.1/−16.0	48.3	97	31.3/−16.0	51.1	0.964	0.07

NR – data not reported or censored in the Food and Drug Administration packet, HAM-D – Hamilton Depression Rating Scale, MADRS – Montgomery-Åsberg Depression Rating Scale
Bold prints indicate a positive trial arm

Table 2 Characteristics of 34 clinical trials for the approval of seven antidepressants after 2000

				Placebo			Investigational antidepressant				
Protocol number	**Dosing schedule**	**Duration (weeks)**	**Primary efficacy measure**	**No. patients**	**Baseline/change score on primary efficacy measure**	**Percent response**	**No. patients**	**Baseline/change score on primary efficacy measure**	**Percent response**	**p value for efficacy calculation**	**Effect size (Hedges' g)**
Escitalopram (2002)											
MD01	Fixed	8	MADRS	119	29.5/−9.4	31.9	118	**28.0/−12.8**	**45.7**	0.0007	0.45
							125	**28.9/−13.9**	**48.1**	0.0001	0.51
MD 02	Flexible	8	MADRS	125	28.8/−11.2	38.9	124	28.7/−12.9	45.0	0.251	0.15
99001	Fixed	8	MADRS	189	28.7/−13.6	47.4	188	**29.2/−16.3**	**55.8**	0.006	0.28
99003	Flexible	8	MADRS	154	28.7/−12.5	43.6	155	**29.0/−15.3**	**52.8**	0.0064	0.31
Duloxetine (2002)											
HMAQa	Flexible	8	HAM-D	57	20.6/−6.5	31.6	56	19.6/−8.5	43.4	0.15	0.27
HMAQb	Flexible	8	HAM-D	55	20.0/−5.7	28.5	61	19.9/−6.2	31.2	0.95	0.01
HMATa	Fixed	8	HAM-D	89	17.8/−4.3	24.2	81	17.4/−5.5	31.6	0.138	0.23
HMATb	Fixed	8	HAM-D	88	17.2/−4.2	24.2	86	**18.1/−7.7**	**42.7**	0.003	0.45
HMBHa	Fixed	9	HAM-D	115	21.1/−5.2	24.5	121	**21.5/−9.3**	**43.0**	0.001	0.43
HMBHb	Fixed	9	HAM-D	136	20.5/−7.2	35.3	123	**20.3/−8.9**	**43.8**	0.048	0.25
Desvenlafaxine (2008)											
332	Fixed	9	HAM-D	150	23.0/−9.6	41.7	150	**23.4/−11.5**	**49.2**	0.02	0.27
							147	23.4/−11.0	47.0	0.09	0.20
333	Fixed	8	HAM-D	161	24.3/−10.8	44.4	164	**24.3/−13.2**	**54.3**	0.004	0.32
							158	**24.4/−13.7**	**56.2**	0.001	0.37
223	Fixed	8	HAM-D	78	NR	NR	63	NR	NR	0.59	0.09
							72	NR	NR	0.52	0.11
306	Fixed	8	HAM-D	118	NR/−7.7	NR	114	**NR/−10.5**	**NR**	0.004	0.38
							116	NR/−9.6	NR	0.076	0.23
							113	**NR/−10.5**	**NR**	0.002	0.41
308	Fixed	8	HAM-D	124	NR/−9.3	NR	121	**NR/−12.6**	**NR**	0.002	0.40
							124	**NR/−12.1**	**NR**	0.008	0.34
304	Flexible	8	HAM-D	114	NR/NR	NR	120	NR/NR	NR	0.28	0.14
309	Flexible	8	HAM-D	120	NR/−12.5	NR	117	NR/−13.4	NR	0.381	0.11
317	Flexible	8	HAM-D	125	NR/−9.8	NR	110	NR/−10.5	NR	0.488	0.09
320	Flexible	8	HAM-D	118	NR/−7.5	NR	117	NR/−9.1	NR	0.078	0.23

Table 2 Characteristics of 34 clinical trials for the approval of seven antidepressants after 2000 *(continued)*

				Placebo			Investigational antidepressant				
Protocol number	**Dosing schedule**	**Duration (weeks)**	**Primary efficacy measure**	**No. patients**	**Baseline/change score on primary efficacy measure**	**Percent response**	**No. patients**	**Baseline/change score on primary efficacy measure**	**Percent response**	**p value for efficacy calculation**	**Effect size (Hedges' g)**
Trazodone ER (2010)											
04ACL3-001	Flexible	8	HAM-D	206	22.4/−9.25	41.3	206	**23.2/−11.2**	**48.2**	0.0055	0.27
Vilazodone (2011)											
GNSC-04-DP-02	Flexible	8	MADRS	199	30.7/−9.7	31.6	198	**30.8/−12.9**	**41.9**	0.001	0.33
CLDA-07-DP-02	Fixed	8	MADRS	231	32.0/−10.8	33.8	232	**31.9/−13.3**	**41.7**	0.009	0.24
Levomilnacipran (2013)											
MD-01	Fixed	8	MADRS	175	35.6/−11.6	32.6	176	**36.0/−14.8**	**41.1**	0.0186	0.25
							177	**36.1/−15.6**	**43.2**	0.0038	0.31
							176	**36.0/−16.5**	**45.8**	0.0005	0.37
MD-03	Flexible	8	MADRS	214	35.2/−12.2	33.8	215	**35.0/−15.3**	**43.7**	0.0051	0.27
MD-10	Flexible	8	MADRS	185	31.0/−11.3	36.5	185	**30.8/−14.6**	**47.4**	0.0027	0.31
							187	**31.2/−14.4**	**46.2**	0.0043	0.30
MD-02	Flexible	8	MADRS	182	35.5/−14.2	40.0	175	NR/NR	NR	NR	NR
F02695 LP2 02	Flexible	10	MADRS	277	30.5/−14.5	47.5	276	**30.7/−18.7**	**60.9**	0.0001	0.55
Vortioxetine (2013)											
11492A	Fixed	6	MADRS	105	33.9/−14.5	42.8	100	**34.0/−20.2**	**59.4**	0.0001	0.55
305	Fixed	8	HAM-D	139	32.7/−11.3	35.6	139	**33.1/−16.2**	**48.9**	0.001	0.40
13267A	Fixed	8	MADRS	158	31.5/−11.7	37.1	149	**31.8/−17.2**	**54.1**	0.0001	0.45
							151	**31.2/−18.8**	**60.3**	0.0001	0.45
315US	Fixed	8	MADRS	153	31.5/−12.8	40.6	145	31.9/−14.3	44.8	0.224	0.14
							147	**32.0/−15.6**	**48.8**	0.023	0.26
316US	Fixed	8	MADRS	155	32.0/−10.8	33.8	154	32.2/−13.0	40.4	0.058	0.19
							148	**32.5/−14.4**	**44.3**	0.002	0.36
11984A	Fixed	8	MADRS	145	NR/−14.8	NR	151	NR/−16.3	NR	0.185	0.15
317	Fixed	8	MADRS	149	33.4/−12.9	38.6	143	34.1/−13.7	40.2	0.597	0.06
							142	33.6/−13.4	39.9	0.745	0.04

NR – data not reported or censored in the Food and Drug Administration packet, HAM-D – Hamilton Depression Rating Scale, MADRS – Montgomery-Åsberg Depression Rating Scale
Bold prints indicate a positive trial arm

Table 3 Evaluation of efficacy outcomes in antidepressant registration trials before and after 2000

	Before 2000	After 2000	p
No. programs	9	7	
No. trials	51	34	
No. active treatment arms	67	48	
Successful treatment arms	47.8% (32/67)	63.8% (30/47)	0.09
% symptom reduction			
Antidepressant	40.6% (±13.7)	46.6% (±7.0)	0.005
Placebo	29.8% (±12.6)	36.2% (±6.6)	0.005
Mean antidepressant-placebo difference	10.5% (±9.2)	10.3% (±5.0)	0.37
Effect size (Hedges' g)	0.30 (±0.24)	0.29 (±0.12)	0.42

arms in post-2000 trials had missing baseline or change score data.

Due to missing data, we calculated placebo response magnitude based on 76 out of 85 placebo arms (89.4%), antidepressant response magnitude based on 98 out of 115 treatment arms (85.2%), antidepressant-placebo differences based on 98 out of 115 antidepressant-placebo group comparisons (85.2%), and effect sizes based on 114 out of 115 treatment arms (99.1%).

Prior to 2000, placebo reduced symptoms on average by 29.8% (±12.6) compared to 36.2% (±6.6) in programs post-2000, resulting in a significant increase in placebo response by 6.4% ($t=-2.9$, $df=74$, $p=0.005$). This represents a 21.5% change over 15 years (Table 3).

Percent symptom reduction as a measure of response magnitude increased by an almost identical 6.0% in the antidepressant treatment arm, from pre-2000 trials at 40.6% (±13.7) to post-2000 trials at 46.6% (±7.0) ($t=-2.9$, $df=96$, $p=0.005$). This represents a 14.8% change over 15 years (Table 3).

Figure 1 shows placebo and antidepressant response rates over time. Growth rate was nearly parallel in placebo and antidepressant treatments, with both treatment conditions having significant positive relationships (placebo: $r=0.46$, $p<0.001$; antidepressants: $r=0.37$, $p<0.001$) between time and percent symptom reduction.

The antidepressant-placebo differences have remained equivalent over the years, as a result of matching growth in both treatment condition responses. The mean antidepressant-placebo difference in trials from pre-2000 was 10.5% (±9.2) as compared to 10.3% (±5.0) in the trials post-2000 ($p=0.37$) (Table 3).

Treatment arms for antidepressant clinical trials conducted prior to 2000 were successful in 47.8% of cases (32 out of 67 treatment arms), compared with a treatment arm success rate of 63.8% (30 out of 47) in antidepressant trials post-2000. Chi-square analysis of proportions determined that this difference was not statistically significant ($p=0.09$).

Effect sizes based on number of patients and p values from individual treatment arm LOCF analysis revealed no significant change over the 31 years of antidepressant program data. The average weighted effect size across trial arms conducted

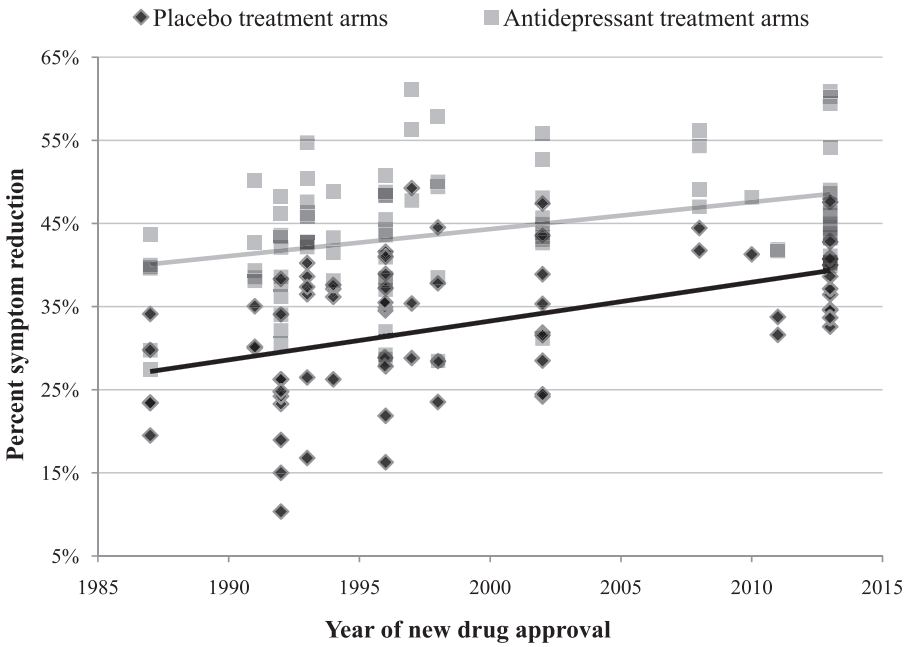

Figure 1 Percent symptom reduction in 74 placebo and 92 antidepressant treatment arms from 85 clinical trials for 16 antidepressant approval programs plotted with time. The correlation between year of new drug approval and percent symptom reduction was significant in both the placebo ($r=0.46$, $p<0.001$) and the antidepressant group ($r=0.37$, $p<0.001$).

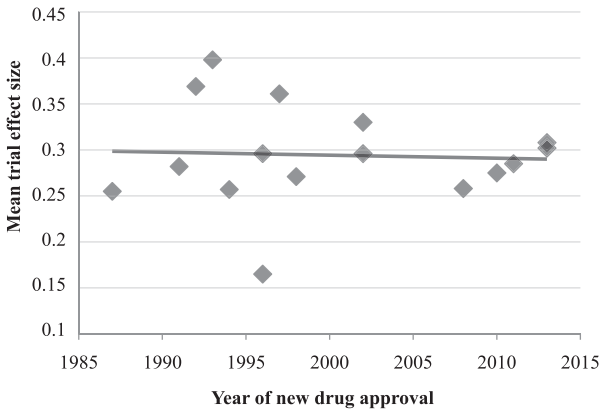

Figure 2 Mean effect size (Hedges' g) of antidepressant clinical trials based on year of approval. There was no significant relationship between year of new drug approval and mean program effect size ($r=-0.06$, $p=0.85$).

before 2000 was 0.30 (±0.24), while for trials after 2000 it was 0.29 (±0.12) ($p=0.42$).

Figure 2 shows this trend of stability in effect size throughout the years simplified by averaging trial effect sizes to generate overall values for each antidepressant program. Program effect sizes were not correlated with any kind of change over time ($p=0.85$).

The trial design suggestions[12], including enhanced rater interview techniques[19-21], put forth by investigators based on *post-hoc* analyses of placebo response were not implemented in recent clinical trials. Specifically, the trends examined were opposite in direction to the modifications in trial design previously suggested: trials were of longer duration, had a greater number of treatment arms, and rarely used flexible dosing schedules; all elements previously corresponding to higher placebo response. There was no observed association between trial design features and trial outcomes in post-2000 trials (see Table 2 for trial design characteristics).

Regarding enhanced interview techniques[19-21], two out of 34 recent antidepressant clinical trials submitted for review by the FDA used such techniques. Neither of these (trial 317 for vortioxetine[43] and trial MD-02 for levomilnacepran[44]) was successful.

DISCUSSION

Given the present state of uncertainty in the research surrounding placebo response in antidepressant clinical trials and the importance of this phenomenon, this study aimed to evaluate if placebo response as measured by symptom reduction has continued to rise over the past 15 years compared to the earlier 15 years. The study also attempted to determine if decreases in success rate and measures of antidepressant-placebo differences accompanied the growth in symptom reduction with placebo.

The study showed that the pattern of increase in placebo response noted in 2001 by Walsh et al[3] has continued. The magnitude of symptom reduction with placebo has steadily increased from 29.8% to 36.2% ($p=0.005$). These results converge with the findings by Khin et al[9] and other investigators[5-8] that placebo symptom reduction has continued to increase in more recent antidepressant clinical trials.

The increase in placebo response observed in recent antidepressant clinical trials is in contrast with a recent study by Furukawa et al[10], reporting a stability in placebo response rate after 1991. We attribute this discrepancy to differences in study design. That study included data from published sources, which have been shown to contain selection bias[39,40] and frequently use different statistical analyses from those performed by the FDA reviewers. Therefore, use of published sources may have resulted in different datasets. Additionally, our study used percent symptom reduction as a measure of placebo response and this value is on a continuum, allowing for analysis of more subtle changes than a binary measure such as number of patients meeting a therapeutic response threshold, as used by Furukawa et al[10] and many others.

Contrary to expectations, given our finding of a continued increase in placebo response over time, the success rate of antidepressant clinical trials has gone up over the past 15 years (from 47.8% to 63.8%, $p=0.09$). This has occurred as the magnitude of the antidepressant response has also gone up considerably (from 40.6% to 46.6%, $p=0.005$).

In essence, both the magnitude of placebo response and antidepressant response have steadily increased over the past thirty years among these sixteen new antidepressant programs. The success rate of antidepressant trials has remained about the same, showing a modest increase in recent years. This is confirmed by the finding that treatment arm effect sizes have remained about the same, with a distribution around 0.30, and antidepressant-placebo differences continue to show a 10% antidepressant advantage regardless of placebo response. In other words, the newer antidepressants appear about as efficacious as the older ones.

Potential remedies that have been suggested in order to mitigate placebo response, such as changes in study designs (use of flexible dosing, shorter duration of trials, and fewer number of treatment arms[12]) seem not to have been systematically implemented or to have had effect on the outcomes of more recent antidepressant trials. Our exploration also suggests that these trial design and conduct factors may not be causally related to the magnitude of placebo response (see Table 2), so that the prospective implementation of these suggestions may not have the effect expected based on theory or observed from retrospective analysis. In particular, the two antidepressant clinical trials that prospectively used enhanced interview techniques failed to show superiority over placebo in NDA programs for vortioxetine and levomilnacepran.

In this context, it is important to note that the current results do not support earlier studies regarding the impact of

placebo response on trial outcomes, which found that the magnitude of placebo response was inversely associated with the frequency of positive outcomes in trials conducted between 1987 and 1999[4]. This relationship holds true for those earlier trials, but has dissolved in the more recent post-2000 trials.

What these current data show is that, in spite of the continuing growth of placebo response, antidepressants appear to maintain an advantage of about 10% (effect size of 0.30, a modest one), suggesting that acting to mitigate placebo response may not be a critical component of the success and outcomes of efficacy analysis in antidepressant clinical trials.

Potential mechanisms explaining the growth in placebo response and relationship to trial outcomes were not fully explored in this study. However, we noticed that there has been a substantial increase in the sample size in both placebo and antidepressant treatment arms in recent years. As described by Liu et al[44], increased sample size has been associated with clinical trial outcomes of investigational hypertension medications, and the relative mechanism calls for further exploration.

A drawback to our study is that it was an observational *post-hoc* analysis rather than prospective in design. More important, FDA medical and statistical reports do not include subject-level data. This summarization of data in FDA reviews of new investigational antidepressants does not allow a more detailed analysis. However, the sponsoring pharmaceutical companies or the FDA may undertake such an analysis to provide better insight into the relationship between placebo response and antidepressant clinical trial outcomes.

In conclusion, the results of this study suggest that the relationship between the magnitude of placebo response and the success of antidepressant clinical trials is weak at best. These data indicate that the antidepressant-placebo differences are about the same for all of the sixteen antidepressants approved by the FDA in the past thirty years. This finding has implications for guiding future clinical trials and warrants exploratory analysis of other potential factors that may influence the outcome of antidepressant trials.

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Risk of suicide, deliberate self-harm and psychiatric illness after the loss of a close relative: a nationwide cohort study

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The loss of a close relative is a common event, yet it is associated with increased risk of serious mental health conditions. No large-scale study has explored up to now the importance of the bereaved person's relation to the deceased while accounting for gender and age. We performed a nationwide Danish cohort study using register information from 1995 through 2013 on four sub-cohorts including all persons aged ≥18 years exposed to the loss of a child, spouse, sibling or parent. We identified 1,445,378 bereaved persons, and each was matched by gender, age and family composition to five non-bereaved persons. Cumulative incidence proportions were calculated to estimate absolute differences in suicide, deliberate self-harm and psychiatric illness. Cox proportional hazard regression was used to calculate hazard ratios while adjusting for potential confounders. Results revealed that the risk of suicide, deliberate self-harm and psychiatric illness was increased in the bereaved cohorts for at least 10 years after the loss, particularly during the first year. During that year, the risk difference was 18.9 events in 1,000 persons after loss of a child (95% CI: 17.6-20.1) and 16.0 events in 1,000 persons after loss of the spouse (95% CI: 15.4-16.6). Hazard ratios were generally highest after loss of a child, in younger persons, and after sudden loss by suicide, homicide or accident. One in three persons with a previous psychiatric diagnosis experienced suicide, deliberate self-harm or psychiatric illness within the first year of bereavement. In conclusion, this study shows that the risk of suicide, deliberate self-harm and psychiatric illness is high after the loss of a close relative, especially in susceptible subgroups. This suggests the need for early identification of high-risk persons displaying adjustment problems after loss of a close family member, in order to reduce the risk of serious mental health outcomes.

Key words: Bereavement, suicide, deliberate self-harm, psychiatric hospitalization, loss of a child, sudden loss

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Death of a close relative is a common experience in adulthood. In the US, it has been estimated that more than 40,000 parents lose a child every year[1], and more than half of the population over 65 years are widowed[2]. Although bereavement is a natural life event, it is often followed by emotional suffering and adjustment challenges. Studies have shown an association between the loss of a loved one and a range of mental health complications, particularly depression and post-traumatic stress disorder[3-9].

Prolonged and complicated grief reactions have been frequently studied, and prolonged grief disorder has recently been suggested for inclusion in the ICD-11[10-14]. The relevant Working Group has concluded that prolonged and complicated grief reactions are significantly associated with serious psychosocial and health problems, including suicidality, substance abuse and cardiovascular disease[11].

A representative population-based survey has shown female gender, old age, and loss of a child or the spouse to be risk factors in grief complications[15], whereas epidemiological studies show male gender to be associated with an excess risk of suicide and mortality after loss[2]. Yet, no studies have investigated suicidal behaviour and psychiatric illness across different types of loss, and considered previous history of mental and physical illness in the bereaved when interpreting the data[15].

The vast majority of individuals exposed to the loss of a loved person exhibit time-limited disruptions to daily functioning, and it has been argued that a mix of genetic, personality and environmental determinants act as protective or risk factors[16]. However, to study this mix of determinants requires large-scale studies. Up to now, few investigations have had sufficient size to quantify the risk of serious mental health conditions in specific subgroups after the loss of different types of close relatives. Understanding the pattern of grief-related disorders and serious mental health conditions is important to health care planning[13,16,17].

In a comprehensive population-based cohort, we investigated the absolute and relative risk of suicide, deliberate self-harm and psychiatric illness in people exposed to the loss of a child, spouse, parent or sibling. We evaluated whether the association was modified by gender, age, urbanization, or pre-existing mental conditions or physical diseases.

METHODS

Study population and design

A population-based cohort was established by using a unique personal identification number which links individual-level data between nationwide Danish registers[18]. The study cohort comprised four sub-cohorts of persons aged 18 years or older and residing in Denmark during the inclusion period from January 1, 1995 to December 31, 2012 (N=1,445,378). Each sub-cohort included all persons exposed to the loss of either a child, spouse/registered partner, parent or sibling.

Exposure to loss was assessed by identifying deceased persons and linking them to their family members using information from the Danish Civil Registration System[19]. Sudden and unnatural loss was defined as suicide, accident or homicide in the Danish Register of Causes of Death[20]. A person could serve

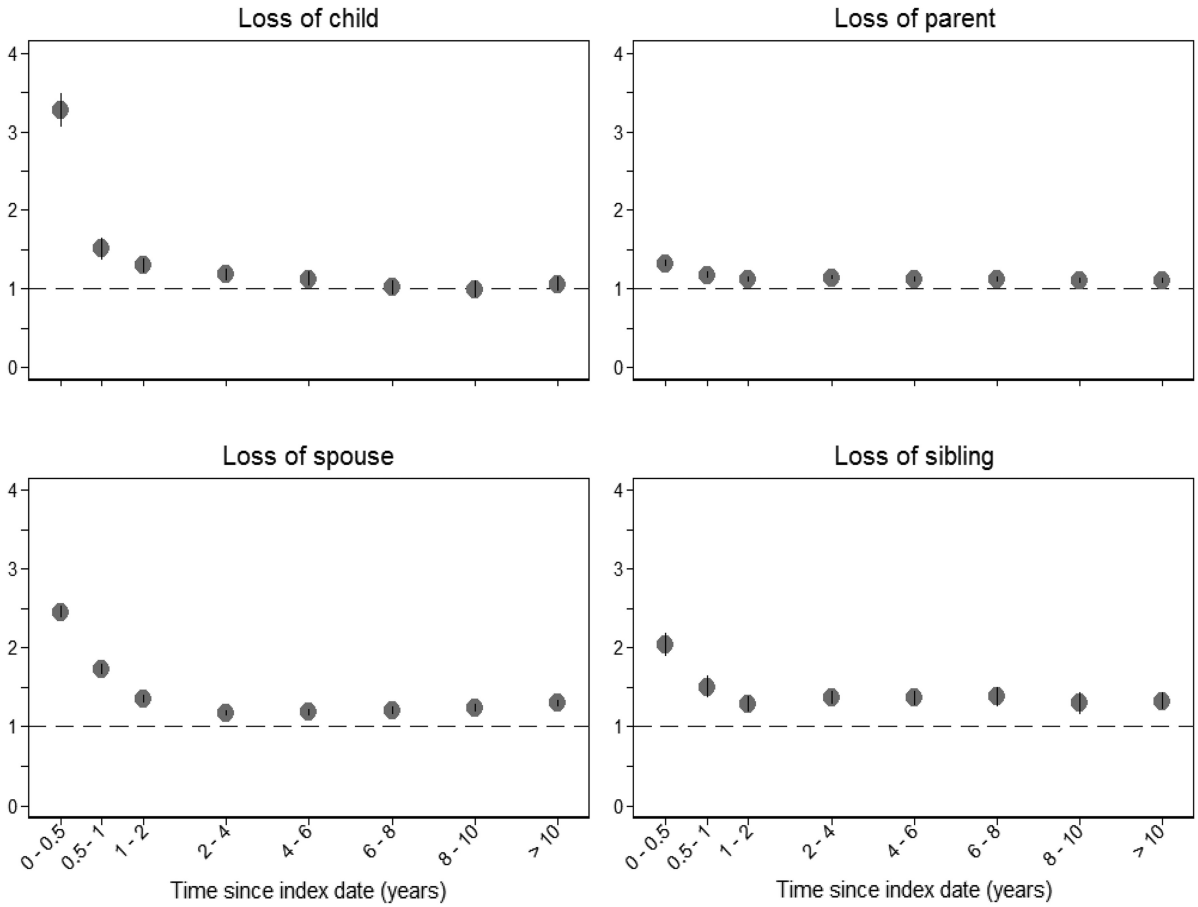

Figure 1 Hazard ratios (Y-axis) for serious mental health outcomes based on time since bereavement (0-10 years)

as exposed in more than one sub-cohort if more than one type of loss was experienced in the study period, but we included only the first loss within each type of loss.

Each person experiencing loss was matched based on gender and birthday (±70 days) with five unexposed reference persons. We ensured that each of the reference persons had a relative of the same type as the one lost by the bereaved person. The matching algorithm was applied with replacements between strata. Each person was followed until one of the studied outcomes, death, emigration, or end of study period, whichever came first.

Outcome variables and data sources

The main outcome was a serious mental health condition defined as suicide, deliberate self-harm, or psychiatric illness. The three events were studied individually and as a composite outcome for all four types of loss. Suicide was identified via the ICD-10 coding system (codes X60-X84) obtained from the Danish Register of Causes of Death[20]. Psychiatric illness was defined as any inpatient or outpatient hospitalization, or psychiatric emergency room contact registered in the Danish Psychiatric Central Research Register[21]. Deliberate self-harm was defined in accordance with the criteria of the Danish National Patient Register[22] or the Psychiatric Central Research Register, which has previously been used in Danish register studies[23].

Potential confounders or effect modifiers included in the analyses were: gender, age, calendar period, degree of urbanization, history of psychiatric diagnosis, past inpatient psychiatric hospitalization, past deliberate self-harm, current use of psychotropic medication, and history of selected somatic diseases. Urbanization was classified according to the DEGURBA variable[24] used by the European Union and Statistics Denmark (densely, intermediately ≥40000, intermediately <40000, thinly ≥15000, or thinly <15000 populated). Past psychiatric diagnoses were categorized based on a five-year history in the Psychiatric Central Research Register. Considered diagnoses were: mood and anxiety disorders (ICD-10 codes F30-F48), schizophrenia and related disorders (F20-F29), and alcohol or drug abuse (F10-F19). History of psychiatric hospitalization was coded by identifying any inpatient hospitalization in the Psychiatric Central Research Register during the five years prior to entry date. Past deliberate self-harm was also considered during the five years prior to the entry date based on the earlier defined criteria. The National Prescription Registry[25] was used to assess a one-year history of redeemed psychotropic

Table 1 Risk differences of suicide, deliberate self-harm and psychiatric illness in the first year after loss per 1,000 persons

	Bereaved		Non-bereaved		
	Events	CIP (95% CI)	Events	CIP (95% CI)	Difference (95% CI)
Loss of child (N=501,954)					
Composite	2,762	33.0 (31.8-34.2)	5,920	14.2 (13.8-14.5)	18.9 (17.6-20.1)
Suicide	30	0.36 (0.25-0.51)	66	0.16 (0.12-0.20)	0.20 (0.07-0.34)
Deliberate self-harm	1,007	12.0 (11.3-12.8)	2,641	6.3 (6.1-6.6)	5.7 (4.9-6.5)
Psychiatric illness	2,447	29.3 (28.1-30.4)	4,912	11.7 (11.4-12.1)	17.5 (16.3-18.7)
Loss of spouse (N=2,242,464)					
Composite	11,002	29.5 (28.9-30.0)	25,110	13.4 (13.3-13.6)	16.0 (15.4-16.6)
Suicide	279	0.74 (0.66-0.84)	204	0.11 (0.10-0.13)	0.64 (0.55-0.73)
Deliberate self-harm	3,612	12.3 (12.0-12.7)	10,324	5.5 (5.4-5.6)	6.8 (6.5-7.2)
Psychiatric illness	9,124	24.4 (23.9-24.9)	20,355	10.9 (10.7-11.0)	13.5 (13.0-14.0)
Loss of parent (N=5,312,274)					
Composite	16,858	19.1 (18.8-19.3)	65,426	14.8 (14.7-14.9)	4.3 (4.0-4.6)
Suicide	187	0.21 (0.18-0.24)	533	0.16 (0.16-0.17)	0.09 (0.06-0.12)
Deliberate self-harm	7,599	8.6 (8.4-8.8)	28,814	6.5 (6.4-6.6)	2.1 (1.9-2.3)
Psychiatric illness	15,086	17.0 (16.8-17.3)	58,961	13.3 (13.2-13.4)	3.7 (3.4-4.0)
Loss of sibling (N=615,576)					
Composite	2,904	28.3 (27.3-29.3)	7,945	15.5 (15.2-15.8)	12.8 (11.8-13.9)
Suicide	21	0.20 (0.13-0.31)	75	0.15 (0.12-0.18)	0.06 (−0.04 to 0.15)
Deliberate self-harm	1,381	13.5 (12.8-14.2)	3,640	7.1 (6.9-7.3)	6.4 (5.6-7.1)
Psychiatric illness	2,576	25.1 (24.2-26.1)	7,102	13.9 (13.5-14.2)	11.3 (10.3-12.3)

CIP – cumulative incidence proportion

medication by the Anatomical Therapeutic Chemical codes for antipsychotics (N05A), anxiolytics (N05B), sedatives (N05C), or antidepressants (N06A). Data on somatic diseases were obtained from the National Patient Register on the basis of diagnoses (ICD-8/ICD-10 codes) of chronic obstructive pulmonary disease (491-492/J41-J44), cancer (140-209/C00-C97), spine disorder (728/M40-M54), asthma (493/I60-I66), diabetes (249-250/E10-E14), and ischemic heart disease (410-414/I20-I25).

The study was approved by the Danish Data Protection Agency (2013-41-1719).

Statistical analysis

To assess the absolute risk of a serious mental health condition, we calculated the cumulative incidence proportion for the bereaved and non-bereaved cohorts while taking into account competing death. The hazard ratios for suicide, deliberate self-harm and psychiatric illness comparing bereaved to non-bereaved persons were calculated by stratified Cox proportional hazard regression with time since bereavement as the underlying time scale to allow for separate baseline hazards in each matching group (one exposed and five matches). The hazard ratios were adjusted for degree of urbanization, past psychiatric diagnoses, past psychiatric hospitalization, past deliberate self-harm, current use of psychotropic medication, and history of somatic diseases. In sub-analyses, hazard ratios were calculated on the basis of both sudden and unnatural losses and disease-related losses.

All data handling and statistical analyses were performed with SAS9 (SAS Institute Inc., Cary, NC, USA) and Stata 14 (StataCorp LP, College Station, TX, USA).

RESULTS

Within the study period, 83,659 persons experienced loss of a child, 373,744 loss of the spouse, 885,379 loss of a parent, and 102,596 loss of a sibling. The matched cohorts were five times larger (N=418,295, 1,868,720, 4,426,895, and 512,980, respectively). During 72,621,128 person-years of follow-up (range = 0-19 years), we identified 128,120 (8.9%) bereaved persons and 530,026 (7.3%) non-bereaved persons ($p<0.0001$) who suffered from one of the three outcomes: suicide (0.1% vs. 0.06%, $p<0.0001$), deliberate self-harm (3.5% vs. 2.8%, $p<0.0001$) or psychiatric illness (5.3% vs. 4.5%, $p<0.0001$).

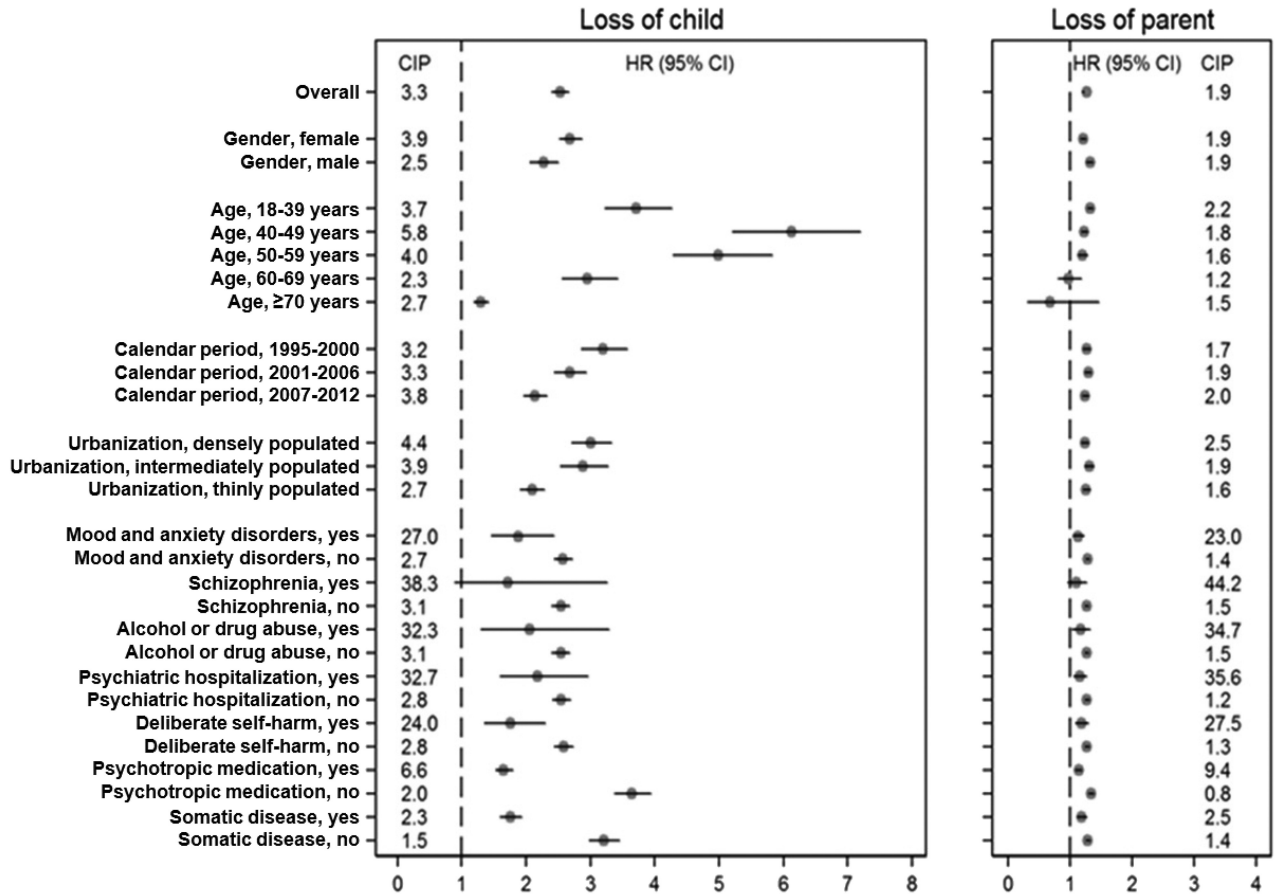

Figure 2 Adjusted hazard ratios (HR) and cumulative incidence proportion (CIP, %) within one year of the loss of a child or parent according to demographic variables and health status at the time of the loss

The hazard ratio of a serious mental health condition was increased in the bereaved cohorts for at least 10 years after the loss, particularly during the first year (Figure 1). In this first year, the risk difference was 18.9 events in 1,000 persons (95% CI: 17.6-20.1) after loss of a child, 16.0 events in 1,000 persons (95% CI: 15.4-16.6) after loss of the spouse, 4.3 events in 1,000 persons (95% CI: 4.0-4.6) after loss of a parent, and 12.8 events in 1,000 persons (95% CI: 11.8-13.9) after loss of a sibling, compared to non-bereaved persons (Table 1). Psychiatric illness was the most frequent outcome.

When we compared bereaved with non-bereaved persons, the overall adjusted hazard ratio at one year post-loss was 2.53 (95% CI: 2.39-2.67) for persons who lost a child, 2.14 (95% CI: 2.08-2.19) for persons who lost the spouse, 1.27 (95% CI: 1.23-1.30) for persons who lost a parent, and 1.85 (95% CI: 1.74-1.97) for persons who lost a sibling (Figures 2 and 3).

The hazard ratio of developing a serious mental health condition was generally highest for 18-39 year-olds after loss of spouse (5.78; 95% CI: 4.70-7.10) and for 40-49 years-olds after loss of child (6.13; 95% CI: 5.21-7.20). The overall risk was similar for males and females, except after loss of child, where females were at higher risk (hazard ratio: 2.68; 95% CI: 2.51-2.87) than males (hazard ratio: 2.29; 95% CI: 2.06-2.49).

The cumulative incidence proportion was considerably higher in persons with a previous psychiatric diagnosis. In general, about one third of these persons experienced serious mental health conditions during bereavement (i.e., 37% of persons previously diagnosed with alcohol or drug abuse who lost a spouse; 44% of persons with a previous diagnosis of schizophrenia who lost a parent). Sub-analyses revealed that sudden unnatural loss resulted in a markedly higher risk of a serious mental health condition in the first year after bereavement (for all types of loss) compared to other losses (Figure 4).

DISCUSSION

In this comprehensive nationwide cohort study, loss of a close relative was associated with higher risk of suicide, deliberate self-harm or psychiatric illness for up to ten years after the loss, but particularly within the first year. Risk profiles varied according to the bereaved person's relation to the deceased, age, gender, history of mental illness, and cause of death. We generally found higher risks for persons who lost a child or the spouse, with a risk difference of 18.9 in 1,000 persons after loss

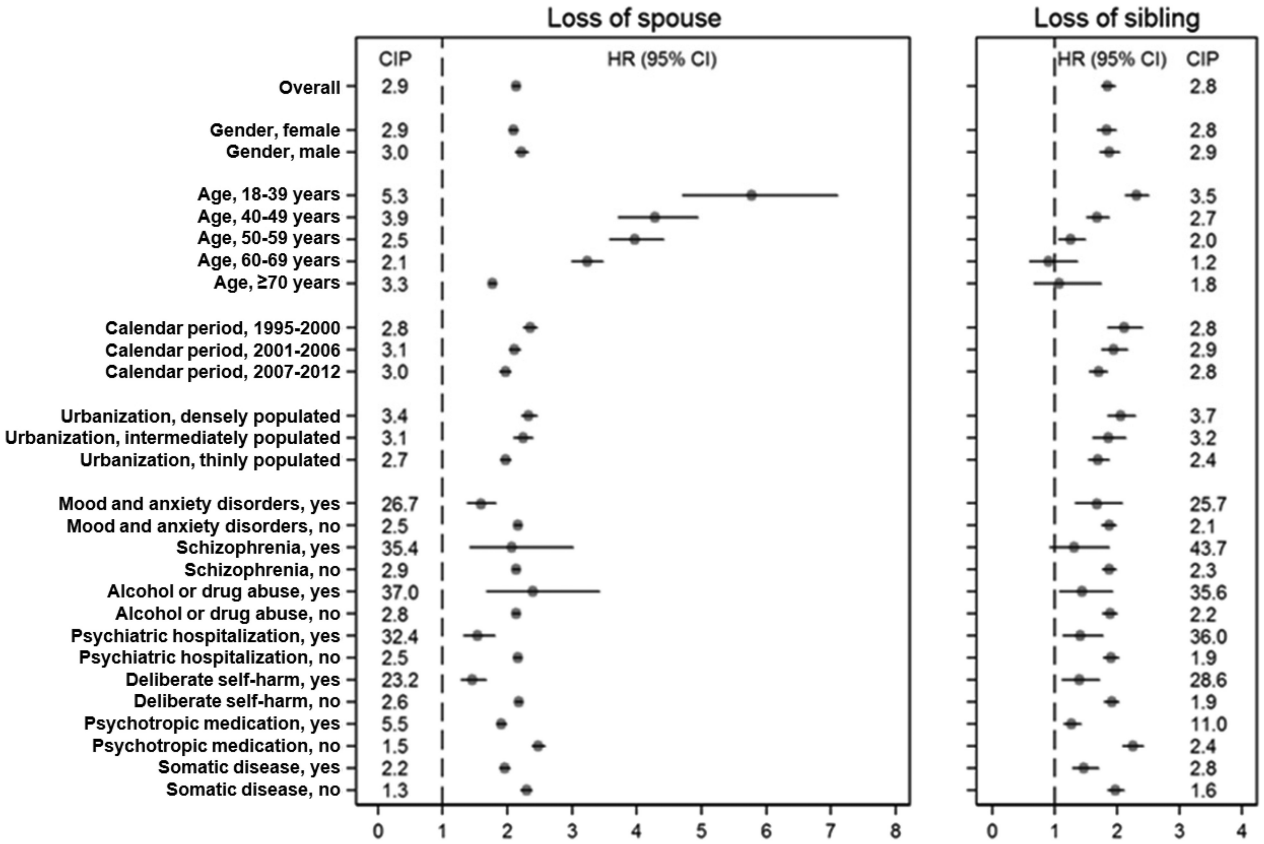

Figure 3 Adjusted hazard ratios (HR) and cumulative incidence proportion (CIP, %) within one year of the loss of the spouse or a sibling according to demographic variables and health status at the time of the loss

of a child and 16.0 in 1,000 persons after loss of the spouse. Hazard ratios were generally highest in younger persons and after sudden and unnatural loss. One in three persons with a history of psychiatric disorders experienced at least one of the three investigated outcomes within the first year of bereavement.

Our finding of increased risk of suicide and psychiatric illness after the loss of a close relative is consistent with earlier studies, which have shown that risk is particularly high within the first year after the loss[3-6,26-29]. To the best of our knowledge, this is the first large-scale study to explore the importance of the bereaved person's relation to the deceased while accounting for gender and age. Death of the spouse has, for many years, ranked as the life event demanding the most intense readjustment when measured by the Social Readjustment Rating Scale[30], but recent studies with data on younger populations have suggested that loss of a child is also associated with intense and persistent grief[2,31], mental illness, and suicide[6]. In our study, the largest risk difference for developing a serious mental health condition was actually seen in persons who lost a child.

The absolute and relative risk of a serious mental health condition increased with young age at the time of bereavement, except for persons who lost of child, for whom the risk peaked at the age of 40-49 years. Earlier findings have been inconsistent. Some studies have reported that younger spouses are at highest risk of negative health consequences[27,28], whereas others have found persons aged >60 years to be at highest risk, especially of prolonged or complicated grief and suicide[3,13,26,32]. The proportion of sudden and unnatural losses was higher in younger age groups, whereas losses in older age were more often due to disease and expected deaths, which may contribute to explain the more severe acute grief responses of the former. Age-specific vulnerabilities could also offer an explanation: younger persons might lack experience with loss adjustment and emotional suffering, which may result in susceptibility to mental illness.

Risk of serious mental health conditions was similar for males and females, yet females were at higher risk after loss of a child. Increased risk of mortality after loss of the spouse has been established in males[26,27,33-35], while increased psychiatric morbidity following loss has especially been found in females[2,15,36]. Different risk profiles have been explained on the basis of differences in attachment patterns, social interaction, and coping strategies[2,6,33,36]: males tend to be less prone to seek help and more likely to suffer from undertreated substance abuse and act on impulse, which increases their risk of deliberate self-harm and suicide[33]. Females tend to be more prone to rumination and react with emotional coping strategies, making them more susceptible to anxiety, depression, and post-traumatic stress, which could complicate their grief response.

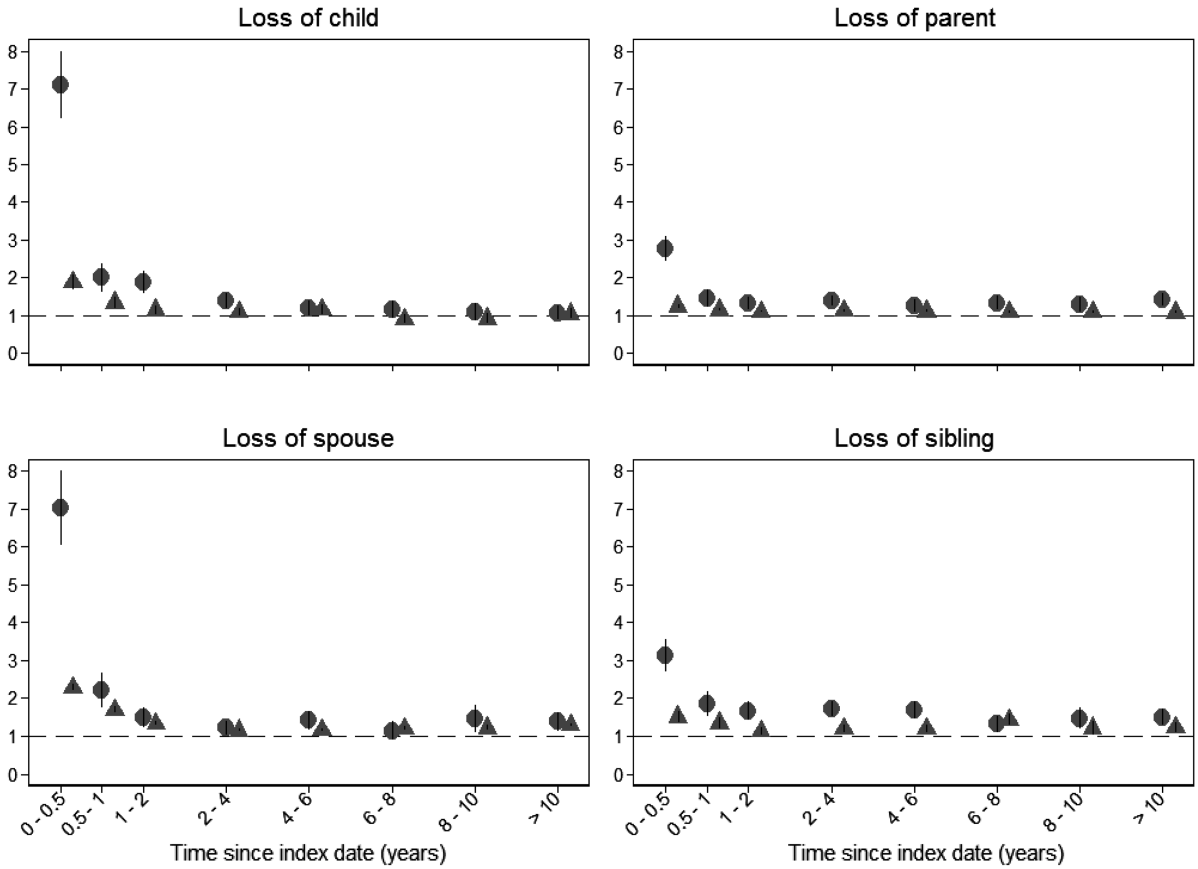

Figure 4 Hazard ratios of serious mental health outcomes for persons who lost a relative due to a disease (triangles) or to an unnatural cause of death (diamonds) according to time since bereavement (0-10 years)

Our study also showed that a history of mental illness is associated with substantial increase in risk, as is sudden loss from suicide, accidents or homicide. Previous studies have established comorbidity between mental illness, substance abuse, and prolonged or complicated grief[13,37-39], between suicide and a family history of suicidal behavior[40,41], and between violent deaths and increased risk of prolonged or complicated grief, mental illness, or suicide during bereavement[13,42,43]. Nevertheless, in our study, one in three bereaved with a history of mental illness experienced a serious mental health condition after loss; this has never previously been established while also adjusting for age and gender. Our finding points to the role of personal vulnerability in adjustment to loss.

The sample size of this study is unparalleled by other studies on risk of health consequences after loss and provides estimates with high statistical precision, while controlling for several confounders, such as history of mental or physical health, that might have been shared with the deceased family member and affected the health of the bereaved person.

In the Danish registration system, the overall validity and completeness of the records of death is close to 100%, which ensured accurate classification of people exposed to bereavement. We followed the entire Danish population for up to 19 years without loss to follow-up; thus, selection bias cannot explain the results. However, information on reasons for contacts with psychiatric outpatient clinics or psychiatric emergency care units was not included. As severity of mental health issues may vary in these contacts, the adversity could have been overestimated. Yet, only contacts with a psychiatric unit were recorded, whereas information on persons who were treated for mental disorders in primary care was not included.

Although we adjusted for several potential confounding factors, residual confounding by unmeasured factors cannot be ruled out. Unfortunately, data on socio-economic factors, educational level and lifestyle factors were not available. However, loss-induced changes in lifestyle, such as alcohol intake, diet or sleeping pattern, are considered as intermediate steps on the causal pathway and should not be adjusted for. Furthermore, our register-based study had no information on potentially modifying factors, such as genetic variables, family attachment pattern, social network, and distress.

The generalizability of our findings may be limited to similar Western societies, with comparable health behaviors and risk factors. Yet, the estimates in this study provide significant information on the far-reaching health consequences of familial loss.

Serious mental health conditions and suicide after loss of a close relative are potentially preventable[13,44]. Early mitigation

of risk may have wide-ranging beneficial effects, especially for distinct high-risk groups. Suicide and psychiatric illness after bereavement may be prevented by early identification of symptom severity and adjustment problems. Future public health strategies should consider policy implications of disseminating knowledge about high-risk groups as well as strengthening the professional competencies in assessing symptom severity. Hence, more studies are needed about assessment methods and early identification of adjustment problems.

In conclusion, this nationwide study provides the first comprehensive assessment of the incidence of serious mental health conditions after the loss of a close relative. A significantly elevated risk of suicide, deliberate self-harm and psychiatric illness is shown, particularly in the first year after the loss. Loss of child or spouse resulted in higher risk, and young age, a history of mental illness and sudden losses were found to be specific risk factors. This study points to early identification of high-risk persons displaying adjustment problems in order to mitigate distress and reduce the risk of serious mental health conditions after loss of a close family member.

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A critique of the "ultra-high risk" and "transition" paradigm

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The transdiagnostic expression of psychotic experiences in common mental disorder (anxiety/depression/substance use disorder) is associated with a poorer prognosis, and a small minority of people may indeed develop a clinical picture that meets criteria for schizophrenia. However, it appears neither useful nor valid to observe early states of multidimensional psychopathology in young people through the "schizo"-prism, and apply misleadingly simple, unnecessary and inefficient binary concepts of "risk" and "transition". A review of the "ultra-high risk" (UHR) or "clinical high risk" (CHR) literature indicates that UHR/CHR samples are highly heterogeneous and represent individuals diagnosed with common mental disorder (anxiety/depression/substance use disorder) and a degree of psychotic experiences. Epidemiological research has shown that psychotic experiences are a (possibly non-causal) marker of the severity of multidimensional psychopathology, driving poor outcome, yet notions of "risk" and "transition" in UHR/CHR research are restrictively defined on the basis of positive psychotic phenomena alone, ignoring how baseline differences in multidimensional psychopathology may differentially impact course and outcome. The concepts of "risk" and "transition" in UHR/CHR research are measured on the same dimensional scale, yet are used to produce artificial diagnostic shifts. In fact, "transition" in UHR/CHR research occurs mainly as a function of variable sample enrichment strategies rather than the UHR/CHR "criteria" themselves. Furthermore, transition rates in UHR/CHR research are inflated as they do not exclude false positives associated with the natural fluctuation of dimensional expression of psychosis. Biological associations with "transition" thus likely represent false positive findings, as was the initial claim of strong effects of omega-3 polyunsatured fatty acids in UHR samples. A large body of UHR/CHR intervention research has focused on the questionable outcome of "transition", which shows lack of correlation with functional outcome. It may be more productive to consider the full range of person-specific psychopathology in all young individuals who seek help for mental health problems, instead of "policing" youngsters for the transdiagnostic dimension of psychosis. Instead of the relatively inefficient medical high-risk approach, a public health perspective, focusing on improved access to a low-stigma, high-hope, small scale and youth-specific environment with acceptable language and interventions may represent a more useful and efficient strategy.

Key words: Ultra-high risk, transition, psychotic experiences, common mental disorder, transdiagnostic expression of psychosis, public health perspective

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Over the last two decades, more than 1,500 studies have been published revolving around the concept of "ultra-high risk" (UHR) or "clinical high risk" (CHR) for "transition" to a psychotic disorder. The basic assumptions behind these studies are as follows: in a group of young people seeking help for mental problems, one can apply criteria for a binary risk diagnosis predicting schizophrenia spectrum disorder, and true positives are people that meet criteria for "transition" at follow-up.

Reviews of UHR/CHR studies tend to be upbeat, taking the shape of "evidence-based recommendations" or "guidance", stating that "the young field of preventive research in psychosis has already resulted in sufficient evidence to formulate recommendations for an early detection of psychosis in the clinical practice"[1], and that "psychological, in particular cognitive-behavioural, as well as pharmacological interventions are able to prevent or at least postpone a first psychotic episode in adult CHR patients"[2].

However, the question arises of the degree to which this optimism is based on logical reasoning and scientific evidence. There is a growing literature on the complexities underlying UHR/CHR research, that are not resolved, clouding the interpretation of data[3-11]. In this paper, we critically review the assumptions underlying UHR/CHR research. In particular, we focus on outstanding issues to do with sampling variability and basic epidemiological parameters, the fixation on psychosis at the expense of other psychopathology, and the lack of transparency arising from the use of two binary concepts for diagnosis and outcome that lie on the same unidimensional scale, and obscure the temporality and dynamics of multidimensional psychopathological states in young people.

We do not wish to dispute that it is better to intervene early rather than late. Rather, we wish to argue that it is conceptually flawed to frame the treatment of early psychopathology in diagnosed help-seeking individuals as prevention of psychotic disorder, just because there is some degree of transdiagnostic expression of psychotic experiences.

CLINICAL HIGH RISK SAMPLING IS SELECTIVE AND NON-EPIDEMIOLOGICAL

In practice, studies that want to apply the UHR/CHR paradigm have to search for young individuals who are slightly-but-not-quite psychotic and have also expressed a wish to receive help. Sampling strategies differ widely from study to study and are based on a mix of advertising, service filters and active searches, thus per definition resulting in selected, non-representative samples that cannot readily be compared across studies.

For example, in the North-American multicentre prediction study[12], it was stated that "each site recruited potential subjects through clinical referrals as stimulated by talks to school counselors and mental health professionals in community settings". In the European Prediction of Psychosis Study (EPOS)[13], UHR/

CHR sampling was described as follows: "knowledge about early warning signs (e.g., concentration and attention disturbances, unexplained functional decline) and inclusion criteria was disseminated (through local workshops, articles in professional journals and newsletters, informational flyers, and web sites) to mental health professionals as well as institutions and persons who might be contacted by at-risk persons seeking help".

Of the two largest CHR psychotherapy trials to date, one did not provide details about the sampling procedure – except that it took screening of 5,705 subjects to include 201 patients (3.5%) in the trial[14] – and the other described sampling as follows: "our ascertainment strategy was to make services familiar with our entry criteria and to liaise on a regular basis; no systematic screening of service populations was carried out"[15].

What becomes clear is that CHR studies have to invest a great deal of resources in detecting and sampling subjects who meet the inclusion criteria. The cost of "finding" rare UHR/CHR subjects is considerable, but not included in cost-effectiveness analyses of UHR/CHR research. Given the apparent rarity of UHR/CHR states, it becomes *a priori* unlikely that early intervention along the UHR/CHR paradigm will have public health impact. A recent study, investigating an early intervention service in an inner city area, found that only a tiny proportion (4.1%) of patients with a first-episode psychotic disorder attending mental health services had been in previous contact with the local prodromal service, indicating that the impact of prodromal services in public health terms may be negligible in relation to their costs[16]. Such a lack of impact associated with the high-risk approach is a well-known phenomenon, referred to as the "prevention paradox"[17].

Given the absence of a consistent sampling frame, it is unlikely that CHR samples are readily comparable from study to study. For example, samples differ widely in exclusion criteria regarding previous use of antipsychotics and mood stabilizers, previous episodes of mania, and previous drug-induced psychotic states. Therefore, referring to CHR patients as if they were a "class" is not warranted. Although many meta-analyses of UHR/CHR samples have been conducted, the question arises whether these studies are sufficiently similar.

Nevertheless, two issues appear to be consistent across UHR/CHR samples. The first is that these samples in essence consist of individuals with a current diagnosis of mainly anxiety, depression or substance use[18,19]. The second is that, of the various CHR criteria, the "attenuated symptom" defines the great majority of individuals[20], the others having minimal relevance. In other words, CHR samples are individuals with common mental disorder or a substance use disorder who also present with low-grade psychotic symptoms.

CLINICAL HIGH RISK = COMMON MENTAL DISORDER WITH SUBTLE PSYCHOSIS ADMIXTURE

The fact that UHR/CHR samples in fact consist of individuals with anxiety/depression/substance use with subtle psychosis admixture is important, as it provides a crucial link to the epidemiological literature with findings derived from representative population-based samples. Attenuated psychotic symptoms at the population level are closely associated with non-psychotic diagnoses and/or sub-diagnostic non-psychotic psychopathology including anxiety, depression, attention-deficit/hyperactivity disorder, post-traumatic stress disorder, substance use disorder, eating disorder and many other forms of psychopathology[21]. Psychosis can thus be regarded as a trans-diagnostic dimension of psychopathology[22].

Epidemiological studies show that the presence of attenuated psychotic symptoms in non-psychotic disorders is associated with greater severity and poorer response to treatment[23-26]. In fact, research has shown that more exposure to genetic and environmental risk factors is associated with more severe non-psychotic psychopathology which in turn is associated with a greater probability of the person also having some degree of expression of psychosis[24,27,28].

PSYCHOTIC EXPERIENCES IN NON-PSYCHOTIC DISORDER: MARKER OR CAUSE OF POOR PROGNOSIS?

Psychotic experiences can thus be considered a *marker* for the severity of non-psychotic states. However, it may not be valid to see them as *causal* for a poor prognosis, as the evidence shows that psychosis may also be considered as something that follows passively as a function of the general severity of multidimensional psychopathology[22]. This is essential with regard to the UHR/CHR framework, where the clinical focus is solely on the binary risk concept of psychosis ("risk" and "transition", measured on the same dimensional scale), while the multidimensional severity of the psychopathological context is ignored. In the UHR/CHR framework, the binary presence of psychotic experiences, under the implicit assumption of impending, mostly "schizo" outcome[29], "trumps" all other dimensional expressions of psychopathology.

A whole generation of UHR/CHR studies has been analyzed from the perspective that outcome of common mental disorder with a degree of psychosis admixture is best predicted on the basis of a binary psychosis "risk" criterion. An alternative hypothesis, however, is that outcome in these states is in fact a consequence of *baseline severity* of multidimensional psychopathology rather than a binary *psychosis risk* criterion (Figure 1). Studies that have looked beyond UHR/CHR criteria confirm this prediction[13,30-34]. In other words, what is presented as "risk" may be better summarized as baseline differences in the severity of multidimensional psychopathology.

DOES THE CONCEPT OF "TRANSITION" REPRESENT A QUALITATIVE SHIFT?

In UHR/CHR research, "high risk" and "transition" are typically measured on the same dimensional scale rating frequency/duration of attenuated positive psychotic symptoms, usually the

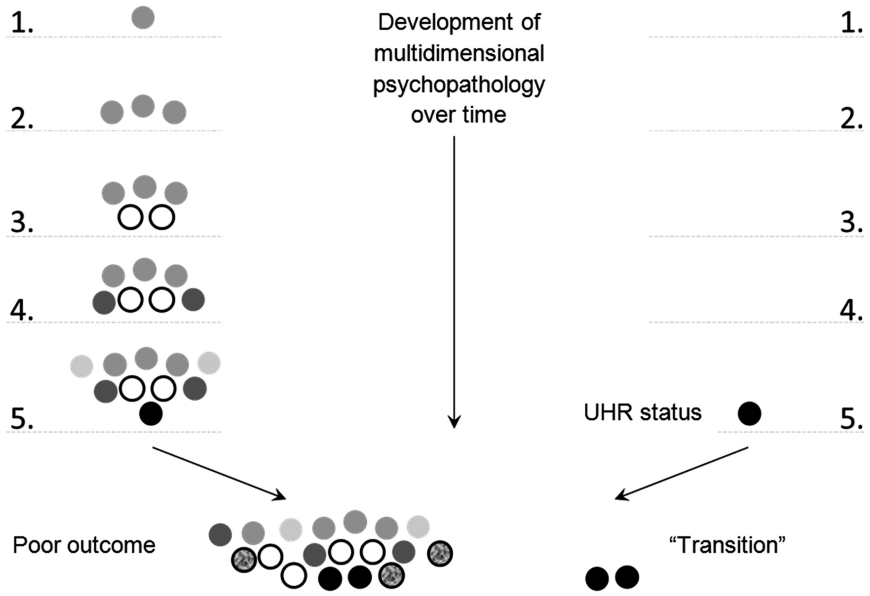

Figure 1 Relative "blindness" of the ultra-high risk (UHR)/transition paradigm. On the left, the natural development of multidimensional psychopathology over time. Black circles indicate (attenuated) positive psychotic symptoms. Other gray-scale circles indicate other psychopathology. As the UHR paradigm ignores multidimensional psychopathology, it remains "blind" and only "sees" psychotic phenomena as precursors of schizo-"transition" (i.e., more severe psychosis; below on the right), while these phenomena are in fact a marker of relative poor outcome of multidimensional psychopathology (below on the left). The restricted focus on positive symptoms in the UHR paradigm means that considerable potential for prevention in phases 1-4 is missed.

Comprehensive Assessment of At-Risk Mental States (CAARMS)[35] or the Scale of Prodromal Symptoms (SOPS)[36]. These frequency/duration ratings appear either impossibly precise (e.g., "at least once a month to twice a week – more than one hour per occasion, or at least 3 to 6 times a week – less than one hour per occasion") or rather broad (e.g., "present for at least 1 week and no longer than 5 years"). The scales for positive symptoms range from 0 to 6, where 3-5, for example, represents "risk for psychosis" and 6 represents "psychosis". Other symptom domains are ignored, regardless of their severity. "Transition" can be present with a 1-point shift on the dimensional scale, thus representing a quantitative, not a qualitative shift from "risk" to "transition" status.

While UHR/CHR criteria are generally clearly described in the literature, accounts of "transition" are usually kept vague. For example, in one recent large UHR/CHR trial[15], transition was described as "operationally defined on the CAARMS using the recommended criteria of a global rating scale score of 6 on either unusual thought content, non-bizarre ideas, or disorganised speech, or 5-6 on perceptual abnormalities, with an associated frequency score of 4-6, and with these experiences lasting longer than one week"[15]. In another trial[14], it was simply stated that "the primary outcome of this study was the transition to psychosis; the transition is defined by the CAARMS criteria". Considering the importance of valid outcomes in randomized controlled trials, these descriptions are opaque and appear to rely on small dimensional shifts. These shifts are nevertheless subsequently transformed into a seemingly important qualitative diagnostic change: as the attenuated psychotic symptoms in the UHR/CHR state cannot be counted as a "full" psychotic symptom in the DSM/ICD diagnostic system, the diagnosis in the UHR/CHR "risk" state remains per definition "non-psychotic". However, with the dimensional shift in the CAARMS/SIPS towards "transition", the attenuated psychotic symptom can now be used as a true psychotic symptom, automatically resulting in a diagnosis of psychotic disorder in DSM/ICD. Thus, dimensional shifts are used to evoke the notion that a "diagnosis is born", creating the suggestion of a qualitative distinction.

IS "TRANSITION" CONFOUNDED BY NATURAL FLUCTUATION OF DIMENSIONAL EXPRESSION OF PSYCHOSIS?

Given the fact that "transition" in fact represents a dimensional shift, false positive ratings of transition are likely to occur given the natural fluctuation in severity of the transdiagnostic psychosis dimension within and between individuals[22].

The only study to date that attempted to reduce false positive ratings of transition by serial examination of individuals, excluding individuals rated as UHR that in fact were in a natural "low" of a clinical psychotic syndrome, reported a 2-year transition rate of 8%[15], well below the meta-analytical estimate of 19% in studies that did not attempt to exclude such false positive ratings[2].

IS THE CONCEPT OF "TRANSITION" RELEVANT?

There is a lack of research on the clinical relevance of the "transition" outcome[37]. However, evidence from long-term follow-up studies suggests that the binary "transition" concept is not particularly relevant in terms of predicting clinical and functional outcome, and that other symptom domains (affective, cognitive, negative – but also how mixed and how severe psychopathology is) are more impactful in this respect[13,32,38,39].

This observation is supported by the fact that meta-analyses of UHR/CHR intervention studies, focussing on the prevention of "transition", fail to show effect on functional outcome[1].

THE TRUE TRANSITION RATE OF ATTENUATED PSYCHOTIC SYMPTOMS IS <1%: THE ROLE OF SAMPLING ENRICHMENT

A common and persisting misunderstanding is that the "risk" function in UHR/CHR research is caused by the UHR/CHR criteria themselves. However, already more than a decade ago, it was pointed out that high risk for transition does not so much depend on UHR/CHR criteria themselves, but rather on the way the sampling procedures ensure progressive enrichment in risk[4,40]. Thus, the true yearly transition rate of attenuated psychotic symptoms in the general population, established in a meta-analysis of representative, population-based samples, is less than 1%[41]. The fact that the transition rate is much higher in UHR/CHR samples, similarly defined by the presence of attenuated psychotic symptoms[20], has to do with the sampling strategies in UHR/CHR research. A recent meta-analysis showed that the CHR sampling risk enrichment strategy occasioned a 3-year transition rate of 15%[42], thus accounting for half of the most recent meta-analytical 3-year transition rate of 29% attributed to CHR criteria[2]. Other reasons for the inflated transition rates in UHR/CHR research (e.g., natural fluctuation) were discussed earlier.

Direct evidence that the transition rate is caused by sampling enrichment and not CHR criteria came from a study in an early psychosis service for young people, showing that young people presenting to the service meeting UHR criteria had essentially the same 10-year transition rate (17.3%) as young people presenting to the same service with non-psychotic disorders (14.6%)[43].

DOES BIOLOGICAL RESEARCH OF "TRANSITION" MAKE SENSE?

Given the attractive binary outcome of transition, a range of biological studies have attempted to find differences between those who do and those who do not make a transition, resembling the classical case-control paradigm that has dominated biological research on the diagnosis of schizophrenia. These studies have reported a range of biological associations with "transition", published in high-impact academic journals. For example, studies have reported that transition to psychosis was associated with thalamic dysconnectivity[44], progressive reduction of cortical thickness[45], and increased glutamate levels in the associative striatum[46].

Given the uncertain status of the transition concept, these findings cannot be readily interpreted and appear to be false positives unless true, rather than approximate, replication is attempted[47]. Analogously, one trial reported an apparently very strong effect of fish oil in reducing transition rates[48], which became an informative null finding in the replication study[49].

DOES UHR/CHR REPRESENT A VALID AND USEFUL SURROGATE FOR EARLY INTERVENTION?

To lay the groundwork for the current UHR/CHR construct, the architects of the construct started with reviewing the previous literature of the prodromal phase: narratives, early depictions, frequency and pattern of formation of signs and symptoms. This comprehensive review of the prodromal period clearly showed that non-psychotic symptoms – concentration difficulties, motivational impairment, depressed mood, sleep disturbance, and anxiety – frequently emerge prior to onset of psychotic symptoms[50]. However, these symptoms were considered not specific enough to target with a therapeutic intervention, because the main driving force was to reproduce successful medical models of indicated prevention for schizophrenia.

This was a hazardous pursuit for several reasons. First, early detection and intervention in psychiatry cannot be easily fit into the framework of preventive medicine, because: a) natural history and underlying biological mechanisms of mental disorders have yet to be understood; b) there are no objective screening tools; c) there is no specific treatment. Second, UHR/CHR is conceptualized after schizophrenia, which is a classic case of the "no true Scotsman fallacy", as formulated by Robins and Guze[51]: "good prognosis 'schizophrenia' is not mild schizophrenia, but a different illness". From this perspective, setting the goal of preventing "transition" to schizophrenia by intervening at the level of UHR/CHR creates a paradox, or even a self-fulfilling prophecy of failure. Third, there is a degree of tautology in the claim that an intervention specific to positive symptoms – the initial research agenda of prodromal research was antipsychotic trials in the UHR/CHR population – shall prevent "transition" to psychosis by reducing positive symptoms in UHR/CHR states that are primarily defined on the basis of milder positive symptoms. This can be likened to saying that increased cholesterol would be reduced by anti-cholesterol treatment to prevent high cholesterol.

Perhaps not surprisingly, findings of UHR/CHR studies have confirmed what could have been expected: the pragmatic

UHR/CHR construct overlooking early expression of nonspecific psychopathology (Figure 1) indeed backfires on early detection and intervention. A retrospective investigation[52] of the population of the psychiatric case register in The Hague, the Netherlands, revealed that over half of the patients who developed psychosis had received treatment for non-psychotic conditions (mood, anxiety and substance use disorders) during the prodromal phase, revealing a lot more prevention potential than the negligible percentage of the prodromal service, that is limited by the prevention paradox[16,17]. Similarly, the vast majority of the North American UHR/CHR cohort had received psychosocial or pharmacological treatment long before the onset of subthreshold symptoms[53,54]. These findings bring into question the utility of UHR/CHR concept: how early is early intervention?

SHOULD TREATMENT FOCUS ON "PREVENTION" OF "TRANSITION"?

There is no doubt that it is useful to offer early treatment to young individuals with anxiety/depression/substance use and a degree of psychosis admixture as a marker of relatively poor prognosis. It may be expected that non-specific psychotherapeutic interventions will be beneficial, similar to the non-specific effects of a range of psychotherapies in anxiety/depression[55]. For example, there is evidence that simple interventions such as non-directive listening yield better results than cognitive-behavioural therapy in UHR/CHR individuals[56].

There is a body of intervention research, consisting of mostly small, highly heterogeneous and variably controlled studies, focusing on the outcome of "transition" in UHR/CHR individuals[1]. However, given the questionable validity and clinical relevance of the "transition" concept, coupled with the fact that these interventions do no impact functioning[1], there seems to be an urgent need to reconceptualize and reorient treatment strategies in individuals with anxiety/depression/substance use and a degree of psychosis admixture as a marker of relatively poor prognosis.

The available evidence suggests that the tradition to observe these states through the "schizo"-prism may be not useful and ethically questionable. Instead, it may be more productive to consider the full range of person-specific psychopathology in all young individuals with mental health problems and to not become disproportionally fixated on the transdiagnostic manifestation of psychosis. Although psychotic experiences in common mental disorder may be associated with a poorer prognosis, and a small minority of people may indeed develop a clinical picture that meets criteria for schizophrenia, it appears neither useful nor scientifically valid to reduce the transdiagnostic expression of psychosis in early states of multidimensional psychopathology to the misleadingly simple binary concepts of "risk" and "transition", with the implicit suggestion that all or most psychosis leads to schizophrenia.

CONCLUSIONS

Early intervention is a progressive movement and should be supported. However, the CHR-cum-transition concept is overly simplified and uncritically presented as "evidence". The tools solely rely on positive symptoms and a family history of psychotic disorders. The implicit paradigm is to treat any subthreshold positive symptom as a pathway to schizophrenia. Currently, less emphasis is put on antipsychotic treatment, which is a good point. However, the "transition" concept is not just fuzzy but overreaching, and should not be used as an "outcome" in research or clinical practice.

It may be asked why, if this is the state of the evidence, the CHR-cum-transition concept continues to be pushed in research and clinical practice. In two separate articles, Schmidt et al[1] and Schultze-Lutter et al[2] appear to provide "guidance" on CHR research and clinical practice on behalf of the European Psychiatric Association. In these days of heightened awareness of the role of not just commercial, but also academic funding, as well as other interests in research[57], and the vagaries of research in small and selected samples, the meta-analysis of which does not resolve the issue of multiple sources of bias[58,59], one would expect guidance by professional bodies to be critical and objective. It may be more useful to reserve journal space for academic debate, rather than uncritically perpetuating fashionable research notions and the academic interests that come with it.

Instead of the medical, relatively inefficient high-risk approach, a public health perspective, focusing on improved access to a low-stigma, high-hope, small-scale and youth-specific environment with acceptable language and interventions, as embedded in the recent Headspace initiative[60], may represent a more useful and more efficient strategy[61].

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Treatment of people at ultra-high risk for psychosis

The ultra-high risk (UHR) criteria were defined to identify young people at high and imminent risk of developing a first episode of psychosis[1]. The criteria have now been in use worldwide for over 20 years and have shown predictive validity for psychotic disorders across different countries and service settings. UHR individuals have a risk of developing a full psychotic disorder of 15-30% within 12 months, and over 36% after 3 years[2]. These "transition rates" are several hundredfold above that of the general population. Most individuals who develop a psychotic disorder have a diagnosis of schizophrenia or a schizophrenia-spectrum disorder. Identification of UHR individuals, therefore, presents the opportunity for prevention of onset of full psychotic disorder, or at least reduction in disability and delay of onset of first-episode psychosis.

Treatment of UHR individuals has two aims: to manage current symptoms and problems, and to reduce the risk of developing a psychotic disorder[1]. Intervention trials tend to have "transition to psychosis" as the primary outcome, with symptoms, level of functioning and distress sometimes included as secondary outcome measures. A recent meta-analysis studied 10 randomized trials that reported effects on transition rates of low-dose antipsychotic medication, cognitive behavioural therapy (CBT), omega 3 fatty acid and integrated treatment including family therapy, cognitive remediation, social skills training and CBT[3]. This study found that receipt of any specific intervention significantly reduced the risk of developing a first episode of psychosis both at 12 months and over the longer term (2-4 years), albeit with diminished effects over time. The reduced effect at long-term follow-up suggests that at least some UHR individuals remain at risk, and that interventions might delay, rather than prevent, onset of psychosis. Even so, such a delay could be of benefit, enabling people to, for example, finish education and develop supportive networks outside the family of origin. Additionally, individuals who develop a first episode of psychosis after having been treated in the prodromal phase have improved outcomes compared to their counterparts who did not receive such very early intervention[4].

Recently some novel treatments have also been piloted in the UHR group. These have had more targeted outcomes, based on hypothesized mechanisms of action of the intervention rather than global aims of reducing transition risk. For example, a small study of lithium postulated that it may have a neuroprotective effect and examined hippocampal T2 relaxation time and proton magnetic resonance spectroscopy as outcomes testing this hypothesis[5]. Glycine has been tested in two small pilot trials with outcomes of symptoms and neurocognitive functioning[6]. A study of biofeedback measured anxiety and distress as outcomes[7], and a trial of processing speed training examined improvement in processing speed and its correlation with social functioning[8]. A trial of a family intervention measured caregiver warmth, family communication and social functioning as outcomes[9]. All studies showed feasibility and either significant results or trends to significance, indicating future avenues of research.

The above approaches are moving towards developing interventions that are more tailored to underlying pathophysiology. Given the heterogeneity of the UHR group and our knowledge that poor outcomes include development or persistence of non-psychotic disorders and chronic social disability, this is a movement that should be welcomed. One problem is that we lack understanding of the factors that predict these different outcomes, including underlying biological mechanisms. This means that we are unable to individualize treatments. Thus, some UHR individuals are having unnecessary treatment, and others are having ineffective interventions that potentially delay initiation of effective treatment. There is, therefore, a need for investigation into factors that predict different trajectories and outcomes. The aim is to stratify the UHR group according to their underlying pathological processes and target treatment accordingly.

Clearly, we will also need to better understand the mechanisms of action of the interventions. Examples include determining if a subtype of the UHR group has high levels of oxidative stress and using an agent that has reduction in oxidative stress as its mechanism of action. For example, N-acetyl cysteine (NAC) is an antioxidant and may be indicated in such individuals. Studies will need to measure both reduction in oxidative stress and its correlation with improvement in symptoms and functioning as outcomes. We will need to investigate if the mechanism of action of NAC in the UHR group is through reduction in oxidative stress or through some other process (such as reduction in inflammation or an effect on neurotransmitters). Similarly, some UHR individuals may have high levels of dysfunctional metacognitive beliefs that lead to misinterpreting events and difficulty in dealing with stressful situations. These individuals could benefit from metacognitive therapy. Reduction in dysfunctional metacognitive beliefs should be measured as an outcome as well as symptoms and distress[10]. Transition to psychosis will also still be a relevant outcome in both scenarios.

Another issue in treatment of UHR individuals is whether specialized services are indicated and if so, where they should be located. A major reform of early intervention in psychosis services has recently been implemented in England. All these services are now required to assess for presence of the UHR state (there called the "at risk mental state") and provide management of UHR individuals. Patients detected through this pathway are likely to have high levels of symptoms as they will have originally been referred as possible first-episode psychosis. They will likely resemble the original cohort of UHR patients identified mainly through this route over two decades ago[1]. It may be therefore that the transition rate in this group

is also higher than cohorts detected through more generalist pathways such as adolescent health services. Thus, it might be that the integration of UHR and early intervention in psychosis services is indicated, facilitating timely treatment of psychosis should that occur.

On the other hand, we now know that young people with depressive and anxiety disorders frequently experience psychotic-like symptoms and may meet criteria for the UHR state. For these individuals, who will most likely present to primary care or adolescent services, it may be that management is optimal in an enhanced primary care youth service, such as Headspace in Australia. Ideally we need to know more about the different subtypes of UHR individuals and move towards stratified pathways of care depending on need, risk profile and likely underlying pathophysiology.

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Persistent persecutory delusions: the spirit, style and content of targeted treatment

We believe that treatments for persecutory delusions can be substantially better. Current standard psychological and pharmacological treatments have small to moderate effects[1,2]. The severity of the problems associated with paranoia is typically considerable, but the treatments are less effective than those for problems such as anxiety disorders. The isolation, feelings of hopelessness, and missed opportunities for patients with persecutory delusions demand a step change in treatment outcomes.

This is a clinical area that is beginning to receive a degree of attention. There are innovations in understanding and treatment emerging[3-5]. Central to our own strategy for improving treatment have been three inter-connected elements: a sustained, specific focus upon persecutory delusions; the development of a precise theoretical model with causal elements amenable to intervention; and a style and content of intervention that follows from our understanding of delusions. Our objective has been to achieve a much higher recovery rate for persecutory delusions.

The strategy behind building a new treatment has been to target in separate interventions each key causal factor identified from our theoretical model, demonstrate that each reduces the delusion, and then bring the evaluated individual components together into one coherent framework – called the Feeling Safe Programme – that can be personalized for patients.

Persecutory delusions are conceptualized as threat beliefs, developed in the context of genetic and environmental risk, that are maintained by several psychological processes, including excessive worry, low self-confidence, intolerance of anxious affect (and other internal anomalous experiences), reasoning biases, and the use of defence strategies[6]. Therefore, the clinical strategy is first to limit the maintenance factors one by one, then enable patients to enter their feared situations in order to learn that they are now safe. Learning of safety counteracts the paranoia. The fundamental learning is that the difficulty is one of tolerating high anxiety, rather than that there is an external threat.

The spirit, style and content of the 20-session Feeling Safe Programme has emerged from theoretical understanding, patient feedback, and our own clinical experience[7]. To start, the three overarching goals of treatment, shared with patients, are simple: to feel safer, happier, and to get people back doing more of what they want to be doing. These positively framed goals are popular with patients, enhance engagement, and embed the mechanism of change – developing feelings of safety – from the outset. The goals also orient the intervention to the future. We are explicit that no significant time is spent going over the past, unless that is requested by a patient.

Secondly, our perspective that there are multiple causal factors, and the consequent development of multiple treatment modules, allows both individual tailoring of the intervention and patient preference. A brief assessment, combining clinical interview and questionnaires, identifies with patients the factors contributing to their difficulties, and leads to the presentation of a treatment menu. Patients choose which interventions they would like and in which order. This gives patients real control from the outset.

Thirdly, targeting each maintenance factor, focusing on one at a time, provides a method to address the undoubted complexity (and often associated feelings of hopelessness) of presenting problems. We acknowledge the complexity with patients, but explain that a way to deal with it is to tackle one problem, then move on to the next, starting with the most manageable. This reduces the influence of maintenance factors but also raises patients' capacity and confidence to face the demands of directly learning safety *in vivo*.

Fourthly, throughout the programme, we monitor the causal mechanism targeted in a module, as well as the three overarching goals of the intervention. This enables us to track and demonstrate change with patients. Scores are also used in the regular, frequent supervision, particularly to rapidly identify cases requiring greater discussion.

Fifthly, the style that has evolved from this systematic step-by-step approach is akin to interval training: bursts of activity and intensity followed by periods of reflection and integration. Of course, within this approach, the absolute pace of the intervention remains tailored to the individual's needs and preference. Time is predominately dedicated to the implementation of strategies in day-to-day life. Substantial additional contact (e.g., telephone calls) between weekly sessions is expected. This is *not* "low intensity" working.

Finally, the clarity of the model, and strong evidence-base for each element, enables the therapeutic style to be encouraging and optimistic, often holding hope when the patient struggles (e.g., many patients with persistent delusions, right at the start, are not expecting improvement). Transparency, offering direct answers to questions, and providing expert opinion (that is accurate), in tandem with the monitoring of progress and collaborative style, helps substantiate that optimism for patients. All written materials are shared between therapist and patient. There is no separate therapist manual. The therapy booklets provide the framework and key messages of the intervention, but are not prescriptive. Creativity by both the therapist and patient is often fostered, ensuring personal meaning and successful embedding of strategies for change.

We are currently testing the full Feeling Safe Programme in a randomized controlled trial[8]. There are, of course, caveats. The approach does not benefit all patients: our target at this stage is recovery in half of patients with persistent delusions. If this is achieved, there will then be a problem of accessibility. We have developed the programme in a highly manualized form to aid later dissemination, but technological solutions may also prove important. For example, we have found that immersive virtual reality can help patients learn safety[9]. Mobile apps and web-based programs also offer alternative delivery methods[10].

New treatments for persecutory delusions obviously require empirical testing in rigorous trials. Different forms of treatment should not be regarded as a single class, given the varied mechanistic targets, delivery methods, and outcomes pursued. We believe that the concept of specificity, inherent in our approach, should be retained when evaluating treatment developments. In this way, promising routes to improved outcomes for patients with persistent delusions will not be obscured.

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Does neuroimaging have a role in predicting outcomes in psychosis?

A key difficulty in the management of psychotic disorders is that clinical outcomes are difficult to predict on the basis of the patient's clinical features. As a result, patients with psychosis are generally treated in a similar way, even though there may be marked differences in their course of illness or response to medication. However, recent research using neuroimaging suggests that, within a sample of patients with psychosis, the pattern of abnormalities may vary in relation to different clinical outcomes. This raises the possibility that neuroimaging could be used to stratify patients according to clinical outcome; subgroups of patients could then be offered different forms of treatment.

Data from a number of structural magnetic resonance imaging (MRI) studies suggest that patients with relatively poor outcomes have, compared to those with good outcomes, more marked reductions in total and regional grey matter volume, and greater ventricular enlargement[1]. However, other studies have not found a relationship between alterations in brain structure and clinical outcomes[2]. This inconsistency may reflect the use of patient samples that were small, and heterogeneous for age, stage of illness, and pharmacological treatment, all of which can affect neuroimaging findings. Moreover, clinical outcomes have often been determined retrospectively, on the basis of clinical records.

Recent neurochemical imaging studies have suggested that the response to antipsychotic medication in patients with psychosis is related to both subcortical dopamine function, as measured using positron emission tomography, and regional brain glutamate levels, as assessed using magnetic resonance spectroscopy. A good therapeutic response has been associated with elevated dopamine function and relatively normal glutamate levels, whereas a poor response has been linked to normal dopamine function and elevated glutamate levels[3]. Independent work has also linked the response to antipsychotic medication to differences in cortical gyrification[4], and to diffusion tensor imaging measures of white matter integrity[5]. However,

again, these studies involved relatively small samples, and the patients were scanned after they had been treated with antipsychotic medication: it is thus unclear whether the neuroimaging findings predated treatment or were secondary to it.

Most studies to date have related clinical outcomes to a single cross-sectional neuroimaging measure. Serial neuroimaging measurements provide data on how the brain changes over time within the same patient, and recent studies involving longitudinal scanning of patients suggest that measuring the progression of findings facilitates the prediction of outcome[6]. For example, longitudinal data from patients with first episode psychosis and from those with childhood-onset schizophrenia suggest that reductions in hippocampal volume over the first few years of illness are associated with poorer functioning at follow-up[7].

All of the studies mentioned above reported differences between *groups* of patients. However, in order for neuroimaging to be useful in a clinical setting, it must be able to facilitate outcome prediction using data from an *individual* patient. Multivariate statistical approaches such as machine learning provide a means of addressing this issue. For example, application of machine learning analyses to MRI data from patients with first episode psychosis showed that baseline neuroimaging data could predict a non-remitting course of illness over the subsequent six years with an accuracy of 72%[8].

Ongoing studies in this field are seeking to address the methodological issues that may have limited earlier work. Sample sizes can be increased through the involvement of multiple research sites. Although multi-centre studies are logistically challenging, and there are significant confounding factors associated with acquiring data on a variety of different scanners, these disadvantages are probably outweighed by the increased statistical power that results from having much larger samples. Similarly, serial neuroimaging studies are more difficult to carry out than those involving a single scan, but may provide more predictive power. Ongoing studies have also sought to enroll samples that are homogeneous with respect to stage of illness and previous treatment, and that are treated in a standardized way subsequent to scanning. A good example of this is OPTiMiSE (Optimization of Treatment and Management of Schizophrenia in Europe), a large multicenter study funded by the European Commission[1]. This involves a neuroimaging assessment of a large multi-centre sample of medication-naïve or minimally treated first episode patients, all of whom are then treated with amisulpride following a standardized protocol. Their clinical outcomes are evaluated prospectively.

Future studies may also benefit from using more than one modality of neuroimaging; there is some evidence that this may improve prediction of outcomes[9], although other data do not support this[10]. Similarly, integrating neuroimaging data with non-imaging measures that have independently been linked with altered outcomes in psychosis, such as polygenic risk score, substance use, inflammatory markers and central nervous system autoantibodies, may enhance predictive power. However, although this may be a reasonable expectation, it has yet to be tested.

Even if a neuroimaging measure is established as a robust statistical predictor of clinical outcomes, this does not necessarily mean that it can be translated into mainstream clinical practice. Financial and practical considerations will apply, such as the cost of scanning and the availability of the scanner. The development of tools that can be used in a clinical setting is likely to require neuroimaging measures that can be acquired without the need for highly specialized training or equipment. Some ongoing studies are explicitly focused on the development of such tools for psychosis (see, for instance, www.psyscan.eu).

Given that psychotic disorders are pathophysiologically heterogeneous, it is reasonable to expect that neuroimaging techniques which can identify pathophysiological differences within patient samples may be useful in predicting clinical outcomes. However, at present, it is unclear which particular neuroimaging measures will be the most useful, and whether combining these with non-imaging biomarkers will enhance their ability to facilitate prediction of outcomes in psychosis.

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The role of expectations in mental disorders and their treatment

Expectations are defined as cognitions which are future-directed and focused on the incidence or non-incidence of a specific event or experience[1]. In the treatment of mental disorders, examining and modifying patients' expectations is discussed as a central mechanism of change[2,3]. This focus on expectations does not disregard any past experiences, but considers them only of relevance if they determine predictions about future events.

The relevance of expectations for clinical conditions and their treatment can be illustrated by the following example: temporary ear noises are no problem for most people, as long as the affected persons expect them to vanish promptly. However, the same experience is difficult to bear if affected people expect them to last forever. Analogously, it may be not the negative mood, the unpleasant stimulation, the adverse life event *per se* that determines whether exposed people develop a mental or psychosomatic disorder, but the expectation about the timeline of the aversive condition, expected future threats, expected curability, and expected competence to cope with the unpleasant experiences.

Neurobiology and psychological sub-disciplines such as developmental psychology and social psychology have focused on expectations for decades. They provide us with detailed knowledge on how expectations are formed, under what circumstances they are modified, or when they persist despite contradictory experiences.

Expectations lead to brain activities that sensitize for the expected experience[4], and they are closely linked to affective reactions[5]. "Prediction error" paradigms and their association with dopaminergic activation, amygdala activation during aversive coding, and the role of contextual information in the generation of expectancies are just a few neurophysiological examples of how the topic has been investigated.

Associative learning, influences via group norms and media, and the phenomenon of sticking to expectations despite expectation violations (cognitive "immunization") are psychologically relevant concepts to better understand why specific expectations are present.

We currently face the challenge of investigating the role of expectations from a clinical perspective and transferring this knowledge into psychotherapeutic and psychopharmacological practice. This approach may allow for a better understanding of the dynamics of mental and psychosomatic disorders, guiding the development of tailored interventions based on highly effective mechanisms. Moreover, focusing on expectations and their persistence helps to explain why some treatments fail.

Some mental disorders are "expectation disorders" by definition. This is particularly so in the case of anxiety disorders, such as phobias, panic disorder and generalized anxiety disorder. In these cases, patients expect adverse consequences when being exposed to specific stimuli, situations, or experiences (e.g., the phobic stimulus, the experience of palpitations). In obsessive-compulsive disorder, the patient expects dreadful consequences if compulsive behaviors are prohibited.

The role of expectations in post-traumatic stress disorder (PTSD) seems to be more complex. While most people feel secure and do not expect horrible events, this basic confidence in everyday life situations is violated if people suffer from trauma[6]. Some patients with PTSD do not want to talk about the trauma because they do not expect to be able to bear the emotions that will arise.

In other mental disorders, expectations are not part of the diagnostic criteria, but are also of relevance. For example, individuals suffering from depression show more depression-specific negative expectations[7]. Even in general medical conditions, expectations and expectation-associated concepts (e.g., fear avoidance in chronic pain) have been shown to predict persistence and survival[8].

Expectations about treatment success are the most prominent predictor of outcome, both in psychopharmacological and psychological interventions, and they are considered to be a major determinant of placebo effects[9]. In most psychopharmacological trials, placebo responses represent a substantial proportion of the overall treatment effect. Optimizing treatment expectations can result in improved outcome and prevention of treatment side effects, while the induction of negative expectations can abolish the effects of highly effective medications[10].

If expectations are one of the most powerful predictors of outcome, interventions must maximally modify illness-specific expectations, and positive outcome expectations should be sufficiently established before treatment starts. One of the traditional psychological interventions that may be considered a powerful tool to change expectations is exposure therapy. However, traditional exposure therapy needs to be reformulated to better focus on the change of expectations (e.g., explicit comparison between pre-exposure expectations and post-exposure experiences)[3].

Expectation-focused psychological interventions (EFPI)[7] place a strong focus on analyzing and summarizing disorder-specific expectations of the patient, developing situational tests to check the credibility of these expectations, and re-evaluating expectations by comparing pre-existing expectations with the experience during exposure.

In addition to disorder-specific expectations, the baseline expectations about positive and negative effects of interventions should play an important role in treatment planning. If patients have negative attitudes about drug therapy, these attitudes should be addressed before starting medication. In psychological therapies, positive outcome expectations should be established before more challenging interventions are suggested.

Considering the large effects that must be attributed to placebo mechanisms in psychiatry, expectations and their modification can be considered the most powerful mechanism for successful treatment. Therefore, there is an urgent need to utilize knowledge about expectations to improve treatment outcomes.

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Why ultra high risk criteria for psychosis prediction do not work well outside clinical samples and what to do about it

The use of ultra high risk (UHR) criteria in selected help-seeking samples is the only clinical possibility to alter the course of psychosis by preventing its onset. The UHR paradigm can additionally reduce the duration of untreated psychosis[1] and provide extended benefits to patients who are experiencing a first episode of psychosis[2].

Because of these potentials, there is a great interest in the use of UHR outside clinical samples, such as in the general population. The first epidemiological study investigating the significance of UHR criteria in the non-help-seeking general population aged 8-40 was published in this journal[3]. It indicated that only 1.3% of the general population met the UHR criteria of the Structured Interview for Psychosis-Risk Syndromes (SIPS)[3]. The longitudinal fate of these individuals has just been released[4]: 143 UHR and 131 controls were followed up for an average of 2.5 years, with three transitions to psychosis in the UHR group (psychosis risk = 2.09%) and no transition in the control group.

These results are of great interest, as they may support the epidemiological validity of the UHR paradigm, although they are likely to be underpowered (assuming a 0.001% risk in the control group as continuity correction and an alpha = 0.05, the resulting power would be of 38% only). Beyond these limitations, the key finding of 2.09% psychosis risk (at 2.5 years) in people meeting UHR from the general population is of crucial clinical relevance. It is strikingly lower than the annualized 2-year 20% (95% CI: 17%-25%)[5] transition risk in help-seeking UHR samples, that are characterized by frequent comorbid affective disorders and functional impairments[6].

These findings clearly confirm that the prognostic accuracy of the UHR criteria strictly depends on the sample to which they are being applied. Indeed, clinical help-seeking samples of individuals undergoing UHR assessment are characterized by a substantial pre-test risk enrichment (pre-test risk for psychosis)[7] of up to 15% at 38 months[8]. As demonstrated in a previous paper in this journal[9], the use of UHR assessment is associated with a small positive likelihood ratio of 1.82 at 38 months and a modest ability to rule in psychosis[9]. Therefore, to reach some prognostic accuracy of clinical utility in individuals meeting UHR criteria, it is necessary to apply them to samples that are already enriched in psychosis risk, i.e., with a significant pre-test risk. For example, a recent study published in this journal[10] has shown that meeting the UHR criteria given an underlying 22q11.2 deletion syndrome, a condition that is characterized by a substantial pre-test risk for psychosis, is associated with a 27.3% risk of psychosis at 32 months.

These considerations clearly limit the practical utility of the UHR outside of clinical samples, as recently recognized by the recommendation no. 4 of the European Psychiatric Association, which suggests that the UHR assessment should be primarily offered to selected samples of subjects "already distressed by mental problems and seeking help for them".

At the same time, because of the potential benefits yielded by the UHR paradigm, it seems important to continue exploring the usefulness of an extended application of UHR assessment in several different samples. A first pragmatic approach to estimating the prognostic accuracy of the UHR assessment in several scenarios would be to use the meta-analytical Fagan's nomogram that we presented in a previous paper in this journal[9]. This nomogram is based on the intrinsic properties of the UHR assessment (such as the positive and negative likelihood ratios[7]) and can be applied to different populations with a given pre-test risk of psychosis onset to estimate their post-test risk of psychosis at 38 months.

Importantly, our nomogram has now been externally validated. In fact, with that nomogram, we had estimated a small post-test psychosis risk (less than 5% at 38 months) in the general population, a value that is similar to the real value observed in the epidemiological study discussed above[4]. Similarly, with our nomogram, we had estimated a post-test psychosis risk of 26% for patients affected with the 22q11.2 deletion syndrome[9], which exactly matches to the real value recently reported in this journal[10].

The use of our nomogram can thus provide reliable estimates (along with 95% CIs) for post-test risk of psychosis in individuals meeting UHR criteria, given a determined pre-test risk. Using the nomogram, researchers can simulate the expected prognostic accuracy, and estimate the required sample size needed to test their hypotheses.

Since the use of the UHR assessment outside clinical samples is likely to be associated with low predictive power, it is fundamental to perform accurate power calculations. In this scenario and considering the probability of infrequent events, a second approach could involve using sequential testing methods[11], for example by using the SIPS in samples already enriched for psychosis risk, as shown in this journal[12]. Sequential testing is traditionally adopted in medicine to enrich the risk of samples that are selected to undergo different diagnostic or prognostic tests.

A third practical approach could be to better investigate the factors that modulate pre-test risk enrichment in samples undergoing a UHR assessment. We have recently shown that it may be possible to stratify help-seeking individuals undergoing UHR assessment through the use of simple socio-demographic and clinical variables[13]. The predictive model has been externally validated and can be used to inform future research in the field, with the scope to improve prognostic accuracy of psychosis prediction.

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Drug use disorders: impact of a public health rather than a criminal justice approach

The Outcome Document of the 2016 United Nations General Assembly Special Session on drugs (UNGASS 2016), unanimously approved by the 193 Member States, has recognized "drug addiction as a complex multifactorial health disorder characterized by chronic and relapsing nature" that is preventable and treatable and not the result of moral failure or a criminal behavior. Historically, most nations' strategies for addressing substance use disorders have centered on punishment, and thus recognition of the need to shift from a criminal justice to a public health approach represents a major shift in mentality by United Nations Member States.

This achievement was the result of a continuous dialogue between policy makers and the scientific community during recent sessions of the United Nations Commission on Narcotic Drugs. In 2015, the United Nations Office of Drugs and Crime and the World Health Organization created an Informal International Scientific Network, consisting of experts in addiction sciences, to advise the Commission. Network members were appointed by Member States and represented widely diverse geographical regions, political systems, and cultures.

The Network's input for the Commission's preparation of UNGASS 2016 provided the scientific support for the concept that substance use disorders are brain disorders[1]; that they can be treated; that people with even the most severe forms can recover with access to evidence-based treatment and social supports[2]; and that criminal sanctions are ineffective at preventing or addressing these disorders. It also highlighted evidence-based approaches to drug policy based on public health principles, emphasizing social protection and health care instead of conviction and punishment.

The Network issued eight recommendations, which were adopted unanimously by all the United Nations Member States at UNGASS 2016 and summarized in the Outcome Document of that meeting. These recommendations are a testament to a momentous shift in mentality, to which science and the Network have contributed.

The recommendations are as follows:

- *Eliminate stigma and discrimination toward individuals with substance use disorders.* Increasing public awareness of addiction/dependence as a chronic but treatable disorder is needed to overcome stigma and promote a shift from exclusion and blame toward support and compassion. This should include national policies that address substance use disorders as neurobiological disorders having complex social and developmental underpinnings.
- *Address substance use disorders as public health problems instead of criminal justice issues.* A comprehensive public health approach should offer accessible evidence-based prevention, treatment, and recovery options to drug users, and engage those who commit criminal offences in evidence-based treatment during and following, or in lieu of, incarceration, to prevent relapse and recidivism. It also includes naloxone distribution for overdose prevention[3], and integration of treatment of substance use disorders with prevention and treatment of infectious diseases (HIV and hepatitis C)[4] and of co-occurring psychiatric conditions[5].
- *Implement evidence-based prevention programs.* Substance use disorders are fully preventable. The use of evidence-based prevention programs, both universal and targeted to high-risk individuals, has shown positive outcomes in reducing drug initiation and escalation of use. Since prevention programs address risk and protective factors that are common to a range of behavioral problems, they produce positive outcomes not just in drug taking but also in reducing aggression, early pregnancies, and drugged driving, and improve mental health and educational outcomes. Highest priority should be given to interventions targeting children and youth, since the earlier the use of drugs the greater the risk for substance use disorders and the higher their severity[6].
- *Implement evidence-based treatments for substance use disorders.* Abundant research shows that these disorders are treatable and that people do recover when given evidence-based care, including behavioral therapies for all these disorders and medication-assisted treatments for alcohol and opioid use disorders and for smoking cessation[7,8]. However,

because changes in the brain function in these disorders can be long-lasting, an individual may be at increased risk for relapse even after years of abstinence. Effective treatment thus requires a chronic care model as used for other chronic conditions such as cardiovascular disease or diabetes, which along with routine screening should be integrated into the general health care system and be affordable and accessible.

- *Collect and utilize scientific data and engage scientific experts in policy making*. Reliable epidemiological data on the economic and social factors that contribute to drug use and substance use disorders should be gathered and analyzed to drive planning and evaluation of drug policy interventions and decision making. The scientific community should provide knowledge of effective prevention and treatment interventions as well as training in their implementation and ongoing evaluation. Member States should establish national early warning systems to monitor changing drug trends and identify emerging public safety and health threats.
- *Engage diverse stakeholders in coordinated policy making*. Because of the complexity of the health and safety issues related to substance use disorders, policy makers should involve diverse stakeholders, including public health, education, law enforcement, science, and health care systems, as well as solicit input from countries with different cultures, resources, and experiences. Stakeholders should cooperate in the planning, implementation, and evaluation of science-informed interventions and policies that address the demand as well as the supply of drugs. This would include diverting offenders into treatment, combating drug production and trafficking, creating alternative opportunities for communities dependent on the drug trade, and ensuring the safety and protection of the most vulnerable as it relates to drug taking but also engagement in drug trading.
- *Support drug-related research*. Ongoing research must address the effects of drugs (especially emerging new synthetic drugs) on the brain and behavior; the social and public health impact of different drug policies; the best ways to tailor prevention and treatment modalities to different cultural contexts; and the therapeutic potential of controlled substances (e.g., cannabinoids). Regulatory impediments to conducting research on scheduled drugs should be minimized and policies that facilitate research across these areas implemented.
- *Ensure access to scheduled medications for therapeutic use*. Some controlled and dependence-producing psychoactive drugs are necessary medicines for treating serious health conditions. The international drug conventions are designed to ensure legitimate medical access to such medicines, under appropriate supervision, through a distribution chain that deters and combats illicit manufacture, sale, and diversion. Necessary steps should be taken to remove barriers to accessing controlled drugs for legitimate medical needs, such as analgesic drugs in the more than 150 countries where pain is undertreated[9].

The public health goal of reducing the world's drug problems cannot be achieved without addressing substance use disorders with the same scientific rigor, compassion, and commitment that other physical and mental health problems are addressed. Substance use disorders are common psychiatric disorders, and access to affordable, quality health care for such disorders has been declared an inherent right for all United Nations Member State citizens.

The strong consensus reached by the Network – scientists representing very different countries that have widely varying policies, political views, and stages of development – is an unprecedented and positive step toward a world where science guides nations' approach to drug misuse and its associated health and safety consequences. Adopting these recommendations will be crucial to fulfilling Member States' joint commitment to effectively address and counter the world drug problem.

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Prevention and early intervention for borderline personality disorder: a novel public health priority

There is now a broad evidence-based consensus that borderline personality disorder (BPD) is a reliable, valid, common and treatable mental disorder[1]. The adverse personal, social and economic consequences of BPD are severe. They include persistent functional disability[2], high family and carer burden[3], incomplete education with fewer qualifications and disproportionately high unemployment[4], physical ill health[5], greater burden of mental disorders, recurrent self-harm, and a suicide rate of around 8%[1]. The high economic costs of BPD (estimated to be €16,852 per patient per annum in the Netherlands) are attributable to high direct treatment costs and high indirect costs, chiefly work-related disability[1]. BPD is a stronger predictor of being on disability support than either depressive or anxiety disorders[6].

Although BPD usually has its onset in the period between puberty and emerging adulthood (young people)[7], delay in the diagnosis and treatment is the norm, and discrimination against people with BPD is widespread. Specific treatment is usually only offered late in the course of the disorder, to relatively few individuals, and often in the form of inaccessible, highly specialized and expensive services[4]. Accumulating evidence indicates that such "late intervention" often reinforces functional impairment, disability and therapeutic nihilism.

The proliferation of knowledge about BPD in adolescents and emerging adults ("youth") over the past two decades[8,9] has provided a firm basis for establishing early diagnosis and treatment ("early intervention") for BPD and for subthreshold borderline personality pathology[7]. Several salient issues arise from this literature. First, personality disorder begins in childhood and adolescence, and can be diagnosed in young people. Second, DSM-5 BPD is as valid and reliable a diagnosis in adolescence as it is in adulthood, based on similarity in prevalence, phenomenology, stability and risk factors, marked separation of course and outcome from other disorders, and efficacy of disorder-specific treatment. Third, BPD is common among young people: the estimated prevalence is 1-3% in the community, rising to 11-22% in outpatients, and 33-49% in inpatients[7,8]. Fourth, when BPD is compared with other mental disorders, it is among the leading causes of disability-adjusted life years (DALYs) in young people[9]. BPD is also a substantial financial burden for the families of young people, with estimated average costs per annum in the US of $14,606 out-of-pocket, plus $45,573 billed to insurance[10]. Fifth, the "first wave" of evidence-based treatments has demonstrated that structured treatments for BPD in young people are effective[4]. Finally, the weight of empirical evidence has led the DSM-5 and the UK and Australian national treatment guidelines to "legitimize" the diagnosis of BPD prior to age 18.

The Global Alliance for Prevention and Early Intervention for BPD had its origins at a meeting convened under the auspices of the National Education Alliance for BPD in New York in May 2014. The Alliance calls for action through a set of scientifically based clinical, research and social policy strategies and recommendations.

Clinical priorities include: a) early intervention (i.e., diagnosis and treatment of BPD when an individual first meets DSM-5 criteria for the disorder, regardless of his/her age) should be a routine part of child and youth mental health practice; b) training of mental health professionals in evidence-based early interventions should be prioritized; c) indicated prevention (preventing the onset of new "cases" by targeting individuals showing subthreshold features of BPD) currently represents the best starting point toward developing a comprehensive prevention strategy for BPD; d) early identification should be encouraged through workforce development strategies (knowledge about BPD as a severe mental disorder affecting young people should be disseminated among trainees and clinicians in the child and youth mental health professions; programs should address clinician-centred discomfort with the label, mistaken beliefs, and prejudicial and discriminatory attitudes and behaviour); e) the diagnosis of BPD should not be delayed (non-diagnosis of BPD is discriminatory because it denies individuals the opportunity to make informed and evidence-based treatment decisions, and excludes BPD from health care planning, policy and service implementation, ultimately harming the young people's prospects); f) misleading terms, or the intentional use of substitute diagnoses, should be discouraged (when sub-threshold BPD is present, terms such as "BPD features" or "borderline pathology" are preferred); g) family and friends should be actively involved as collaborators in prevention and early intervention (typically, family and friends are the "front line" for young people with BPD, and their central role should be recognized and supported).

Research priorities are as follows: a) prevention and early intervention for BPD must be integrated with similar efforts for other severe mental disorders, such as mood and psychotic disorders, acknowledging the "equifinal" and "multifinal" pathways for the development of psychopathology; b) building a knowledge base for a health care system response to prevention and early intervention for BPD can take two approaches (for indicated prevention and early intervention, a critical task is to identify risk factors for the persistence or worsening of problems, rather than the "onset" or incidence of disorder *per se;* or treatment development can be based upon causal mechanisms that underlie risk, such as environmental adversities); c) novel, low-cost preventive interventions that can be widely disseminated should be developed and evaluated (such interventions will need to be developmentally appropriate, and stage/phase specific, incorporating stepped care service models); d) education and skill development programs for families with a young person with BPD are a key priority for treatment research; e) research needs to fully quantify the educational, vocational and social

outcomes for young people with BPD; f) further development and validation of brief and "user-friendly" assessment tools is needed to promote the systematic use of standardized evaluation in research and clinical settings; g) detailed health economic data are needed to support prevention and early intervention programs for BPD and should be included in all clinical trials; h) research identifying methods to improve access to evidence-based treatments and reduce treatment dropout is a priority (this should include novel locations and formats for delivery of treatments, such as in schools, out-of-home care, or youth forensic settings).

Social and policy priorities include the following: a) BPD needs to be recognized as a severe mental disorder at all levels of the health system; b) evidence-based policy is needed to address BPD from primary through to specialist care, with the aim of building a health care system response to prevention and early intervention with young people and those who care for them as its focus, and including young people and families as partners in the design of such systems; c) discriminatory practices in health care systems must be eliminated, especially regarding BPD as a "diagnosis of exclusion" from services and refusing health insurance coverage for people with BPD.

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Integrated care for mental, neurological and substance use disorders in non-specialized health settings: rising to the challenge

Worldwide, mental, neurological and substance use (MNS) disorders are major contributors to the global burden of disease as estimated by disability adjusted life years, and this is rising especially in low- and middle-income countries (LMIC)[1]. MNS disorders commonly co-occur with other chronic health conditions, both communicable (e.g., HIV/AIDS) as well as non-communicable (e.g., diabetes, cardiovascular disease) and, if untreated, worsen the outcome of these conditions. People with MNS disorders and their families are doubly challenged by stigma that further worsens their quality of life, affects social acceptability, employability and interferes with help seeking.

Financial resources for developing and maintaining mental health services in LMIC are very low. The level of public expenditure on mental health is less than US$2 per capita. Furthermore, the number of mental health workers is below 1 per 100,000 in LMIC compared to over 50 in high-income countries[2]. The scarcity and unequal distribution of services means that 76-85% of people with MNS disorders in LMIC do not receive the care they need.

Recognizing the urgent priority to scale up services for MNS disorders, global initiatives have pressed for reforms to ensure that people with these disorders receive care that is effective and affordable, and respects their rights and dignity[3,4]. In line with the World Health Organization (WHO)'s leadership in the field of global public health, the Mental Health Gap Action Programme (mhGAP)[5] was initiated, with the objectives to scale up services and enhance coverage. Through its objectives, the mhGAP is contributing towards achieving the targets of the Comprehensive Mental Health Action Plan 2013-2020, particularly in providing comprehensive, integrated and responsive mental health and social care services in community-based settings. The underlying principle of mhGAP is to strengthen non-specialist primary health care systems and providers to deliver MNS services, thus facilitating the vital link to integrate mental and physical health[6].

To support countries to strengthen MNS care by non-specialist health care providers, the mhGAP Intervention Guide (mhGAP-IG) was developed in 2010 using evidence-based guidance and extensive stakeholder consultation. The mhGAP-IG was translated in over 20 languages and has had widespread application by a range of stakeholders in over 90 countries for integrated management of priority MNS disorders. It has been

used as a key tool in the phased approach to scale up mental health services and reduce the treatment gap on a regional-national-subnational level, as a capacity building tool for a wide range of health professionals and para-professionals, and for developing and updating undergraduate and postgraduate curricula for health professionals. It has also been used to scale up mental health response in emergency settings[7,8].

The WHO has incorporated feedback and recommendations from international experts as well as latest evidence in the field to update the mhGAP-IG and has now released the mhGAP-IG Version 2.0[9]. The key developments include: content update in various sections based on new evidence; design changes for enhanced usability; a streamlined and simplified clinical assessment that includes an algorithm for follow-up; inclusion of two new modules (Essential Care and Practice, and Implementation), and revised modules for Psychoses, Child and Adolescent Mental and Behavioural Disorders, and Disorders due to Substance Use. An interactive electronic version of the mhGAP-IG is currently under development and will have benefits in terms of increased ease of use, added functionality and cost savings.

The inclusion of mental health and substance abuse in the Sustainable Development Goals (SDGs) at the 70th Session of the United Nations General Assembly in September 2015 has paved the way for mental health to be integrated into the broader development plans of countries over the next 15 years. There is now fresh impetus for countries to provide sufficient financial and human resources for mental health care; improve access to care for people with mental illness and their families; and integrate mental health care across different sectors such as social, education and employment, and implement community programmes. In order to initiate a collaborative, multisectoral commitment to put the mental health agenda at the centre of global health and development priorities, the World Bank Group and WHO co-hosted the Out of the Shadows: Making Mental Health a Global Priority meeting in April 2016, that emphasized the cross-cutting nature of mental health issues and the need to integrate mental health services into general health systems[10].

To realize the goal of universal health coverage, it is essential for health care providers and planners to maximize efforts to scale up care for people with MNS disorders, and the mhGAP-IG Version 2.0 will be a valuable tool to facilitate this process.

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Causes and predictors of premature death in first-episode schizophrenia spectrum disorders

As highlighted by the Forum in the February 2017 issue of this journal[1], patients with schizophrenia spectrum disorders have significantly higher risk of premature death due to suicide and physical illness; their expected reduction in life expectancy is 10-20 years[2-4]. Since the disorders affect 2-3% of the population, with peak onsets in early adulthood, their impact on public health is considerable[5].

We report findings from a 10-year prospective study of 281 patients with DSM-IV schizophrenia spectrum disorders recruited consecutively at first treatment in four Nordic catchment areas over four years. They were assessed during their first week of treatment, with follow-ups after one, two, five and ten years[6,7]. Data were linked to the central registries of persons and causes of death at Statistics Norway and Statistics Denmark. Information about two- and ten-year average age-specific mortalities was used to compute cause-specific expected numbers of deaths. Crude standardized mortality ratios (SMRs) were calculated as observed deaths/expected deaths.

Thirty-one participants (11%) were dead at follow-up (SMR 11.56; 95% CI: 7.86-16.42). Sixteen (6%) died by suicide (SMR 46.50, 95% CI: 26.58-75.51); seven (2.5%) by accidental overdoses or other accidents, and eight (2.8%) from physical illnesses, including three (1%) from cardiovascular illness. Time to death was significantly shorter in those who committed suicide compared to the two other groups (mean 1,274 ± 1,032 days vs. 2,706 ± 1,046 days for accidents and 3,000 ± 792 days for natural deaths, $p<0.001$). Six (37.5%) of those who died by suicide did so within the first two years (two-year SMR estimate 81.91, 95% CI: 30.05-178.28). Only one accident and no natural deaths occurred in this period.

All-cause mortality was higher for men than for women. Univariate analyses showed that those alive at the ten-year follow-up were significantly older at baseline compared to those who died by suicide, and significantly younger than those who died from other reasons. Those alive had significantly shorter duration of untreated psychosis (DUP), lower baseline rates of drug and alcohol misuse, longer education and higher employment than those with all-cause deaths.

There were no significant associations with baseline clinical symptoms or lifetime/current measures of depression/suicidal behaviors and no significant between-group differences in time to first remission or time being psychotic or in treatment during the first two years (including length/dosage of antipsychotic medication and number/length of hospital admissions). Measures of depression and suicidal behavior at last follow-up were, however, significantly higher in those who died by suicide.

A multinomial logistic regression analysis indicated significant influences of lower age, longer DUP and baseline alcohol misuse on increasing risk of death by suicide; and of higher age, longer DUP and baseline drug misuse on increasing risk of death from other reasons. Kaplan-Meyer survival analyses showed that long DUP and baseline substance misuse (alcohol + drugs) were significantly increasing risk of all-cause mortality (Mantel-Cox χ^2 (3)=36.98, $p<0.001$), with a significant contribution of substance misuse also after removing overdose deaths.

Our results confirm previous findings of high mortality rates in patients with schizophrenia spectrum disorders. We clearly demonstrate for the first time that long DUP is a significant risk factor for all-cause mortality, including suicides, accidents and physical illnesses. Long DUP can in this context best be seen as a marker of problematic help-seeking behaviors, in line with recent register studies reporting that patients with schizophrenia dying from physical illnesses enter treatment late[8].

That substance use diagnoses increase risk of premature death in patients with severe mental disorders has been demonstrated previously[9]. We here show that also substance use below the diagnostic threshold for use disorders is a risk factor. The strong association between baseline substance misuse and all-cause mortality is striking. This can be based in shared underlying risk factors for suicide, including impulsivity, emotion regulation difficulties and interpersonal problems. The effects of substances during intoxication can also increase impulsive behavior and lack of self-care, adding to risks for accidents or physical illnesses.

The two-year SMR estimate for suicide was >80. Previous studies have shown a particularly high suicide risk before or during the first months of treatment[10]. Our participants were recruited through an early treatment and intervention study and thus very early compared to studies recruiting at discharge from first inpatient treatment or later. The findings can thus be seen as an illustration of the particularly high risk for suicide at this early stage, and underline that mortality estimates based on multi-episode patient samples significantly underestimate the suicide risk in schizophrenia spectrum patients. The number of deaths from cardiovascular disorders was low. The participants were, however, still in their late thirties and not yet into the main cardiovascular risk period.

In conclusion, we found a high mortality rate during the first ten years of treatment, with the risk of dying by suicide being particularly high during the first two years. Long DUP and substance misuse at baseline were significant predictors of all-causes mortality. This is of clinical importance, since help-seeking behaviors and substance use can be responsive to interventions.

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A reassessment of the relationship between depression and all-cause mortality in 3,604,005 participants from 293 studies

As reported in the February issue of this journal[1], over three decades of research suggest that depression is associated with an increased risk of all-cause mortality, although some large recent studies have found negative or null associations[2,3]. To better inform clinical decision making and evidence-based service provision, it is crucial to resolve this discrepancy.

Here we summarize the principal findings of the largest ever investigation of the relationship between depression and all-cause mortality, comprising 3,604,005 participants and over 417,901 deaths, based on a reassessment of 293 studies derived from 15 systematic reviews. We observed that several factors moderate the relationship between depression and mortality, and found no evidence of an association when controlling for comorbid mental disorders and health behaviors (see https://osf.io/svywu/ for the complete report and the extracted data).

The purpose of this reassessment was to better understand the features of studies that have sought to address the depression-mortality relationship, to delineate some methodological reasons for heterogeneity between studies (sample size and characteristics, number of deaths and follow-up periods, and adjustment for mental disorders and health behaviors), and to explore whether estimates of the relationship between depression and mortality on the basis of the methodologically most rigorous studies differed from those of previous meta-analyses. The three main results of the study are as follows.

First, there was a pronounced publication bias[4], as indicated by the positive intercept (1.02; 95% CI: 0.72-1.31) of effect estimates on their standard errors favoring imprecise studies with large positive associations. The largest estimates consistently came from studies with small samples, low number of deaths, and brief follow-up periods.

Second, only 16 (~5%) of the included studies adjusted for at least one comorbid mental condition. This is surprising, given that more than half of individuals diagnosed with major depressive disorder suffer from at least one additional comorbid mental disorder in their lifetime[5]. The pooled relative risk (RR) of these 16 estimates (1.08; 95% CI: 0.98-1.18) was smaller than the RR of the 266 estimates that were unadjusted for comorbid mental disorders (1.33; 95% CI: 1.29-1.37). Additionally, there was no evidence of an association between depression and all-cause mortality among the fraction of eight of these estimates that also adjusted for health behaviors (smoking, drinking or physical inactivity) (1.04; 95% CI: 0.87-1.21).

Third, apart from sample size, follow-up duration, and lack of adjustment for important variables, other substantial sources of heterogeneity between studies emerged. Over two-thirds of the estimates comprised respondents who were pre-selected on the basis of medical conditions. This is problematic, because many symptoms of major depression (e.g., insomnia, fatigue) are shared with various physical conditions[6], or may arise as side effects of medications used to treat existing pathologies. Preselecting participants on the basis of medical conditions could therefore result in confounding by reverse causality among those who are physically unwell at baseline. Given that somatic symptoms that are not confounded by physical conditions are integral to a diagnosis of major depression, studies based on medical samples that use rating scales (instead of diagnostic interviews that query the source of these somatic symptoms) may be particularly likely to misclassify individuals who are of relatively poorer health as depressed. Furthermore, we found that over forty different instruments were used to measure depressive symptoms, which is problematic due to the considerable content heterogeneity among commonly used instruments[7]. Even studies that used the same questionnaire frequently adopted different cutoff scores for a probable diagnosis of major depressive disorder. The interaction of three of the aforementioned points – the use of scales encompassing physical symptoms that may indicate comorbid medical conditions; the use of samples pre-selected based on medical conditions; the lack of adjustment for comorbidities when estimating the effect of major depressive disorder on mortality – points to significant weaknesses in the literature.

We therefore estimated the association of depression and mortality among studies that used DSM-based structured interviews requiring the presence of core depressive symptoms (sad mood or anhedonia) prior to assessing for more general physical, somatic and cognitive symptoms, in community-based samples and based on survival analysis methodology. Only four estimates (1% of all studies) met these criteria, among which the pooled hazard ratio was 1.17 (95% CI: 0.75-1.60).

Given the overall poor quality of the available evidence, we are unable to draw strong conclusions about the relationship between depression and mortality. Studies with large samples, extensive follow-up periods, adjustment for mental disorders and health behaviors, and time-to-event outcomes assessed using survival analysis methodology are especially needed.

More work of a higher quality is also required to examine which variables related to depression and mortality may modify this relationship. For example, the subsequent onset of health behaviors such as smoking, drinking and physical inactivity appear to play an important role in mediating the risk of adverse cardiovascular outcomes among depressed individuals[8]. This could account for a variety of adverse health outcomes that are not limited to cardiovascular disorders. Moreover, the risk of depression and mortality are both influenced by a subset of common variables. For example, smoking at baseline is associated with increased risk of depression onset at follow-up[9], and smoking is associated with many causes of death[10].

More rigorous research is needed to better understand whether depression does, in fact, pose an increased risk of all-cause mortality. We hope that our work will encourage such efforts.

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Correction

It has been brought to our attention that the Acknowledgements section of the paper "Disorders related to sexuality and gender identity in the ICD-11: revising the ICD-10 classification based on current scientific evidence, best clinical practices, and human rights considerations", by Reed et al, published in the October 2016 issue of *World Psychiatry*, should contain the following additional statement: "The authors are grateful to the other members of the 2011-2013 ICD-11 Working Group on Sexual Disorders and Sexual Health, including R. Coates, J. Cottingham, S. Krishnamurti, A. Marais, E. Meloni Vieira, S. Winter and A. Giami, for their contributions to the proposals discussed in this article".

Report on WPA activities in the triennium 2014-2017

The WPA has delivered on almost all major aspects of the Action Plan 2014-2017 as had been agreed and approved by the General Assembly in Madrid in September 2014.

- *Public mental health*. A curriculum and policy statements on the following topics have been produced: a) gender-based interpersonal violence and mental health (chaired by P. Chandra and D. Stewart); b) children's physical, emotional and sexual abuse (chaired by G. Milovic and B. Leventhal); c) lesbian, gay, bisexual and transgender (LGBT) individuals (chaired by P. Levounis and K. Eckstrand); d) migrant mental health (chaired by M. Schouler-Ocak and M. Kastrup)[1]; e) individuals with intellectual disability and their mental health (chaired by S. Bhaumik)[2]; f) prisoners' mental health (chaired by A. Forrester and M. Piper); g) mental health promotion (several short films about mental illness have been produced by A. Sharma). All these documents and films are available on the WPA website.
- *World Mind Matters Day*. September 5 of each year has been identified as World Mind Matters Day. In 2015, the WPA launched statements on migrant mental health. This had major implications as globally there are several million migrants, refugees and asylum seekers. The Second World Mind Matters Day in 2016 saw the launch of our findings from a global survey covering 193 countries (which are member states of the United Nations) on discrimination against persons with mental illness. The WPA looked at discrimination against people with mental illness in four areas: political, social, economic and personal in the laws of each country. The levels of discrimination remain a cause of worry across the globe. Nearly one third of the countries do not allow people with mental illness to get married. Fewer countries provide supported employment or right to vote. As a result of these findings, the WPA produced a Bill of Rights. Over 60 organizations around the globe have signed up their support for this. This Bill of Rights was launched in the House of Lords in London in October 2016. The logo of Blue Butterfly is the campaign symbol for Social Justice for People with Mental Illness[3]. A special issue of the *International Review of Psychiatry*[4] has published these findings in details along with examples of minimum standards of service as well as good clinical practice[5].
- *Round table meetings*. We had a very successful round table meeting on violent radicalization hosted by the WPA Collaborating Centre in London in October 2016 and another one on early interventions in psychiatry hosted by the Hong Kong College of Psychiatrists in December 2016. These have been in addition to round table meetings in Colombia, Dominican Republic, Costa Rica, Mexico and Guatemala[6]. There was a follow-up round table on migrant mental health in Oslo in March 2017.
- *Position statements*. The WPA has launched several position statements which are available on the WPA website. These include those on migrant mental health in Europe (with Careif), on migrant mental health in Latin America (with the Latin American Psychiatric Association, APAL), on high quality training in psychiatry, on five reasons to be a psychiatrist, on gender identity and same-sex orientation, attraction and behaviours[7], on environmental sustainability, on recruitment in psychiatry, on suicide prevention, on preventive psychiatry, and on spirituality and religion in psychiatry[8]. Joint declarations on migrant mental health were launched following round table meetings in Costa Rica, Guatemala, Mexico and Dominican Republic. Other statements included the Bucharest Declaration on Primary Care Mental Health (2015), the Manila Declaration on Mental Health Promotion (2016), the Kochi Declaration on Collaborative Care (2015), and the Tbilisi Declaration on Integrated and Collaborative Care (2016). On International Children's Day in 2016, WPA launched a Bill of Rights for Children and Young People. On International Women's Day in 2017, WPA launched a position statement on perinatal mental health.
- *Translations*. As part of the Action Plan, it was agreed that papers from other languages should be translated into English. Papers from Spanish and Portuguese have been translated in special issues of the *International Review of Psychiatry* that have been published or are in publication[9,10]. Papers from Italian, Mandarin and Russian are being translated.
- *WPA-Lancet commission on psychiatry*. This commission has completed its data analysis and six writing groups were set up to explore and discuss these findings. The first draft of the report will be ready by September 2017 and the full report will be published in time for the World Congress of Psychiatry in October 2017.
- *Diplomas in psychological medicine and in mental health*. This initiative, in partnership with the University of Melbourne, aimed at psychiatrists and other mental health professionals, continues apace and we hope to have it ready later this year.
- *WPA collaborating centres*. These centres have been established in London (K.S. Bhui), Naples (M. Maj), Nairobi (D. Ndetei), Cape Town (D. Stein), Cairo (T. Okasha), Hong Kong (L. Lam) and Bangalore (S. Chaturvedi). Each centre is focusing on training, research or policy and will also act as repository for information for the region[11].
- *WPA goodwill ambassadors*. WPA goodwill ambassadors have been identified in India and three major figures have agreed to take on this role which focuses on disseminating messages on mental health promotion. M. Agashe (psychiatrist and film actor/director); M. Shivani (a religious leader) and S. Oberoi (a Bollywood actor) have consented to take on this role. We are looking for goodwill ambassadors in other countries.

Dinesh Bhugra
President, World Psychiatric Association

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News from WPA Scientific Sections

The current triennium has seen an increasing visibility of Scientific Sections as important and integral components of the WPA, especially in supporting the Association's promotion and dissemination of scientific knowledge around the globe. We are now having 72 Sections and there is still an interest in having more of them to cover some other scientific sub-specialties.

During the triennium there has been a noticeable increase in the number of WPA co-sponsored meetings, joint intersectional activities and other related intersectional accomplishments[1,2]. Sections' participation in the recently held WPA International Meeting in Cape Town has been outstanding, with more than 26 sessions in the programme. The Sections also organized training workshops, round table discussions and educational activities in that well attended meeting.

Scientific Sections have continued to produce position statements and discussion documents on important topics that correspond to their expertise. Adding these documents to the WPA website did generate a lot of interest among the WPA membership[3,4]. Several of these position statements have been published in *World Psychiatry,* such as those on spirituality and religion in psychiatry[5]; gender identity and same-sex orientation, attraction and behaviours[6]; and recruitment in psychiatry[7]. The Sections on Education and Early Career Psychiatrists have prepared a key document for promoting psychiatry as an inspiring medical specialty and as a prospective career for medical students. This work was presented in Sections' business meeting at Cape Town. It is hoped that Sections will prepare further materials for promotion of psychiatry in undergraduate medical education and explore innovative ways of engaging medical students to increase their interest in the specialty.

There has always been an added value of the contributions from the newly established Sections. Current interest in promoting intersectional work is equally evident from activities of many of the new Sections. Furthermore, several Sections – including those on Early Career Psychiatrists, Education in Psychiatry and Transcultural Psychiatry – are actively involved in organizing teaching and training workshops aiming to develop leadership skills of young psychiatrists.

The WPA Action Plan for 2014-2017[8] has continued to be a focal action point for many Sections' activities. Sections have adapted the theme of promotion of mental health as a priority in their work along with initiating various programmes in the areas of preventive psychiatry by producing educational materials for the WPA website[3].

Whereas Sections enjoy a great degree of independence within the framework of the statutes and by-laws of the WPA, the relevant Operational Committee is considering some revisions in the by-laws that would make the work of Sections more in line with current needs and expectations. There have also been some initial discussions on clustering of Sections on the basis of common interests and activities. This will hopefully promote further collaboration and links among various Sections.

As we are approaching our next World Congress, Sections are also preparing their triennium activity reports for the General Assembly along with plans for their new elections. We are encouraging all the Sections to involve younger members in officer and committee positions, to enhance their enthusiasm for future contributions towards WPA's work.

Section officers and members are also contributing extensively to the WPA official journal *World Psychiatry*[9-11]. Their interest and participation in the development of the chapter on mental disorders of the ICD-11 is another ongoing effort to improve classification and nosology in psychiatric practice[12-15].

It is hoped that the current enthusiasm of Sections' leadership and their committed work will keep on contributing to enhance the quality of scientific knowledge in different fields of psychiatry. Whereas this requires dedicated expertise, it is anticipated that the Sections will offer valuable additions to the profession's changing perspectives. It is trusted that Scientific Sections will also continue with their current contribution to the development of pioneering approaches in psychiatric practice.

Afzal Javed
WPA Secretary for Sections

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WPA International Competency-Based Curriculum for Mental Health Providers on Intimate Partner Violence and Sexual Violence Against Women

Intimate partner violence (IPV) and sexual violence (SV) are public health and human rights problems worldwide which have profound effects on the health and wellbeing of individuals, families and communities[1].

The World Health Organization (WHO) defines IPV as "behaviour by an intimate partner that causes physical, sexual or psychological harm, including acts of physical aggression, sexual coercion, psychological abuse or controlling behaviours"[2]. It may be perpetrated by a current or past intimate partner, occur in heterosexual or same-sex relationships, and include stalking. At its core it is a means to control and dominate the abused partner.

SV is defined by WHO as "any sexual act, attempt to obtain a sexual act, unwanted sexual comments or advances, or acts to traffic or otherwise directed against a person's sexuality using coercion, by any person regardless of their relationship to the victim, in any setting, including but not limited to home and work"[2,3]. It includes marital, dating, stranger and acquaintance relationships, sexual slavery, forced marriage or cohabitation and wife inheritance and may occur during peace or war[2,3]. It may also take place when someone is not able to give informed consent (e.g., a child or a person who is intoxicated, drugged, asleep or physically or mentally incapacitated).

While IPV and SV can occur to both women and men, the most serious forms overwhelmingly happen to women at the hands of men[2,3].

Prevalence rates of IPV/SV varied from 15 to 71% (lifetime) or 4 to 54% (last 12 months) across a 10-country study by WHO[4]. Prevalence is greatly underreported due to guilt, shame, social stigma, inadequate social support, financial or emotional dependence on the perpetrator, or fears for safety, child custody, immigration status, or other repercussions[3]. A public health ecological model of risk factors for IPV/SV includes those related to the individual, partner, family and community (including social and cultural), which may all contribute[5].

Both IPV and SV can result in numerous physical (including death) and mental health sequelae, thereby making it imperative that health care professionals know the risk factors, how to assist disclosure and safely respond[6]. Mental health sequelae may include depression, anxiety, post-traumatic stress disorder, psychosis, self-harm, sexual problems, inability to trust others, and a host of psychosomatic conditions and risky behaviours that may be referred. Therefore, psychiatrists must be familiar with the best evidence-based short- and long-term management of IPV and SV mental health sequelae to best assist victims[6].

Evidence shows that 30% or more (depending on location and presenting symptoms) of psychiatric patients have been exposed to IPV or SV[7]. As IPV and SV are often not disclosed, or enquired about by psychiatrists, this may affect diagnosis, treatment and outcome. Needs assessments have indicated that IPV and SV are key determinants of women's mental health, but 60% of mental health professionals report that they lack adequate knowledge and want more education on these topics[8].

The WPA Action Plan for 2014-2017 developed by President D. Bhugra listed IPV and SV as priorities for a position paper and curriculum. Under the leadership of D.E. Stewart (Canada) and P.S. Chandra (India) and a Steering Group of six experts from across the globe (three from WHO), plus two educational consultants, a competency-based curriculum for medical students, psychiatric trainees and practicing psychiatrists was developed. This includes suggestions of how to test nine core competencies and their related subtopics (definitions, prevalence, misconceptions, health sequelae, assessment, psychological first aid, resources, documentation, and psychiatric management of related mental health traumas). The psychiatric management curriculum includes the initiation and monitoring of first line methods indicated for the treatment of IPV/SV psychological trauma, such as cognitive behavioural therapy with a focus on the trauma, exposure therapy, eye movement desensitization and reprocessing, pharmacological interventions and comprehensive care for complex post-traumatic stress disorder.

Different types of educational tools are employed in the curriculum to enhance knowledge, attitudinal change and skills, and thereby provide real life competencies. The curriculum links to WHO clinical and policy guidelines[9], a WHO clinical handbook[2], key paper abstracts, a list of books, manuals and toolkits, and a teaching set of powerpoints on IPV and SV. It provides twelve international case vignettes with teaching points and two video-based learning vignettes in which two senior psychiatrists each interview a woman who has experienced IPV.

A trauma-informed model of care advocated by WHO uses the acronym "LIVES", where "L" means listen (empathic and non-judgmental), "I" means inquire (about needs and concerns), "V" means validate (believe and understand the victim), "E" means enhance safety (help protect against further harm), and "S" means support (help connect to services and social support)[2].

A WPA position paper on IPV/SV was also developed by the Steering Group of experts.

The curriculum and the position paper were approved by the WPA Executive Committee in July 2016 and posted on the WPA website (www.wpanet.org). Initial response has been encouraging, with several universities, medical schools and non-governmental organizations across five continents requesting permission to

use the curriculum in whole or in part. The curriculum has been presented at several annual national psychiatric association meetings (with more planned) and has been featured in news articles. We welcome comments on the curriculum and feedback about its use at donna.stewart@uhn.ca.

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