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Child maltreatment, attachment and psychopathology: mediating relations

Studies of the developmental consequences of child maltreatment are essential for enhancing the quality of clinical, legal, and policy-making decisions for maltreated children. Decisions about reporting a child as maltreated, removing a child from the home, developing interventions to meet the specific psychological needs of maltreated children, and evaluating the efficacy of these interventions, all necessitate a solid and sophisticated database on the developmental sequelae of child maltreatment. “Without rigor in design and method… myth will be put forward in place of knowledge as a guide to social actions”.

Numerous outcomes are possible for maltreated children, including healthy adaptation. However, the deleterious biological and psychological sequelae of child maltreatment not only often result in adverse consequences during childhood, but may also initiate a negative developmental cascade that continues throughout the life course. Indeed, consistent with the concept of multifinality, maltreated children may develop a broad range of psychopathological outcomes. The knowledge that there are multiple pathways to similar manifest outcomes (equifinality) and that there are different outcomes of the same pathway (multifinality) may contribute to the implementation of important refinements in the extant diagnostic classification of mental disorders.

The literature indicates that exposure to child maltreatment increases the lifetime risk for many psychopathological symptoms and disorders, including depression, anxiety disorders, bipolar disorder, schizophrenia, post-traumatic stress disorder, antisocial personality disorder, internalizing and externalizing symptoms, and dissociation. (see also Morgan and Gayer-Anderson in this issue of the journal). Likewise, maltreatment increases the risk for poor physical health outcomes, including immune dysfunction, obesity, fibromyalgia, inflammation, and diabetes.

Much research conducted on the effects of child abuse and neglect has been guided by an organizational perspective on development. This perspective identifies a progression of qualitative reorganizations within and among the biological and psychological systems that proceed through differentiation and subsequent hierarchical integration.

Organizational theorists conceive development as comprising a number of age- and stage-relevant tasks. Although their salience may wane in relation to newly emerging issues, the tasks remain important to adaptation. A hierarchical picture of adaptation emerges in which the successful resolution of an early stage-salient issue increases the probability of subsequent successful adjustment. As each new stage-salient issue comes to the fore, opportunities for growth and consolidation arise. The tasks include the development of emotion regulation, the formation of attachment relationships, the development of an autonomous self, the formation of effective peer relationships, and successful adaptation to school.

The establishment of a secure attachment relationship between an infant and his or her caregiver represents a primary task during the first year of life. The capacity for preferential attachment originates during early affect regulation experiences and interactions with the caregiver. These early parent-child experiences provide a context for children’s emerging bio-behavioral organization. Specifically, the pre-attachment parent-child environment helps to shape children’s physiological regulation and bio-behavioral patterns of response. As development proceeds, attachment theorists have posited that a secure attachment relationship provides a base from which to explore and, ultimately, contributes to the integration of neurobiological, cognitive, affective, and behavioral capacities that influence ongoing and future relationships, as well as the understanding of self.

Children construct “internal working models” of their attachment figures out of their interactions with their caregivers, their own actions, and the feedback they received from these interactions. Once organized, these internal working models tend to operate outside of conscious awareness and are thought to be relatively resistant to change. Children formulate their conceptions of how acceptable or unacceptable they are in the eyes of their attachment figures (i.e., their self-image) based on their interactional history with their primary caregivers. Exposed to insensitive and pathological care, maltreated children develop negative expectations regarding the availability and trustworthiness of others, as well as mental representations of the self as incompetent and unworthy.

Maltreated infants are especially at risk for developing insecure/disorganized attachments with their primary caregiver. Maltreating behaviors are arguably among the most frightening parenting behaviors, placing children in an irresolvable paradox in their attachment figure is simultaneously their source of safety and their source of fear.

Through Bowlby’s influence, a growing number of theorists and researchers have conceptualized early attachment organization as remaining critical to the ongoing adaptational strivings of the person. However, attachment, as other major developmental tasks, continues to differentiate beyond its period of developmental ascendance. Once an attachment develops, it continues to transform and integrate with subsequent accomplishments such as autonomy and peer relations throughout the life course. Thus, persons are continuously renegotiating the balance between being connected to others and being autonomous as they encounter each new developmental phase.

The representational models that emerge from the caregiving matrix of maltreated children exert influences on their...
conceptualization of self and their responses to potential relationship partners. Although representational models most likely contain information specific to a given relationship, these specific models may contribute information to more generalized models of relationships. Because the internal representational models of the early caregiving relationship are largely insecure in maltreated children, these children may be more likely to transmit the maladaptive relationship patterns of their childhoods to their offspring. The fact that not all maltreated children do so lends hope to a potentially bleak scenario and also speaks to the potential benefit of theoretically grounded approaches for the prevention of maltreatment, as well as for the treatment of those who have experienced caregiving trauma.

An insecure attachment may render individuals more likely to respond adversely to stress and hence be more vulnerable to pathological breakdowns. Within attachment theory, psychopathology is conceived as a developmental construction. According to this perspective, variations in early attachment are not considered to be pathology, or as directly causing pathology. However, they do lay the foundation for disturbances in developmental processes which can eventuate in psychopathology.

In terms of examining the interrelations between maltreatment, attachment organization, and psychopathology, a review of the extant literature reveals that most studies have assessed them concurrently within a cross-sectional design. Although several of these studies have indeed discovered interrelations, the non-longitudinal nature of this work precludes making definitive causal interpretations of the findings.

In order to render veridical claims about causality, additional longitudinal studies examining the interrelations among child maltreatment, attachment organization, and psychopathology must be carried out. Such multi-wave longitudinal research will enable investigators to address the causal nature of the interrelations through a mediational analysis.

A mediating variable is one that is intermediate in the causal process relating a predictor variable to an outcome variable. The development of insecure/disorganized attachment may represent an underlying mechanism (i.e., mediator) by which children with maltreatment experiences develop future psychopathology. Longitudinal designs with at least three waves of data are ideal for testing mediation, so that temporal ordering can be established between the independent variable (maltreatment), the mediator (attachment organization), and the outcome variable (psychopathology). Without temporal precedence, the time ordering among the variables is hypothetical but not empirically supported.

Multilevel research conducted in the context of longitudinal designs will enable researchers to ascertain how and why the statistically significant pathways from the independent variable to the mediator and from the mediator to the outcome variables occurred. Moreover, the inclusion of DNA in measurement batteries will help to discern whether genotypic variation moderates the significant mediation path(s). Finally, longitudinal randomized control trial interventions aimed at improving the quality of attachment organization in maltreated children can shed important light on the mediational links between maltreatment, attachment, and psychopathology.

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Shorter hospitalizations at the expense of quality? Experiences of inpatient psychiatry in the post-institutional era

From the early 1950s, effective drug and psychological therapies coupled with pressures from antipsychiatry have driven a very persuasive vision of deinstitutionalized psychiatry in which the vast bulk of psychiatric care was to be delivered in the community. It was thought that small psychiatric units in general hospitals might be sufficient, although some asylum patients would need longer-term care in sheltered accommodation, mainly because they had lost skills and family contact.

In 1955, there were some 150,000 hospital beds for the mentally ill in England. By 2012 there were just 22,300, and by the end of last year 2,000 more had gone. This dramatic reduction has been helped along by developments in community care, such as assertive community treatment and crisis home treatment. Of these, crisis home treatment has had the largest impact, shown in controlled trials to be a clinical and cost-effective means of reducing hospitalization.

Of course, even the best functioning crisis home treatment cannot safely manage all crises in the community, and so in parallel there has been an ongoing effort to shorten the length of hospital stay for all who cannot be dealt with elsewhere. The latest manifestation of this has been the introduction of “triage” wards. These highly staffed wards cap length of stay at around 7 days, with patients either discharged home (with crisis home treatment support as needed) or transferred to a longer-stay ward in the hospital. But therein lies a problem. Patients who are transferred to the other wards in the triage system tend to be those who have the more challenging disorders, with severe breakdown of community tenure and of relationships within the community team. In one of the few studies to examine the impact of introducing a triage system on the overall length of hospital stay, we showed that the accumulation of these more complex patients with lengthy hospital stay soon filled the other wards, effectively negating any economic benefits of the triage ward.

The reduction in acute hospital beds might be viewed as a tremendous success for deinstitutionalization in the UK, were it not that the demand for inpatient care now grossly outstrips supply, accompanied by a rising tide of demoralization and dissatisfaction with care among hospital staff and patients. A recent survey showed that the number of patients having to be hospitalized outside their home area because of a shortage of local beds doubled, from 1,301 in 2011/12 to 3,024 in 2013/14, with typical bed occupancy in excess of 100%.

Only the most acutely ill are admitted, and the proportion who are compulsorily detained has risen while voluntary admissions have fallen. There are reports that many patients asking for admission are being told that they are “not ill enough” to warrant it. On the other hand, around one-sixth inpatients in the above survey were sufficiently recovered to be discharged, but were languishing in hospital because they needed a longer period of residential rehabilitation or were waiting for housing and other community services.

For at least a century it has been known that dramatic failures and hospital scandals occur when staff are too preoccupied by bureaucracy, and too burnt out or detached from their patients and other members of the care team to be able to feel and show appropriate compassion and care. While mercifully such dramatic failures are rare, there is realistic concern that the staff working in overcrowded “pressure-cooker” environments can become demoralized and feel swamped by fire-fighting behavioural problems and attending to paperwork, leaving little time for therapeutic activities with their patients. While international standards recommend a variety of group and individual therapeutic activities that together come to an average of at least 2.5 hours daily over and above the time spent in one-to-one contact, these standards are seldom met. In a recent survey of acute inpatient wards, we found that structured activity and one-to-one contacts amounted to only 4.5 hours per week. There was a wide variation between wards, with some patients reporting no participation in any formal activity.

There are several publications of standards and guidelines backed up by inspection and voluntary quality improvement initiatives, that if followed would certainly result in improved standards of care. There are also specific skills-based interventions aimed at better management of violence and risk supported by controlled trial evidence, and much written on simple procedures linked with effective leadership that are known to improve the patient experience of general hospital care that apply equally to the psychiatric setting.

While the UK continues reducing beds, the picture is different in other European countries, with Germany, Croatia, Lithuania and Latvia actually increasing provision, and Belgium and the Netherlands having far higher number of beds per capita. Nevertheless, in the opinion of many UK psychiatrists, we probably have sufficient beds if only something could be done to solve the problems of delayed discharge. Some even argue that, rather than trying to increase hospital care, we should be looking to replace it with residential alternatives in the community. This has been a successful pathway in some European settings, but in England these are rather more localized efforts, such as crisis houses linked to home treatment teams. Most provide fewer beds than a typical acute inpatient ward, and the majority only accept voluntary admissions. Many do have fewer problems with staff morale and are preferred by patients but, because of their relatively isolated community base, they are not viewed as sufficiently safe places to take the more acutely unwell, especially where there are risks of violence. Paradoxically, when run alongside rather than replacing hospitals, they may have even contributed to the worsening inpatient situation, as they divert admissions of the more compliant, less chaotic

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patients, leaving the most disturbed and disabled to enter acute care.

It seems obvious that longer-term residential care is needed for the complex more disabled patients that are clogging acute care, but in the decades following the closure of the asylums, the UK also quietly disinvested in longer-term care, so that there are now fewer rehabilitation beds per capita than elsewhere in Europe. At one point it was even a matter of policy that the new assertive community services would enable all psychiatric rehabilitation beds to close, and around half of the community rehabilitation teams were wound up, the staff being re-tasked to provide for the home treatment and other new community teams. Similar processes were seen elsewhere in Europe and North America, with the provision of longer-term residential care bearing little relation to local mental health needs. In the U.S., Sisti et al pointed out that the numbers of patients now cared for in long-term state facilities are around 10% of what they were in 1955, and noted (as have many North American commentators) the growing numbers of mentally ill in jails and prisons, that they argued have now become the nation’s largest mental health care facilities.

In conclusion, we are where we are because we have ignored much of our own advice to the world on ensuring we provide what we need in the community before rushing to shut down hospital care. I believe the one thing we can do to improve the quality of inpatient care is to take steps to reduce the current "pressure-cooker" environments of acute care and so allow inpatient teams the space to deliver quality care to their patients. To achieve this, while I am certain that a return to the large asylums is not the solution (see also Cohen et al in this issue of the journal), it is clear that we need to ensure adequate provision of inpatient rehabilitation and closer implementation of the guidelines for rehabilitation pathways that already exist. In these settings, as indeed all inpatient care, the ultimate determinants of quality rest on good leadership by example and the presence of compassionate staff, trained and supervised appropriately.

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5. MIND. Listening to experience: an independent enquiry into acute and crisis mental healthcare. www.mind.org.uk.

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Childhood adversities and psychosis: evidence, challenges, implications

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There is a substantial body of research reporting evidence of associations between various forms of childhood adversity and psychosis, across the spectrum from experiences to disorder. This has been extended, more recently, to include studies of cumulative effects, of interactions with other factors, of specific effects, and of putative biological and psychological mechanisms. In this paper we evaluate this research and highlight the remaining methodological issues and gaps that temper, but do not dismiss, conclusions about the causal role of childhood adversity. We also consider the emerging work on cumulative, synergistic, and specific effects and on mechanisms; and discuss the broader implications of this line of research for our understanding of psychosis. We conclude that the current balance of evidence is that childhood adversities – particularly exposure to multiple adversities involving hostility and threat – do, in some people, contribute to the onset of psychotic experiences and psychotic disorders.

Key words: Childhood adversity, childhood abuse, psychotic experiences, psychotic disorders, cumulative effects, gene-environment interaction, protective factors

(World Psychiatry 2016;15:93–102)

There has been a flurry of research on the relationship between childhood adversity and psychosis over the past ten years. This has extended, more recently, to studies that have sought to elaborate on the nature of the relationship, by examining cumulative effects, interactions with other risk factors (e.g., genes), specificity of effects, and putative mechanisms.

For some authors, the accumulated evidence unequivocally establishes that difficult and unpleasant experiences in childhood contribute to the development of psychoses\(^1\). For others, the evidence is not so clear cut\(^2\). At issue, in part at least, are fundamental questions about the nature and aetiology of psychosis. Much, then, is at stake and a further appraisal of the evidence is warranted.

In this paper, we first summarize and critically evaluate research on the association between childhood adversities and psychosis (including low-level experiences, at risk states, and disorders). In doing this, we focus particularly on remaining methodological issues and gaps in the literature, and on research that has further investigated the nature of the association. We then reflect on the broader implications of this work for our understanding of psychosis.

CHILDHOOD ADversITY

Childhood adversity is a broad term that denotes exposure to a range of difficult or unpleasant situations or experiences, usually before the age of 16. The adversities typically considered in studies of psychoses include household poverty, separation from a parent (i.e., family breakdown), death of a parent, neglect, abuse (including emotional, psychological, physical, and sexual), and peer bullying.

Estimates suggest that large numbers of children are exposed to such situations and experiences. In the UK, for example, according to estimates, over 3 million children (~28%) live in poverty (defined as less than 60% of the average household income)\(^3\), over 3 million children (~23% of those living in families) live in lone parent households\(^4\), around 6% of those aged 0-10 years and around 19% of those aged 11-17 years experience some form of severe maltreatment, and around 30% to 40% experience some form of bullying (including name calling, social exclusion, threats, and – increasingly – cyber bullying) in a given year\(^5\).

More broadly, the World Health Organization (WHO) World Mental Health Surveys estimate that – across all countries, irrespective of level of economic development – the prevalence of exposure to at least one childhood adversity (including loss, maltreatment, economic adversity, and illness) is around 40%\(^6\). What is more, adversities tend to co-occur and persist over time, often in worsening cycles of disadvantage and vulnerability, in which one difficulty leads to and compounds others. As a consequence, many children are exposed to multiple adversities that persist and become entrenched throughout childhood and adolescence, often with lifelong consequences. For example, the WHO World Mental Health Surveys found that most adversities were highly correlated: of those reporting any, around 60% reported exposure to multiple adversities\(^7\).

PSYCHOSIS

In recent years, substantial evidence has accrued that sporadic and non-distressing psychotic experiences (e.g., fleeting hallucinations, suspiciousness and paranoia, magical thinking) are common in the general population (the most recent meta-analysis suggests a lifetime prevalence of around 7%\(^8\)) and are associated with the later development of psychotic and other disorders\(^9\).
<table>
<thead>
<tr>
<th>Review</th>
<th>Year</th>
<th>Number of papers</th>
<th>Target population</th>
<th>Exposure(s)</th>
<th>Overall summary effect, OR (95% CI) unless otherwise specified</th>
<th>% exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Read et al10</td>
<td>2005</td>
<td>66</td>
<td>In- and out-patients, at least 50% with psychosis (no comparison group)</td>
<td>Sexual abuse&lt;br&gt;Physical abuse&lt;br&gt;Either&lt;br&gt;Both</td>
<td>48% F, 28% M&lt;br&gt;48% F, 50% M&lt;br&gt;69% F, 59% M&lt;br&gt;36% F, 19% M</td>
<td></td>
</tr>
<tr>
<td>Morgan and Fisher11</td>
<td>2007</td>
<td>20</td>
<td>In- and out-patients with psychosis (no comparison group)</td>
<td>Sexual abuse&lt;br&gt;Physical abuse&lt;br&gt;Either&lt;br&gt;Both</td>
<td>42% F, 28% M&lt;br&gt;35% F, 38% M&lt;br&gt;50% F, 50% M&lt;br&gt;26% F, 18% M</td>
<td></td>
</tr>
<tr>
<td>van Dam et al12</td>
<td>2012</td>
<td>7</td>
<td>Psychotic experiences</td>
<td>Bullying</td>
<td>2.70 (2.00-3.60)</td>
<td></td>
</tr>
<tr>
<td>Varese et al1</td>
<td>2012</td>
<td>41</td>
<td>Any psychosis (including experiences and disorder)</td>
<td>Any adversity</td>
<td>2.78 (2.34-3.31) (population attributable risk: 33%)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sexual abuse&lt;br&gt;Physical abuse&lt;br&gt;Emotional abuse&lt;br&gt;Neglect&lt;br&gt;Parent death</td>
<td>2.38 (1.98-2.87)&lt;br&gt;2.95 (2.25-3.88)&lt;br&gt;3.40 (2.96-5.62)&lt;br&gt;2.90 (1.71-4.92)&lt;br&gt;1.70 (0.82-3.53) when an outlier was excluded: 2.30 (1.63-3.24)&lt;br&gt;2.39 (1.83-3.11)</td>
<td></td>
</tr>
<tr>
<td>Bonoldi et al13</td>
<td>2013</td>
<td>23</td>
<td>Psychotic disorder (no comparison group)</td>
<td>Sexual abuse&lt;br&gt;Physical abuse&lt;br&gt;Emotional abuse</td>
<td>26%&lt;br&gt;39%&lt;br&gt;34%</td>
<td></td>
</tr>
<tr>
<td>de Sousa et al14</td>
<td>2013</td>
<td>20</td>
<td>Psychotic disorder</td>
<td>Parent communication deviance</td>
<td>Hedge's g: 0.97 (0.76-1.18)</td>
<td></td>
</tr>
<tr>
<td>Matheson et al21</td>
<td>2013</td>
<td>25</td>
<td>Schizophrenia</td>
<td>Any adversity (including abuse, neglect, loss, witness domestic violence, life events)</td>
<td>3.60 (2.08-6.23) vs. controls&lt;br&gt;1.23 (0.77-1.97) vs. affective psychoses&lt;br&gt;2.54 (1.29-5.01) vs. anxiety&lt;br&gt;1.37 (0.53-3.49) vs. depression&lt;br&gt;0.03 (0.01-0.15) vs. post-traumatic stress disorder/dissociation&lt;br&gt;0.69 (0.29-1.68) vs. other psychoses&lt;br&gt;0.65 (0.09-4.71) vs. personality disorder</td>
<td></td>
</tr>
<tr>
<td>Cunningham et al15</td>
<td>2015</td>
<td>7</td>
<td>Any psychosis (including experiences and disorder)</td>
<td>Bullying</td>
<td>2.15 (1.14-4.04)</td>
<td></td>
</tr>
<tr>
<td>Kraan et al16</td>
<td>2015</td>
<td>6</td>
<td>Ultra high risk (for psychosis)</td>
<td>Trauma (including abuse and neglect)</td>
<td>Hedge's g: 1.09, Z ~ 4.60, p &lt; 0.01 (confidence intervals not given)</td>
<td></td>
</tr>
<tr>
<td>Trotta et al17</td>
<td>2015</td>
<td>9</td>
<td>Persistence of psychotic experiences or symptoms</td>
<td>Any adversity (including abuse, neglect, parent death or separation, bullying, being in care)</td>
<td>1.73 (1.26-2.32) non-clinical samples:&lt;br&gt;1.76 (1.19-2.32) clinical samples: 1.55 (0.52-2.77)</td>
<td></td>
</tr>
<tr>
<td>Velikonja et al18</td>
<td>2015</td>
<td>25</td>
<td>Schizotypal traits</td>
<td>Trauma (including abuse, neglect, bullying, parent death or separation, or other traumatic experiences, such as household discord, a life- or injury-threatening event)</td>
<td>OR range: 2.01 to 4.15</td>
<td></td>
</tr>
</tbody>
</table>
This evidence has led to a rapid growth of research investigating risk factors for these experiences, on the basis that they may tell us something about the putative causes of psychotic disorders. This is part of a broader trend for research to focus on earlier (e.g., at risk mental states) and both broader (i.e., all psychotic disorders) and more specific (i.e., psychotic symptoms or complaints) psychosis phenotypes. These trends reflect ongoing debates and disputes about the very nature of psychoses (e.g., continuum vs. categorical models). Research on childhood adversity extends across the spectrum of psychosis outcomes.

EVIDENCE

Since Read et al\textsuperscript{10} published their review of studies of physical and sexual abuse and psychosis in 2005, there have been at least thirteen narrative or systematic reviews (including at least eight meta-analyses) on one form or other of childhood adversity and psychosis\textsuperscript{11-12}. Those that report either summary proportions exposed to adversity or summary effects of adversity on psychosis are detailed in Table 1.

The evidence that has emerged is consistent. Most indicators or forms of adversity that have been considered are associated with around a 2 to 4-fold increased risk or odds of psychosis. For example, Varese et al\textsuperscript{1}, in the most comprehensive meta-analysis to date, identified 36 studies and found that, irrespective of study design, childhood adversity was overall associated with a 2.78 increased odds of psychosis (95\% CI: 2.34-3.31). Considering the specific forms of adversity, the odds ratios were 2.38 (95\% CI: 1.98-2.87) for sexual abuse; 2.95 (95\% CI: 2.25-3.88) for physical abuse; 3.40 (95\% CI: 2.06-5.62) for emotional abuse; 2.39 (95\% CI: 1.83-3.11) for bullying; and 2.90 (95\% CI: 1.71-4.92) for neglect. Only parental death was not strongly associated with psychosis (OR = 1.70, 95\% CI: 0.82-3.53).

In the short time since the publication of that review, over twenty additional studies have been published, most of which provide further evidence that childhood adversities are more common among those with psychosis, again across the spectrum\textsuperscript{23-44}. Perhaps most notably, in a prospective study of 1,112 adolescents, Kelleher et al\textsuperscript{51} found that cessation of trauma was associated with subsequent cessation of psychotic experiences.

Other meta-analyses that have focused on specific adversities (e.g., bullying\textsuperscript{15}) or specific psychosis outcomes (e.g., schizophrenia\textsuperscript{21}, at risk mental states\textsuperscript{16}, schizotypy\textsuperscript{18}) report similar findings, i.e., a 2 to 4-fold increased risk or odds (Table 1). Further, another recent meta-analysis suggests that childhood adversity is associated with a persistence of psychotic experiences over time, a finding that is of particular interest as it is persistence of low-level experiences that most strongly predicts later development of psychotic disorder\textsuperscript{17}.

On the face of it, then, there is a remarkably consistent convergence of evidence that various forms of childhood adversity are associated, perhaps in linear fashion (see below), with psychosis outcomes across the spectrum. Further, those studies that have adjusted for potential confounders do not find evidence that associations can be accounted for by genetic or other established risk factors\textsuperscript{1,37,45}.

CHALLENGES

However, there remain several caveats and gaps. First, a majority of the studies are of low-level psychotic experiences in general population samples. This is important for at least three reasons. One, measurement of these experiences is often limited, e.g. to single questions, and measurement error is no doubt high (i.e., misclassification of experiences as psychotic that are not). We include our own work in this\textsuperscript{46}. Two, low-level psychotic experiences very often co-occur with, and may not be easy to distinguish from, symptoms of depression, anxiety, and post-traumatic stress disorder – all of which are strongly associated with adversity and trauma. Three, it does not necessarily follow that experiences associated with endorsement of psychosis-related items on questionnaires will be associated with psychotic disorder or vice versa. For example, recent studies have failed to find any association between psychotic experiences and polygenic risk scores for schizophrenia\textsuperscript{47}. Consequently, the extent to which associations between childhood adversities and psychotic experiences hold for psychotic disorders – which are characterized by multiple severe and distressing psychotic symptoms and functional impairment – is far from clear.

Second, studies of psychotic disorder are fewer and – with some notable exceptions\textsuperscript{48-50} – of poor methodological quality, often comprising small convenience samples of prevalent cases (including some restricted to subgroups, e.g. late onset\textsuperscript{21,52} women\textsuperscript{53} and of controls. Associations in these studies could arise due to selection biases if, for example, those with a more severe and/or long-standing disorder are more likely to have experienced adversities. This noted, the small number of larger and more robust studies do, overall, suggest associations with childhood adversities, but with important nuances. For example, in the AESOP study of first-episode cases and randomly sampled controls, we found, first, some evidence of associations with parental loss and with separation from a parent\textsuperscript{54} and, second, some evidence of associations between physical and, more tentatively, sexual abuse among women, but not men\textsuperscript{49} (incidentally, gender differences remain underexplored). Further, Cutajar et al\textsuperscript{50}, in a study of 2,759 individuals known to have been sexually abused in childhood and a matched control group, found evidence for an association specifically with sexual abuse involving penetration that occurred between age 12 and 17 years. More studies of disorder are evidently needed to further clarify these associations.

Third, most studies have relied on retrospective recall of exposure to abuse and other adversities in childhood. How-
ever, memory of past experiences is dependent, to some extent, on cognitive ability and is clouded and shaped by subsequent experiences, fluctuating moods, and re-tellings. This may be especially true for traumatic events and could bias findings if there is differential recall by those with and those without psychosis: for example, greater recall among those with psychosis due to the influence of current mental state (e.g., more paranoia) or effort after meaning (i.e., searching past experiences to explain current problems). As Susser and Widom\(^2\) note in their commentary on Varese et al\(^1\), this is not a problem that can be addressed with meta-analyses: “Pulling together many studies that share a similar bias will produce a biased result”. This noted, it seems unlikely that recall bias alone could explain the repeated findings. In fact, there is some evidence that reports of abuse among those with psychosis are stable over time and not influenced by current mental state\(^35\). Furthermore, studies that have established exposure to adversities before measurement of psychotic experiences or onset of psychotic disorder have also reported associations\(^37,45,50\). For example, in the E-Risk Study of 2,232 twins, Arseneault et al\(^55\) found that parent reports of maltreatment and of bullying by age 7 were associated with, respectively, a 3.48 (95% CI: 1.93-6.27) and a 2.19 (95% CI: 1.25-3.83) increased odds of psychotic experiences at age 12. Moreover, the study by Cutajar et al\(^50\) established exposure prior to onset of disorder.

Fourth, the measurement of childhood adversities has been relatively crude, with most studies considering presence or absence of exposure at any point during childhood, with only limited consideration of the type, timing, severity, or duration of exposure. We noted this limitation in an early paper\(^11\), and data addressing this have been slow to emerge. What available data (e.g., those by Cutajar et al\(^50\) mentioned above) do suggest is that these dimensions matter and further underscore the importance of more extensive research utilizing more detailed assessments of exposure to adversities throughout childhood and adolescence.

To be clear, these methodological issues do not invalidate the current evidence. What they do is to add caveats, urge some caution, and highlight areas to be considered in future research.

EXPLORING THE NATURE OF THE ASSOCIATION

Research has begun to further elaborate on the nature of the association between childhood adversity and psychosis (although many of the limitations highlighted above also apply to this work). This is driven by three observations. First, and as noted at the outset, specific adversities rarely occur in isolation. Second, many children are exposed but only a minority develop psychotic experiences, fewer still a psychotic disorder. Third, childhood adversity is associated with a range of negative mental health and other outcomes (e.g., substance use).

If childhood adversity is indeed involved in the development of psychosis, these observations raise further questions about the cumulative effect of exposure to multiple adversities, about other factors that may amplify or minimize effects (i.e., causal partners), about whether there is any specificity for psychosis, and – ultimately – about the mechanisms through which risk is increased.

CUMULATIVE EFFECTS

There is evidence that the effect of multiple adversities on risk or odds of psychosis is cumulative\(^27,31,33,48,56,57\). For example, Wicks et al\(^57\), in their study of Swedish population register data, found that there was a modest linear increase in risk of psychotic disorder for each additional indicator of childhood adversity. Further, while not part of the meta-analysis, Varese et al\(^1\) report that 9 of 10 studies that examined multiple adversities found some evidence of a linear effect, i.e. greater risk or odds with each additional adversity.

There are, however, some limitations to these findings. For example, simply adding the number of exposures assumes that each has an equivalent effect, which is unlikely to be the case. Further, analyses assume that effects are linear; this is rarely formally tested and the possibility that there are threshold effects has not been considered. Finally, alternative approaches may yield additional insights (e.g., using latent class analyses to identify groups of individuals characterized by exposure to varying clusters of adversities).

CAUSAL PARTNERS

Childhood adversities are neither sufficient nor necessary for the onset of psychosis. This means that their impact must be dependent on the presence of other factors or causal partners. Reflecting this, there is a developing body of research examining the combined (synergistic) effects of childhood adversity and both genetic and other environmental factors.

Gene-environment interaction

Studies of gene-childhood adversity interaction have produced mixed results. Some have used indirect proxy markers for genetic risk, usually a history of psychosis in a first-degree relative. For example, Tienari et al\(^58\) examined whether the effect of family communication on risk of schizophrenia was dependent on genetic risk, using an adoption study design. They, first, assessed family communication patterns (dichotomized into low-dysfunction and high-dysfunction) in a sample of adoptees of mothers with a diagnosis of a schizophrenia spectrum disorder (high genetic risk group; N=145) and a sample of adoptees of mothers without a diagnosis of a schizophrenia spectrum disorder (low genetic risk group; N=158) and, second, followed the adoptees – up to 21 years later – to determine who developed a schizophrenia spectrum disorder.
They found strong evidence that the effect of dysfunctional family communication patterns on odds of disorder at follow-up was dependent on level of genetic risk. In the high genetic risk group, odds of disorder were ten times greater in the high-dysfunction than in the low-dysfunction group (OR=10.00, 95% CI: 3.26-30.69); in the low genetic risk group, the odds of disorder for each level of family dysfunction were roughly the same (OR=1.11, 95% CI: 0.37-3.39).

In a more recent analysis of data from the AESOP study, we used family history of psychotic disorder in a parent as a proxy for genetic risk to examine interaction between genetic risk and physical abuse in childhood in 172 cases with a first-episode psychosis and 246 controls. We found no evidence that the combined effect of abuse and family history was greater than the effect of each alone (i.e., no evidence of interaction). This study, however, was not designed to examine gene-environment effects and the sample was no doubt underpowered to detect anything other than a large interaction effect. This noted, others have also failed to find any evidence of interaction using indirect proxy measures of genetic risk, including Arseneault et al in their analyses of data from the E-Risk Study.

Other studies have used direct measures of genetic variation to examine interactions with candidate genes, i.e., genes either implicated in psychoses or in exposure-relevant systems, e.g., hypothalamic-pituitary-adrenal (HPA) axis or dopamine systems. Collip et al, for example, examined interactions between polymorphisms in the FKBP5 gene (a modulator of the feedback loop determining glucocorticoid receptor sensitivity, for which there is evidence of interaction with childhood trauma in post-traumatic stress disorder and depression) and childhood trauma (i.e., mean trauma scores from the Childhood Trauma Questionnaire) in a series of analyses of data from samples with expressions of psychosis across the spectrum. There was some evidence of interactions between trauma and two FKBP5 single nucleotide polymorphisms on psychotic symptoms, but these were not consistent across samples.

In another study of FKBP5 and maltreatment, in a sample of 444 cases with schizophrenia and 292 controls, Green et al found some evidence that a FKBP5 single nucleotide polymorphism (not one of those implicated in Collip et al's study) and maltreatment combined to affect cognition (specifically attention) in both cases and controls.

Other genes studied include those coding for brain-derived neurotrophic factor (BDNF), involved in neuronal development and cell survival in response to stress, and catechol-O-methyltransferase (COMT), involved in metabolism of catecholamines, including dopamine, in the central nervous system. Some studies found evidence of interactions (e.g., COMT and BDNF) and others did not (e.g., BDNF).

The evidence, then, is at present limited, with little consistency in methods and measures used. Further investigations are ongoing. These are likely to make use of emerging findings from molecular genetic studies to move beyond crude proxy markers of genetic risk or pain-staking analyses of one candidate gene at a time. That is, these new studies will almost certainly make use of direct measures of total (or pathway specific) genetic risk, derived from genome wide association studies (i.e., polygenic risk scores, which provide weighted summaries of effects of multiple risk genes), to model gene-environment interaction. Such research is, however, time consuming and it is likely that relevant findings will be slow to emerge and to replicate.

**Environment-environment interaction**

A small number of studies have examined interactions between childhood adversity and other environmental factors, notably cannabis use and adult life events and adversities. So far, these studies have been fairly consistent in finding evidence that childhood adversities do combine with subsequent cannabis use and adult adversities in psychoses.

With regard to cannabis use, there are six studies that we are aware of, only one of which did not find at least suggestive evidence of interaction. To illustrate this, in our analyses of data from a household survey of around 1,700 individuals, we found that odds of psychotic experiences were increased five-fold in those who both reported abuse in childhood and cannabis use in the preceding year (compared with around a two-fold increased odds for those reporting only abuse or only cannabis use).

As for adult adversity, there are four studies that we are aware of, all of which found evidence of interaction. In our analyses of data from the household survey, for example, we found strong evidence that abuse and life events combined synergistically to increase odds of low-level psychotic experiences, over and above the effects of each alone. Latasa et al similarly found evidence that early and recent adversity combined synergistically to increase risk of low-level psychotic experiences in their analyses of data from the Early Developmental Stages of Psychosis study. The other studies suggest that these combined effects extend to psychotic disorder. For example, Bebbington et al, using data from the 2007 UK Adult Psychiatric Morbidity Survey, found some evidence that sexual abuse combined with re-victimization in adulthood amplified risk of probable psychotic disorder.

**Protective factors**

What has not yet been considered to any great extent is whether there are protective factors that can offset the effects of childhood adversity. In general, there is strong evidence that social support, in particular the support of an adult, can limit the negative consequences of abuse and other adversities in childhood. In a secondary analysis of data from the AESOP study, we found some evidence – albeit among women only – that the effect of severe physical abuse on odds of psychosis was lower among those with more extensive networks.
Beyond this, we are not aware of any other studies that have examined the modifying effect of protective factors in relation to childhood adversity and psychosis. This, then, is an important avenue for future research. Investigating why some people are resilient in the face of often extensive adversities in childhood is of direct relevance to understanding how we can intervene at early stages to minimize risk and maximize resilience.

**SPECIFICITY**

At a broad level, most forms of childhood adversity are associated with a range of negative mental health and other outcomes. This raises the question of whether effects, if causal, are non-specific (with the particular forms that distress and disorder take being shaped by other factors, e.g. genes) or whether any types of adversity particularly increase risk of psychosis or, indeed, certain psychotic experiences.

There are good reasons to expect both non-specific and specific effects. It may be, for example, that most forms of adversity – in activating a stress response – exert general effects on processes involved in many outcomes. Non-specific effects, then, are likely. What is more, identifying specific effects is difficult, because not only adversities but also symptoms frequently co-occur (and indeed many symptoms may be sequentially and causally related). Disentangling effects is far from straightforward. This noted, some specificity is likely. Different types of experiences may impact on different psychological and, perhaps, biological processes, e.g. on attributions about self and the world, on threat anticipation, on activation of brain regions regulating perception of and response to stress, which in turn may underpin specific experiences. As Bentall et al argue, we might expect partial specificity.

It is perhaps no surprise, then, that there is evidence for both non-specific and specific effects. To begin with, at the broad level of any childhood adversity and mental disorder, there is limited evidence of specificity. In their meta-analysis, Matheson et al found no evidence that the magnitude of the association between childhood adversity and schizophrenia was different from that for other psychoses, depression, or personality disorders. There was some evidence that the effect was greater than for anxiety and, not surprisingly, lower than for post-traumatic stress disorder or dissociation, but childhood adversities, broadly defined, were associated with an increased risk of all these disorders.

When research moves from this broad level to consider particular types of adversity, there is some evidence for specificity. For example, in a further analysis of AESOP data, we found some tentative evidence that physical abuse (but not sexual abuse) – particularly by mother before age 12 years – was specifically associated with psychotic disorder, a finding that mirrors what has been found in relation to other disorders when researchers have carefully separated the effects of each. In this context, it is relevant to note again that Cutajar et al found an effect for sexual abuse only at the most extreme and violent level.

Others have found similar evidence for specific effects of adversities involving threat and hostility, most notably Arsenault et al in their analyses of data from the E-Risk Study. When the specific effects of three negative events or experiences – a serious accident, bullying, and maltreatment – were considered, bullying and maltreatment, but not a serious accident, were associated with an increased risk of psychotic experiences. The authors speculated that negative experiences involving intention to harm may be particularly important for psychotic experiences. In an analysis of data from the Dutch NEMESIS studies, van Nierop et al found further evidence for a specific effect of events involving intent to harm. This mirrors some earlier findings (e.g., Bebbington et al) and ties in with evidence from studies of adults which tentatively suggest that intrusive life events (e.g., physical assault) may be specifically associated with psychoses.

Intriguingly, in one of the few studies to directly investigate associations between racial discrimination and psychosis, Karlsen et al found that the strongest effect was for discrimination involving physical assault. The high rates of psychosis in some migrant and minority ethnic groups may, then, in part be a consequence of greater exposure to hostility, threat, and violence in the context of wider social disadvantage and discrimination – not social defeat (a misnomer anyway), as has been proposed. In general, it may be that these experiences are particularly linked to the development of suspiciousness, paranoia, and ultimately delusions of persecution and reference, which are the most common symptoms in schizophrenia and other psychoses.

At the level of symptoms, there is some evidence for a specific association between sexual abuse and hallucinations, disrupted early attachments or victimization experiences and paranoia, and parental communication deviance and thought disorder.

**MECHANISMS**

**Biological**

There are a number of connected biological mechanisms through which exposure to childhood adversities may increase risk for psychoses, including via effects on the HPA axis, dopamine systems, and neurocognition.

The plausibility of these hypothesized mechanisms derives from studies demonstrating dysfunctions and deficits in these biological systems among those exposed to childhood adversities, especially trauma, and among those with psychoses. First, there is strong evidence that childhood adversities are associated with hyperactivation and sensitization of the HPA axis and, in recent years, there has been an accumulation of evidence of dysregulation of the HPA axis in those with psychoses. For example, a number of studies have found...
differences in basal cortisol levels between those with a psychotic disorder and those without, with a majority reporting elevated cortisol levels at different points during the day\textsuperscript{86,89}. There is also some evidence that the pituitary gland may be enlarged among those with a psychotic disorder\textsuperscript{90}. Further, overactivity of the HPA axis increases dopamine release.

Second, there is evidence that hippocampal volume is decreased both among those exposed to childhood adversity\textsuperscript{87} and those with a psychotic disorder\textsuperscript{86}. For example, meta-analyses suggest that hippocampal volume is reduced bilaterally in those with a first episode and in those with a long-standing disorder\textsuperscript{91,92}. This is relevant because the hippocampus is involved in regulating the HPA axis stress response, and there is some direct evidence that smaller hippocampal volume at first psychotic episode is partly explained by stress-related processes, measured by cortisol secretion\textsuperscript{93}.

Third, there are studies that show reduced levels of BDNF – which is necessary for hippocampal neurogenesis – following exposure to stress\textsuperscript{86} and in those with psychosis\textsuperscript{94}.

Finally, there is evidence that dopamine release is elevated following exposure to stress (albeit mainly in animal models\textsuperscript{89}) and in those with psychosis, across the spectrum\textsuperscript{96-98}. This has led to speculation that prolonged exposure to stress may, in combination with other factors including genes (e.g., FKBP5) and early neurodevelopmental insults, contribute to dysregulation of connected biological systems that converge on increased dopamine release, leading to the development of (positive) symptoms of psychosis\textsuperscript{97-99}. Studies are beginning to emerge that provide some direct evidence consistent with this model\textsuperscript{98,100,101}. At present, however, direct evidence that these mechanisms do mediate the association between childhood adversities and psychoses is limited.

This caveat accepted, it may be that childhood adversities and associated neurobiological processes underpin, in part, the neurocognitive deficits often seen among those with a psychotic disorder, particularly schizophrenia. There is evidence, for example, that childhood adversities are associated with cognitive impairments among people with psychosis, and that the neurobiological abnormalities sketched above (e.g., dysfunction of the HPA axis, reduced hippocampal volume) are associated with cognitive deficits in a number of domains, including verbal and non-verbal memory, attention, and processing speed\textsuperscript{102-106}. What is more, these cognitive deficits may then compound risk by impacting on the capacity of individuals to cope with further stressors.

**Psychological**

There are also a number of psychological processes through which exposure to childhood adversities may increase risk for psychoses, including via effects on reasoning, cognitive schemas, and affect.

Research on psychological mechanisms has tended to focus on links between specific processes and specific experiences or symptoms. For example, consideration of psychological mediators of the association between childhood abuse, especially sexual abuse, and auditory hallucinations has centred on source monitoring biases (i.e., the tendency to attribute internal thoughts to external sources) and dissociation, both of which are implicated in the development of those hallucinations. The evidence, however, is limited and mixed\textsuperscript{79}. For example, in a study of patients with current and with past hallucinations and controls, Varese et al\textsuperscript{107} found no evidence that performance on source monitoring tasks was associated with childhood abuse. There is, however, some suggestive evidence from a small number of cross-sectional studies that dissociation may mediate the relationship between childhood abuse and psychosis\textsuperscript{79}.

Further, childhood adversities may influence psychological processes implicated in the development of paranoia and delusions of persecution and reference. Freeman and Garety\textsuperscript{108} identified six psychological processes that may be involved in the emergence of paranoid ideas and for which there is some evidence: worry, negative beliefs about self, interpersonal sensitivity, sleep disturbance, anomalous internal experiences, and reasoning biases. Experiences of adversity, particularly during childhood and adolescence, when thinking styles and beliefs about the self and the world crystallize, may impact on each of these. Repeated experiences of threat, for example, may contribute to the development of a worrying thinking style, to negative beliefs about self, and to reasoning biases (i.e., a tendency to jump to conclusions or anticipate threat on the basis of limited information)\textsuperscript{108}. These processes, moreover, may be interlinked (e.g., excessive worry leading to insomnia). Once again, however, the direct evidence that these processes mediate the association between childhood adversities and psychosis is limited, and more work is needed\textsuperscript{109}.

Finally, childhood adversities may increase risk for psychoses via an impact on affect. There is some evidence, including from longitudinal studies, that the association between childhood adversities and psychotic experiences is mediated via self-esteem and symptoms of depression and anxiety\textsuperscript{109,110}. In an analysis of data from the Avon Longitudinal Study of Parents and Children, Fisher et al\textsuperscript{110} found that self-esteem and affective symptoms substantially mediated the association between abuse and psychotic experiences.

The above-mentioned putative biological and psychological mechanisms represent different and complementary levels of explanation. For example, the dysfunctions and deficits observed in biological systems (e.g., stress sensitivity, increased dopamine release) may be the neurological substrata that underpin the relevant psychological processes (e.g., worry, reasoning biases). This is acknowledged in a number of integrated models of psychoses\textsuperscript{98,101,111}.

**SOME IMPLICATIONS**

The research summarized in this paper highlights several points. First, exposure to adversity in childhood – even
multiple adversities – is neither sufficient nor necessary to cause psychoses. This is true of all risk factors for psychoses. Other causal partners must be involved, including genetic and both non-social and other social environmental factors. The evidence, broadly, supports this. Second, many difficult and unpleasant situations and experiences in childhood may have general and lasting effects on biological systems and on cognitive abilities and schemas that predispose to a range of poor mental health outcomes, including psychoses. Third, certain types of situations and experiences may particularly increase risk for specific disorders or symptoms. On the basis of the evidence sketched in this review, exposure to contexts and events involving high levels of interpersonal hostility, threat, and violence – especially if severe and prolonged – may specifically increase risk for psychotic experiences and disorders.

These observations prompt a number of reflections on their implications for our understanding of psychosis more broadly. First, psychotic experiences and disorders, for most people, probably emerge from patchworks of causal factors – some general, some specific – that are woven over the course of development. To paraphrase Kagan112, risk factors for psychosis form a seamless and complex tapestry that is not easily unwound. The current balance of evidence is that childhood adversities, for some people, form part of this tapestry.

Second, the precise clusters of genetic and environmental factors that together push each individual along a developmental path to psychosis may be highly idiosyncratic. That is, the causal partners involved and their relative contribution will vary from person to person.

Third, this may explain both the varied manifestations of psychotic disorders and the overlaps (comorbidities) with other disorders. If some risk factors or indicators – particularly those measured at a broad level, e.g. social class – are generic to a number of disorders, then comorbidity would be expected. If specific risk factors – to some extent at least – underpin different symptoms and features of disorder, then variations (e.g., in age of onset, in mode of onset, in the balance of positive and negative symptoms, in prognosis) would be expected according to particular clusters of causes. There is some evidence for this (e.g., genetic risk and neurodevelopmental markers associated with earlier age of onset; social adversities associated with positive symptoms; sexual abuse associated with hallucinations).

Finally, this leads to the proposition that, broadly, there will be some individuals for whom the aetiology is predominantly genetic and neurodevelopmental and others for whom the aetiology is predominantly socio-environmental, e.g. a product of repeated exposure to severe interpersonal hostility and threat in the context of enduring social adversity and isolation. Taken one step further, it may be that psychoses rooted in adversity and trauma share more in common with post-traumatic stress disorder and other trauma-related distress than with psychoses rooted in neurodevelopment.

CONCLUSIONS

To sum up, the current balance of evidence suggests that childhood adversities – particularly exposure to multiple adversities involving hostility and threat – do, in some people, contribute to the onset of psychotic experiences and psychotic disorders.

There remain weaknesses and gaps in the evidence, and this means that some caution is still warranted. However, addressing these weaknesses and filling in the gaps may tell us much about the very nature of psychoses and – perhaps more importantly – about how we can most effectively reduce risk, minimize distress, and improve outcomes.

REFERENCES


Understanding the burnout experience: recent research and its implications for psychiatry

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The experience of burnout has been the focus of much research during the past few decades. Measures have been developed, as have various theoretical models, and research studies from many countries have contributed to a better understanding of the causes and consequences of this occupationally-specific dysphoria. The majority of this work has focused on human service occupations, and particularly health care. Research on the burnout experience for psychiatrists mirrors much of the broader literature, in terms of both sources and outcomes of burnout. But it has also identified some of the unique stressors that mental health professionals face when they are dealing with especially difficult or violent clients. Current issues of particular relevance for psychiatry include the links between burnout and mental illness, the attempts to redefine burnout as simply exhaustion, and the relative dearth of evaluative research on potential interventions to treat and/or prevent burnout. Given that the treatment goal for burnout is usually to enable people to return to their job, and to be successful in their work, psychiatry could make an important contribution by identifying the treatment strategies that would be most effective in achieving that goal.

Key words: Burnout, work engagement, psychiatric staff, health care, depression, exhaustion, cynicism, burnout measures, burnout interventions

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For many years, burnout has been recognized as an occupational hazard for various people-oriented professions, such as human services, education, and health care. The therapeutic or service relationships that such providers develop with recipients require an ongoing and intense level of personal, emotional contact. Although such relationships can be rewarding and engaging, they can also be quite stressful.

Within such occupations, the prevailing norms are to be selfless and put others’ needs first; to work long hours and do whatever it takes to help a client or patient or student; to go the extra mile and to give one’s all. Moreover, the organizational environments for these jobs are shaped by various social, political, and economic factors (such as funding cutbacks or policy restrictions) that result in work settings that are high in demands and low in resources. Recently, as other occupations have become more oriented to “high-touch” customer service, the phenomenon of burnout has become relevant for these jobs as well¹.

DEFINING BURNOUT

Burnout is a psychological syndrome emerging as a prolonged response to chronic interpersonal stressors on the job. The three key dimensions of this response are an overwhelming exhaustion, feelings of cynicism and detachment from the job, and a sense of ineffectiveness and lack of accomplishment. The significance of this three-dimensional model is that it clearly places the individual stress experience within a social context and involves the person’s conception of both self and others.

The initial research on burnout was exploratory and relied primarily on qualitative techniques. Because the earliest researchers came from social and clinical psychology, they gravitated toward relevant ideas from these fields. The social perspective utilized concepts involving interpersonal relations, i.e. how people perceive and respond to others; these included detached concern, dehumanization in self-defense, and attribution processes. It also brought in concepts of motivation and emotion (and especially coping with emotional arousal). The clinical perspective also dealt with motivation and emotion, but framed these more in terms of psychological disorders, such as depression. Subsequent researchers came from industrial-organizational psychology, and this perspective emphasized work attitudes and behaviors. It was also at this point that burnout was conceptualized as a form of job stress, but the primary focus was on the organizational context and less on the physical characteristics of the experienced stress.

What emerged from this descriptive work were the three dimensions of the burnout experience. The exhaustion dimension was also described as wearing out, loss of energy, depletion, debilitation, and fatigue. The cynicism dimension was originally called depersonalization (given the nature of human services occupations), but was also described as negative or inappropriate attitudes towards clients, irritability, loss of idealism, and withdrawal. The inefficacy dimension was originally called reduced personal accomplishment, and was also described as reduced productivity or capability, low morale, and an inability to cope.

Assessment of burnout

As the characteristics of burnout became more clearly identified, the next step was to develop measures that could assess them. Various measures were proposed, based on different assumptions about burnout, and many of them relied on the
face validity of the measurement items or statements. The first burnout measure that was based on a comprehensive program of psychometric research was the Maslach Burnout Inventory (MBI)\(^2,3\). The MBI was specifically designed to assess the three dimensions of the burnout experience which had emerged from the earlier qualitative research. It has been considered the standard tool for research in this field, and has been translated and validated in many languages\(^4\). In contrast, other initial measures of burnout focused only on the dimension of exhaustion\(^5,6\).

This distinction between measures that assess several dimensions of burnout, and those that assess the sole dimension of exhaustion, continues to the present day, and reflects different conceptualizations of burnout. For example, the Bergen Burnout Inventory (BBI)\(^7\) assesses three dimensions of burnout: exhaustion at work, cynicism toward the meaning of work, and sense of inadequacy at work. The Oldenburg Burnout Inventory (OLBI)\(^8\) assesses the two dimensions of exhaustion and disengagement from work. Other burnout measures focus on exhaustion alone, although they differentiate between various aspects of exhaustion. For example, the Shirom-Melamed Burnout Measure (SMBM)\(^9\) distinguishes between physical fatigue, emotional exhaustion, and cognitive weariness; and the Copenhagen Burnout Inventory (CBI)\(^10\) makes a distinction between physical and psychological exhaustion.

There have been other changes and modifications of burnout measures over the years. Because the initial concern about burnout emerged from caregiving occupations, such as health care and human services, the measures developed in the 1980s tended to reflect the experience of those professions. Later, however, other occupational groups became interested in the occurrence of burnout, but had some difficulties in adapting the existing measures to their work situation. For the MBI, the solution was the development of a General Survey that could be used within any occupation (MBI-GS)\(^11\). Not only were various items revised to be more “occupation-neutral”, but the dimension of depersonalization (which was more specific to human services) was broadened to refer to a negative detachment from work and was renamed *cynicism*, and the dimension of personal accomplishment was broadened and renamed *professional efficacy*. More recent burnout measures utilized more occupation-neutral wording from the outset.

However, some measures also added some new dimensions to the concept of burnout. For example, the Spanish Burnout Inventory consists of four dimensions: enthusiasm towards the job, psychological exhaustion, indolence, and guilt\(^12\). Meanwhile, some researchers were concerned that the more neutral wording meant a loss of the specific interpersonal issues for human service workers, so they developed a new measure of interpersonal strain\(^13\). It remains an open question whether these additional elements are essential components of burnout *per se*, or whether they assess experiences or conditions that often accompany the experience of burnout.

**Engagement**

An important development, at the beginning of the 21st century, has been that researchers have tried to broaden their understanding of burnout by extending their attention to its positive antithesis. This positive state has been identified as “engagement”. Although there is general agreement that engagement with work represents a productive and fulfilling state within the occupational domain, there are differences in its definition.

For some burnout researchers, engagement is considered to be the opposite of burnout and is defined in terms of the same three dimensions as burnout, but the positive end of those dimensions rather than the negative. From this perspective, engagement consists of a state of high energy, strong involvement, and a sense of efficacy\(^14\). By implication, engagement is assessed by the opposite pattern of scores on the three MBI dimensions.

However, a different approach has defined work engagement as a persistent, positive affective-motivational state of fulfillment that is characterized by the three components of vigor, dedication, and absorption. In this view, work engagement is an independent and distinct concept, which is not the opposite of burnout (although it is negatively related to it). A new measure, the Utrecht Work Engagement Scale (UWES)\(^15\), was developed to assess this positive state, and extensive research has been carried out in the last decade\(^16\).

The relationship between burnout and engagement continues to be debated, however, and a recent approach has been to use dialectical theory to synthesize conflicting views on the two constructs, and to develop an alternate model\(^17\).

**Conceptual models**

There have been various conceptual models about the development of burnout and its subsequent impact. At first, the focus was on the relationship between the three dimensions of burnout, which was often described in sequential stages. Exhaustion was assumed to develop first, in response to high demands and overload, and then this would precipitate detachment and negative reactions to people and the job (depersonalization or cynicism). If this continued, then the next stage would be feelings of inadequacy and failure (reduced personal accomplishment or professional inefficacy).

More recently, burnout models have been based on theories about job stress, and the notion of imbalances leading to strain. The first such model was the transactional one, which served as the conceptual bridge between sequential stages and imbalances\(^18\). Its three stages are: a) job stressors (an imbalance between work demands and individual resources), b) individual strain (an emotional response of exhaustion and anxiety), and c) defensive coping (changes in attitudes and behavior, such as greater cynicism).
Subsequently, two developmental models of the demands-resources imbalance have emerged: the Job Demands-Resources (JD-R) model and the Conservation of Resources (COR) model. The JD-R model focuses on the notion that burnout arises when individuals experience incessant job demands and have inadequate resources available to address and to reduce those demands\textsuperscript{19}. The COR model follows a basic motivational theory assuming that burnout arises as a result of persistent threats to available resources\textsuperscript{20}. When individuals perceive that the resources they value are threatened, they strive to maintain those resources. The loss of resources or even the impending loss of resources may aggravate burnout. Both the JD-R and the COR theory of burnout development have received confirmation in research studies.

A different variation of an imbalance model of burnout is the Areas of Worklife (AW) model, which frames job stressors in terms of person-job imbalances, or mismatches, but identifies six key areas in which these imbalances take place: workload, control, reward, community, fairness, and values. Mismatches in these areas affect an individual's level of experienced burnout, which in turn determines various outcomes, such as job performance, social behaviors, and personal wellbeing. The greater is the mismatch between the person and the job, the greater the likelihood of burnout; conversely, the greater the match, the greater the likelihood of engagement. Initial empirical support for the AW model has been provided by both cross-sectional and longitudinal studies\textsuperscript{21}.

**CAUSES AND OUTCOMES**

Most models of burnout make explicit the causal theorizing that has always been implicit in burnout research: certain factors (both situational and individual) cause people to experience burnout, and once burnout occurs, it causes certain outcomes (both situational and individual). However, these causal assumptions have rarely been tested directly. Most research on burnout has involved cross-sectional designs or studies using statistical causal models. This correlational database has provided support for many of the hypothesized links between burnout and its sources and effects, but it is unable to address the presumed causality of those linkages. The recent increase in longitudinal studies is beginning to provide a better opportunity to test sequential hypotheses, but stronger causal inferences will also require appropriate methodological designs (and these are often difficult to implement in applied settings). One other critical constraint is that many of the variables have been assessed by self-report measures (rather than other indices of behavior or health).

Over two decades of research on burnout have identified a plethora of organizational risk factors across many occupations in various countries\textsuperscript{22,23}. Six key domains have been identified, as mentioned earlier: workload, control, reward, community, fairness, and values. The first two areas are reflected in the Demand-Control model of job stress\textsuperscript{24}.

Work overload contributes to burnout by depleting the capacity of people to meet the demands of the job. When this kind of overload is a chronic job condition, there is little opportunity to rest, recover, and restore balance. A sustainable and manageable workload, in contrast, provides opportunities to use and refine existing skills as well as to become effective in new areas of activity.

A clear link has been found between a lack of control and burnout. On the contrary, when employees have the perceived capacity to influence decisions that affect their work, to exercise professional autonomy, and to gain access to the resources necessary to do an effective job, they are more likely to experience job engagement.

The area of reward refers to the power of reinforcements to shape behavior. Insufficient recognition and reward (whether financial, institutional, or social) increases people's vulnerability to burnout, because it devalues both the work and the workers, and is closely associated with feelings of inefficacy. In contrast, consistency in the reward dimension between the person and the job means that there are both material rewards and opportunities for intrinsic satisfaction.

The area of community has to do with the ongoing relationships that employees have with other people on the job. When these relationships are characterized by a lack of support and trust, and by unresolved conflict, then there is a greater risk of burnout. On the contrary, when these job-related relationships are working well, there is a great deal of social support, employees have effective means of working out disagreements, and they are more likely to experience job engagement.

The area of fairness emerges from the literature on equity and social justice. Fairness is the extent to which decisions at work are perceived as being fair and equitable. People use the quality of the procedures, and their own treatment during the decision-making process, as an index of their place in the community. Cynicism, anger and hostility are likely to arise when people feel they are not being treated with the appropriate respect.

Finally, the area of values picks up the cognitive-emotional power of job goals and expectations. Values are the ideals and motivations that originally attracted people to their job, and thus they are the motivating connection between the worker and the workplace, which goes beyond the utilitarian exchange of time for money or advancement. When there is a values conflict on the job, and thus a gap between individual and organizational values, employees will find themselves making a trade-off between work they want to do and work they have to do, and this can lead to greater burnout.

In terms of outcomes, burnout has been frequently associated with various forms of negative reactions and job withdrawal, including job dissatisfaction, low organizational commitment, absenteeism, intention to leave the job, and turnover\textsuperscript{25}. For example, cynicism has been found to be the pivotal aspect of burnout to predict turnover\textsuperscript{25}, and burnout mediates the relationship between being bullied in the workplace and the intention to quit the job\textsuperscript{26}. On the other hand, for people who stay...
on the job, burnout leads to lower productivity and impaired quality of work. As burnout diminishes opportunities for positive experiences at work, it is associated with decreased job satisfaction and a reduced commitment to the job or the organization.

People who are experiencing burnout can have a negative impact on their colleagues, both by causing greater personal conflict and by disrupting job tasks. Thus, burnout can be “contagious” and perpetuate itself through social interactions on the job.27-28 The critical importance of social relationships for burnout is underscored by studies that show that burnout increases in work environments characterized by interpersonal aggression.29,30 Such findings suggest that burnout should be considered as a characteristic of workgroups rather than simply an individual syndrome.

Burnout has a complex pattern of relationships with health, in that poor health contributes to burnout and burnout contributes to poor health.31 Of the three burnout dimensions, exhaustion is the closest to an orthodox stress variable, and therefore is more predictive of stress-related health outcomes than the other two dimensions. Exhaustion is typically correlated with such stress symptoms as headaches, chronic fatigue, gastrointestinal disorders, muscle tension, hypertension, cold/flu episodes, and sleep disturbances. These physiological correlates mirror those found with other indices of prolonged stress. Parallel findings have been found for the link between burnout and substance abuse.32

A ten-year longitudinal study of industrial workers found burnout to predict subsequent hospital admissions for cardiovascular problems.33 Other research found that a one-unit increase in burnout score was related to a 1.4 unit increase in risk for hospital admission for mental health problems, as well as a one-unit increase in risk for hospital admissions for cardiovascular problems.34 Other studies have provided a more detailed examination of the link between burnout and cardiovascular disease, noting the role of high-sensitivity C-reactive protein and fibrinogen concentrations in the link.35

BURNOUT IN PSYCHIATRY

To a large extent, the research literature on burnout in psychiatry echoes those previous themes. Workplace variables have been found to be more stressful for psychiatrists than other factors, and thus may be more likely to perpetuate burnout.36 These variables include too much work, long working hours, chronic staff shortages, an aggressive administrative environment, and lack of support from management. Poor relationships with management and supervisors have also been identified as related to burnout among psychiatry residents.37 However, research has found mixed results with regard to the role of job satisfaction in burnout, with some studies reporting no relationship,37,38 and other studies reporting that job satisfaction did play a role.39,40

The rate of burnout among those employed in the health care field tends to be reported in the moderate to high levels, and it is generally believed that the burnout risk in health care is higher than in the general working population. Reported burnout rates for psychiatrists are quite similar to this overall trend.41-43 Some studies have raised the possibility that psychiatrists show an even more negative risk profile for burnout than do other health care employees.44,45 For example, one study found that 89% of psychiatrists had either thought about or experienced a clear threat of severe burnout.45

There are other critical risk factors that may be more unique to the field of psychiatry. Chief among these is the working relationship that psychiatrists, and other mental health professionals, have with clients who are experiencing psychological trauma. The challenging demands posed by these and other difficult clients can lead to greater stress and frustration among psychiatrists, which in turn can fuel the exhaustion, cynicism, and inefficacy of burnout. This process has also been described in terms such as compassion fatigue, secondary traumatic stress, and vicarious traumatization.46-48 The burnout experience can become especially overwhelming when the psychiatrist becomes the target of anger, hatred, and even violence, as a result of negative transference.49 Violent incidents with patients can be emotionally draining and difficult to manage, and can lead health providers to psychologically distance themselves from their work. The occurrence of violence can also make providers feel that they lack control over their job, and thus challenge their sense of professional efficacy.

Higher levels of burnout are correlated with more negative feelings about patients,50 and a poorer quality of patient care.51 This link between burnout and poor care is supported by research on how burnout is manifested in psychiatrists, by changes in appearance (e.g., look of fatigue), behavior (e.g., becoming avoidant, making less eye contact), and mood (e.g., becoming more irritable and agitated, communicating poorly). In addition, perfectionist and obsessive traits may perpetuate burnout, particularly when the workload is heavy or stressful.52

Working with demanding patients and working with patients’ families have been found to be closely associated with psychiatrists’ levels of exhaustion and depersonalization.53 These relationships reflect psychiatrists’ frustrations with the limits of their craft. Contact with patients’ families intensified these feelings, especially when family members expressed unrealistic expectations for treatment. Psychiatrists are emotionally drained by their inability to meet the strenuous demands they put upon themselves, and the demands inherent in their interactions with patients and patients’ families. In contrast, diminished personal accomplishment reflects problematic relationships with superiors and colleagues, rather than demands from patients. Colleagues provide the most relevant source of information regarding one’s sense of efficacy in professional life. When those relationships are strained, it is difficult to find meaningful confirmation of one’s job performance.
Research on burnout has always recognized a central role for social relationships in the development and resolution of the syndrome. Initially, the research focus was primarily on the therapeutic relationship between the provider and the service recipient. Over time, studies have confirmed that relationships with colleagues and supervisors are equally, if not more, relevant to the potential for providers to experience burnout. For example, recent research on attachment styles found that attachment anxiety was accompanied by more frequent incivility from colleagues, and was associated with more exhaustion and cynicism. Attachment avoidance was linked to fewer instances of positive social encounters at work, and was associated with a greater sense of inefficacy. In sum, negative social interactions seem to drain energy and distance people from their job, and the absence of positive social encounters is discouraging.

CURRENT ISSUES

There are many interesting questions about burnout and engagement which are being studied in many countries around the world. A few inter-related themes should be of particular significance for the profession of psychiatry. First is the question of the relationship between burnout and mental illness. Second is the question of the value of simplifying the multi-dimensional construct of burnout to the single dimension of exhaustion. And third is the question of how best to ameliorate burnout in terms of treatment and prevention.

Burnout and mental illness

When the construct of burnout was first proposed in the 1970s, there were arguments that it was not a distinctly different phenomenon, but rather a new label for an already known state – i.e., “old wine in a new bottle”. However, there were a lot of differing opinions about what the “already known state” actually was. These included job dissatisfaction, anomic, job stress, anxiety, anger, depression, or some combination of them. For example, one psychoanalytic perspective argued that burnout was not distinguishable from either job stress or depression, but represented a failure to achieve narcissistic satisfaction in the pursuit of ideals. As a result of these critiques, subsequent research often focused on testing the discriminant validity of burnout by assessing whether it could be distinguished from these other phenomena. The results of many studies have established that burnout is indeed a distinct construct.

Much of this prior discussion has focused on depression, thus raising the question of whether burnout is a precipitating factor for depression, and thus is a predictor for it, or whether burnout is the same thing as depression, and thus is itself a mental illness. Research has demonstrated that the two constructs are indeed distinct: burnout is job-related and situation-specific, as opposed to depression, which is more general and context-free.

However, a recent article has renewed debate on the distinction between burnout and depression by claiming that at high levels the two states are indistinguishable. This position is in contrast to the view that burnout is an occupationally-specific dysphoria that is distinct from depression as a broadly based mental illness. But close examination of the new research article reveals problems with its argument.

A necessary condition to examine the distinction between burnout and depression is a set of measures that provide a complete and accurate operationalization of each construct, and the new study fell short of this criterion. Specifically, the nine-item depression measure (Patient Health Questionnaire, PHQ-9) used in this study includes five items that refer explicitly to fatigue (lack of interest, trouble sleeping, trouble concentrating, moving slowly, and feeling tired). The other four items include one referring to loss of appetite and three referring to negative thoughts (suicidal thoughts, feeling depressed, negative self-evaluation). The measure produces a single factor score; clearly that factor is heavily weighted towards fatigue (Cronbach alpha .88). It may be argued that these nine items fail to capture the full complexity of clinical depression. In any case, the depression construct operationalized in this measure is one dominated by fatigue, accompanied by negative thoughts. To measure burnout, the study used the SMBM, which is a one-factor fatigue scale with items referring explicitly to trouble concentrating, feeling tired, and thinking in a slow, unfocused, and unclear manner. Although conceptualized as representing three distinct factors of cognitive, physical, and emotional fatigue, the measure consistently reduces to a single factor of fatigue (Cronbach alpha .96). Given the overlap in the explicit reference of the two measures to fatigue in the majority of their items, it is not surprising that the two scales are correlated highly ($r = .77$).

The high correspondence of burnout and depression in this new study reflects a large level of concept redundancy between the SMBM and PHQ-9. The two instruments primarily measure exhaustion, leading to a strong correspondence between them, especially at high levels of exhaustion. The correlation was especially high in this study; earlier research that used these identical measures reported correlations at three different times as $.51$, $.53$, and $.54$. These results are consistent with other research that finds that burnout and depression are interrelated conditions.

Research using the MBI departs further from depression measures in its three-component definition of the syndrome as exhaustion, cynicism, and inefficacy. Some studies that have used the MBI and different measures of depression have found the following range of correlations. The Profile of Mood States (POMS) depression scale correlated with the MBI - Human Services Survey (MBI-HSS) exhaustion ($r = .33$), depersonalization ($r = .30$), and personal accomplishment ($r = -.14$). The Depression Anxiety Stress Scale (DASS-21) depression subscale
correlated with the MBI-GS exhaustion (r=.37), cynicism (r=.47), and efficacy (r=-.21). The Beck negative emotions and attitudes subscale correlated with the MBI-GS exhaustion (r=.46) and cynicism (r=.28), and the Beck performance difficulties and somatic complaints subscale correlated with MBI-GS exhaustion (r=.61) and cynicism (r=.36).

The wide range of correlations between burnout and depression argues for a complex relationship between the two constructs. Clearly, they are linked to each other. For example, one study found that 90% of the respondents with severe burnout (i.e., daily occurrence of burnout symptoms) reported a physical or mental disease, with musculoskeletal pain and depression as the most common problems. A longitudinal study found that increases in burnout predicted increases in subsequent prescriptions of antidepressant medication.

A new understanding of this linkage comes from a recent longitudinal study in Finland, which found a reciprocal relationship between burnout and depression, with each predicting subsequent developments in the other. It was noteworthy that burnout fully mediated the relationship of workplace strains with depression: when problems at work contribute to depression, experiencing burnout is a step in the process. It was noteworthy that burnout fully mediated the relationship of workplace strains with depression: when problems at work contribute to depression, experiencing burnout is a step in the process.

These studies confirm that burnout and depression are not independent. Each state has implications for the other. However, that relationship is far from saying that burnout and depression are the same mental illness.

Single or multiple dimensions

Although the original construct acknowledged exhaustion as a key aspect of burnout, it argued that exhaustion is not the whole story. Indeed, if burnout were solely exhaustion, then the word “burnout” would be unnecessary, as it would not be providing any added value. “Exhaustion” would suffice. To rename “exhaustion” as “burnout” would definitely be inviting the criticism of putting old wine in new bottles.

And yet, that simplification of burnout to exhaustion has been taking place not only among researchers, but also among practitioners. The driving force seems to be the goal of establishing a clinical diagnosis for burnout, so that health professionals can then receive reimbursement for treating individuals suffering from that condition.

This shift to defining and diagnosing burnout as an individual disorder or disability has been taking place in Northern Europe, primarily in Sweden and the Netherlands. There, burnout has been likened to neurasthenia or other syndromes with a quality of chronic fatigue. Sweden began using work-related neurasthenia as a burnout diagnosis in 1997; soon, that was within the five most frequent diagnoses. Researchers developed a similar diagnosis in the Netherlands, using clinically validated cut-off scores on the MBI.

To provide more precise diagnostic direction, Sweden in 2005 revised the ICD-10 burnout diagnosis (Z73.0) as a difficulty in life management characterized by “vital exhaustion.” The signs of vital exhaustion include two weeks of daily experiences of low energy, with difficulties in concentration, irritability, emotional instability, dizziness, and sleep difficulties. Additionally, these symptoms must interfere with the patients’ capacity to perform their work responsibilities.

In the Netherlands, the term overspannenheid or “overstrain” is used to indicate burnout. This diagnostic approach estimates burnout prevalence at 3-7% across various occupations, with psychotherapists at 4%. In terms of MBI scores, Dutch researchers recommended that a burnout diagnosis should be connected with very negative scores on exhaustion accompanied by negative scores on one of the other two subscales (cynicism and inefficacy).

The use of burnout as a medical diagnosis implies one-dimensionality, and it is clear that exhaustion has emerged as that single dimension. Moreover, since 1997, the Dutch census bureau has been assessing “burnout” among the working population by using an index of work-related exhaustion (that is based on the MBI) in its annual national survey. As a consequence, public discourse about burnout in the Netherlands is increasingly limited to exhaustion alone. The risk is that a focus on just exhaustion (and its connection to work overload) will miss the distinct quality of burnout as reflecting a crisis of meaning or values. The exhaustion dimension captures the problem of lacking sufficient energy to make a useful and enduring contribution at work. But it is the cynicism dimension that captures the difficulty in dealing with other people and activities in the work world. Furthermore, efficacy captures the core self-evaluation people make regarding the value of their work and the quality of their contribution. To ignore these core aspects of the burnout experience would truly be a “mis-diagnosis” that could have important ramifications for both policy and practice.

It is interesting that North American jurisdictions have been reluctant to recognize burnout as a clinical diagnosis, partially due to concerns about a flood of requests for disability coverage. The lack of an official diagnosis of burnout limits access to treatment, disability coverage, and workplace accommodations. Alternatively, disability applications have referred to depression, neurasthenia, or chronic fatigue. An unfortunate consequence is that inaccurate diagnoses may reduce possibilities for successful recovery and return to work.

New research has begun to focus on an innovative use of the three burnout dimensions, which allows for multiple distinct patterns along the burnout-engagement continuum. In addition to the two standard endpoint patterns of Burnout (high on all three dimensions) and Engagement (low on all three dimensions), this approach can identify people who are only experiencing one of the dimensions, rather than all of them. A particularly relevant comparison is between people with the complete Burnout profile and those with only high exhaustion (the Overextended profile). The research findings show that these two patterns are decidedly different in terms of their workplace experience, so it is clear that exhaustion alone is not a proxy for burnout. Instead, the profile that
comes closer to the negative endpoint of Burnout is the cynicism-only one (Disengaged profile), which suggests that the experience of cynicism may be more of a core part of burnout than exhaustion. Cynicism is more clearly linked to the job environment, in terms of the poor quality of social relationships at work and the lack of critical resources, and that will lead to reduced job satisfaction and poor job performance.\textsuperscript{73}

**Treatment and prevention**

The personal and organizational costs of burnout have led to proposals for various intervention strategies. Some try to treat burnout after it has occurred, while others focus on how to prevent burnout by promoting engagement. Intervention may occur on the level of the individual, workgroup, or an entire organization. In general, the primary emphasis has been on individual strategies, rather than social or organizational ones, despite the research evidence for the primary role of situational factors.

Many of these individual strategies have been adapted from other work done on stress, coping, and health. The most common recommendations have included: a) changing work patterns (e.g., working less, taking more breaks, avoiding overtime work, balancing work with the rest of one’s life); b) developing coping skills (e.g., cognitive restructuring, conflict resolution, time management); c) obtaining social support (both from colleagues and family); d) utilizing relaxation strategies; e) promoting good health and fitness; and f) developing a better self-understanding (via various self-analytic techniques, counseling, or therapy).\textsuperscript{74}

Initiatives to moderate workload demands complemented by improvements in recovery strategies through better sleep, exercise, and nutrition have direct relevance to the exhaustion component of burnout. Cynicism, in contrast, pertains more directly to a sense of community or to the congruence of personal and workplace values. For example, an intervention that improved workplace civility among health care providers showed that cynicism declined as a function of improved civility,\textsuperscript{75} and that this change was sustained at a one-year follow-up assessment.\textsuperscript{76} A sense of efficacy, in contrast, could be more responsive to improvements in the forms of recognition from colleagues and leaders within an organization or the profession. An alternative proposal has been that people can make various changes in how they do their job (a process known as “job crafting”), and that such job alterations could lead to less burnout.\textsuperscript{77}

Unfortunately, there is very little research that has evaluated the efficacy of any of these approaches in reducing the risk of burnout. Especially rare are studies modeled even loosely on randomized control trials. More common are studies with a single intervention group of volunteer participants for whom there are rarely follow-up assessments after treatment has ended.\textsuperscript{78} It is not yet clear whether burnout is generally susceptible to a range of strategies or whether it is crucial to fit the strategy to the specific context of a workplace to be effective.

The same basic points can be made about studies examining interventions specific to psychiatrists. There have been several recommendations about possible interventions, but no thorough research on whether these ideas are viable solutions. One fairly common recommendation emphasizes the importance of various forms of support, such as peer support groups, formal support via regular feedback and performance evaluation, or the use of a community-based approach in the workplace. Interestingly, medical students and residents have also identified support as a critical factor, including support from faculty, peers, outside personal relationships, and counseling services.\textsuperscript{79}

Another suggestion involves having psychiatrists evaluate their workload frequently, to ensure they are not putting themselves at additional risk for burnout. A related recommendation is that psychiatrists should develop a more versatile lifestyle, in which they diversify their work (e.g., take on a part-time teaching job, do some writing, or extend one’s practice to other types of clients) and/or engage in activities outside of work (such as hobbies and other personal interests).

Mental health professionals who have worked in the areas of trauma and palliative care have made additional recommendations on how to deal with burnout\textsuperscript{80,81}. Notably, one approach emphasizes the need to take care of oneself – and not only in terms of personal health and physical fitness, but also in terms of psychological wellbeing. Professionals who deal with trauma survivors are encouraged to work through their own personal traumatic experiences in order to prevent becoming “wounded healers” or secondarily traumatized therapists. Professionals working in hospice and palliative medicine are encouraged to focus on spirituality and human nature, via prayer, meditation, or religious services. Other methods for self-care include taking regular breaks from work, advocating for better social recognition of the difficult work that is being accomplished, and focusing on the positive aspects of life, both at work and home, so that one is not overwhelmed by adversity and misery.

Although various studies have provided excellent ideas to explore as interventions, the logistics of funding, designing, implementing, and evaluating these ideas remain the primary obstacles to better knowledge about the best solutions for burnout. For example, a Swedish group contrasted two therapeutic modalities for people who had been on long-term leave from work with a diagnosis of “work-related depression”. They found that both cognitive group therapy and focused psychodynamic group therapy were effective in facilitating their return to work, but found no difference in effectiveness between the two approaches.\textsuperscript{82} This study raises two important issues for further research. First, to what extent does “work-related depression” map upon clinical depression, in contrast to mapping upon burnout? Second, what are the common qualities of the two therapeutic modalities that could serve as mechanisms in treatment efficacy?
CONCLUSIONS

Research to date indicates that the three aspects of burnout do present challenges for psychiatrists. Many of the issues for psychiatrists are similar to those facing other professionals providing human services to people in need of help. But additionally, psychiatric work entails close contact with people in emotional distress, and in some cases the potential for threats from some of these patients. Both of these stressors make demands on psychiatrists’ energy, their capacity for involvement with others, and their sense of professional efficacy.

An issue of special significance to psychiatry is the alignment and differentiation of burnout and depression. The concept of workplace depression as a basis for workers’ disability coverage in some European countries raises important issues for practitioners, which have extensive implications for employees, employers, and insurance providers. Research and conceptual development that includes multidisciplinary participation is needed for definitive progress.

Psychiatry is in a strong position to contribute to the growth of knowledge regarding burnout. The question of burnout’s status as a basis for disability claims requires precise and objective assessment. Further, psychiatric-based treatments may be relevant to burnout, especially regarding return to work for people experiencing severe burnout. Finally, effective research on preventing and alleviating aspects of burnout among psychiatrists requires giving the issue a high priority within the profession.

REFERENCES

Draft diagnostic guidelines for ICD-11 mental and behavioural disorders available for review and comment

From the beginning, practicing psychiatrists and other mental health professionals around the globe have played an integral role in the development of the ICD-11 classification of mental and behavioural disorders by the World Health Organization (WHO) Department of Mental Health and Substance Abuse. A central aspect of practitioners’ contribution has been their participation in a series of developmental field studies1 conducted by the WHO to gather information about the performance of draft versions of the ICD-11 guidelines. Findings from these studies are being used to improve the reliability, validity and clinical utility of the final versions2. As one specific example, data from a field study in which participants applied the proposed diagnostic guidelines for Disorders Specifically Associated with Stress to standardized case material in the form of vignettes showed that, while the ICD-11 guidelines were generally an improvement over ICD-10, clinicians did not clearly understand the new diagnostic requirement of re-experiencing post-traumatic stress disorder and also found that the disorder was too narrowly defined3. Based on these results, specific changes were made to the diagnostic guidelines.

These field studies are currently being implemented via the Internet in multiple languages through the Global Clinical Practice Network (GCPN)4. The WHO Department of Mental Health and Substance Abuse established the GCPN as a realistic and feasible tool to collect truly global information about whether the proposed ICD-11 diagnostic guidelines lead to more accurate and consistent clinical decision-making than those of ICD-10. The GCPN was partly an extension of an earlier collaboration between the WHO and the WPA on a large international survey of nearly 5,000 psychiatrists in 44 countries regarding their use and attitude towards diagnostic classification systems5.

The GCPN now consists of more than 12,600 mental health and primary care professionals in nearly 150 countries. The largest group of GCPN participants – over half – are psychiatrists, followed by psychologists (29%). Nearly four in ten GCPN members are from low- and middle-income countries, where the large majority of the world’s population lives.

The WHO’s strong emphasis on participation by the anticipated daily users of the classification has sometimes been taken to suggest that we are managing the ICD-11 development as a popularity contest, making decisions about categories and diagnostic requirements based on whether or not practitioners “like” them. In fact, the proposals made by the ICD-11 Working Groups have been based on a careful consideration of the available scientific evidence. We believe that utility and validity are related and overlapping concepts6, and that a dichotomy between science and practice is false as applied to the approach we are taking to ICD-11 field studies.

But the WHO has also gone beyond traditional evidence reviews to develop a robust research agenda that treats the extent to which the ICD-11 can be accurately and easily used by practitioners as a serious scientific question7. For the WHO, the importance of clinical utility is closely related to the key aim of reducing the disease burden of mental and behavioural disorders and to the objectives of the WHO’s Mental Health Action Plan of providing comprehensive, integrated and responsive mental health and social care services in community-based settings and strengthening information systems, evidence and research for mental health8,9. If the ICD-11 is too cumbersome to use and fails to provide mental health professionals with clinically useful information, they simply won’t apply it consistently. In that case, information collected at the health encounter level will not provide a valid basis for health policy or resource allocation at the system, national or global level.

Data collection is now beginning for multi-site ecological implementation field studies that will assess the clinical utility and diagnostic reliability of the ICD-11 guidelines in the global clinical settings in which they will ultimately be implemented. One arm of these clinic-based studies will involve the participation of major international field study centers. A second arm will provide the opportunity for GCPN members to contribute data regarding the implementation of the guidelines in the context of their own clinical practices.

The general proposed structure of the entire ICD-11, covering all health conditions, as well as brief glossary definitions for all categories are available for public review on the ICD-11 beta platform (http://apps.who.int/classifications/icd11/browse/1-m/en). Registered users may comment on the categories and definitions provided. However, the information available on the beta platform constitutes the statistical version of the classification, designed primarily for use by government health statistics agencies and coders of medical records and death statistics. The WHO does not consider this information to be sufficient for application of the ICD-11 by mental health professionals9. The latter is the purpose of the diagnostic guidelines.

Previously, we described the structure, nature and rationale for the ICD-11 diagnostic guidelines being developed for use by mental health professionals in global health care settings10. The complete guidelines are too lengthy to be practical for field studies, so an abbreviated version of the guidelines is being used for that purpose that consists of three core sections. Essential features provide explicit guidance regarding the symptoms or characteristics needed to confidently make the diagnosis. Their format is intended to conform to the way clinicians actually make psychiatric diagnosis, i.e., with the flexible exercise of clinical judgment. The field studies version of the guidelines also contains a section on Boundary with other disorders and with normality, which indicates those disorders that should be considered in the differential diagnosis and provides specific guidance related to each, as well as regarding the differentiation.
Can separation anxiety disorder escape its attachment to childhood?

The definition of separation anxiety disorder (SEPAD) has undergone significant changes in DSM-5, the most important being the lifting of the age restriction (18 years of age in DSM-IV) for assigning the diagnosis. There may be resistance, however, amongst some clinicians and researchers to extending the diagnosis to adulthood. We consider the arguments in favour and against this change in the hope of stimulating debate and research aimed at achieving a consensus on this issue.

Why do clinicians traditionally restrict the diagnosis of SEPAD to childhood (here used broadly to cover the period from infancy to early adolescence)? The main reason is that the construct of separation anxiety (SA) has long been central to developmental theories that exert a strong influence in guiding clinical practice. Within the broad developmental framework of psychoanalytic and attachment theories, SA is regarded as representing a repertoire of neurophysiological, intrapsychic and behavioural responses specifically designed to protect children from danger by ensuring the maintenance of close proximity to an adult caregiver, typically the mother. The SA mechanism is of particular importance to our species because of the prolonged period of dependency of the child on the caregiver. In attachment theory, heightened expressions of SA are regarded as indicating disturbances in the child's working models or internal representations of attachment figures, shaped by past and ongoing bonding experiences with primary caretakers. SEPAD as a diagnosis therefore lies at the extreme end of a spectrum of responses that extend from the normative to the pathological, its presence signifying that the child has been exposed to severe disruptions and/or disturbances in his/her primary bonds. Classical symptoms of SEPAD (excessive clinging, tantrums, school refusal, abdominal pain and headaches, refusal to sleep alone, and nightmares of being attacked or abducted) reinforce further the phase-specific nature of the response.

Yet attachment theory has long acknowledged that the drive to form and maintain close bonds is fundamental to humans throughout the life course. The corollary must be that the SA response can occur in persons of all ages. Indeed, reciprocity in the SA response between the mother and the child is critical to the mechanism's protective function; by mirroring the alarm signals of the lost child, the mother's anxiety ensures that she engages in intensive searching behaviour to rescue the young person from potential harm. More generally, in collective species
such as *homo sapiens*, the drive to maintain proximity to close others is fundamental to ensuring the survival of individual members.1

In summary, there is an evident tension within attachment theory between the tendency to regard SA as a specific characteristic of childhood and the recognition that attachment anxiety extends throughout the life course. From a clinical perspective, Bowlby’s developmental model of agoraphobia provided a partial resolution for this problem. He proposed that, if high levels of SA persisted into later years, they manifested as typical symptoms of agoraphobia.4 According to this model, symptoms such as carrying transitional objects, reliance on phobic companions, and the preference for staying at home (as a symbol of a secure base) reveal the underlying SA roots of adult agoraphobia.4

Initially, empirical research provided support for the SA-agoraphobia model; in a series of studies, adult patients with agoraphobia reported much higher levels of early SEPAD (assessed by the proxy indicator of school phobia) in their early lives compared to those with other anxiety or depressive disorders.5 The SA-agoraphobia model became firmly embedded in developmental theory over time, incorporating panic disorder as an adult outcome when DSM-III linked that category to agoraphobia. Since then, researchers have searched for evidence of a common biological substrate underlying SEPAD, panic disorder and agoraphobia, by examining the family aggregation, shared pattern of genetic inheritance and distinctive psychophysiological responses associated with the three constellations.6,7

In parallel, however, other studies have produced evidence that calls into question the SA-agoraphobia model. In particular, several studies have found that the link between early SA and panic disorder/agoraphobia is not specific, but represents a general characteristic of adults with a range of anxiety and depressive disorders.6 Two decades ago, observations at a clinic for anxiety patients at the University of New South Wales led to the formulation of an alternative developmental model of SEPAD.9 The team found that, when symptoms were specifically inquired into, many adult anxiety patients revealed the presence of SEPAD, commonly dating the onset of the problem to childhood.9 This discovery suggested a continuity model in which SEPAD was a disorder that extended across the life course, although symptoms showed pathoplastic changes commensurate with maturation. For example, adults feared for the safety and whereabouts of a wider range of attachment figures, including parents, romantic partners and spouses. Moreover, symptoms manifested in more subtle ways: for example, adults employed complex rationalizations to avoid work or travel and tended to find pretexts to make repeated phone contact with attachment figures throughout the day.

Following these observations, several measures were developed to assess SEPAD in adulthood.10 The clinic-based studies that followed indicated that 20–40% of patients attending ambulatory facilities met criteria for SEPAD.9,10 The relationship between reported early SA symptoms and adult SEPAD proved to be highly specific; once that relationship was accounted for, there was no evidence to support a specific link between SA and panic disorder or agoraphobia.

A recent analysis of the World Mental Health Survey dataset indicated that the lifetime prevalence of SEPAD across countries approximated 5%; persistence of the disorder into adulthood was common; and adult onset occurred in 40% of all cases.11 SEPAD showed a high level of comorbidity with a range of common mental disorders, not specifically with panic disorder and agoraphobia. Adults and children with SEPAD reported a consistent pattern of disturbances in their early family lives and high levels of exposure to a wide range of traumas.12 Taken together, these findings offer support for the model of SEPAD proposing that symptoms in adulthood commonly represent the continuation or recurrence of those experienced in childhood.

Why, in the face of these recent findings, has the SA-agoraphobia model persisted? Several factors are likely to be at play. The overriding reason is that adherence to established developmental theory discourages clinicians from recognizing SEPAD symptoms in adults. Also, by its very nature, SEPAD occurs within an interpersonal field, involving the family and close attachments. It is common in clinical practice to find that close attachments accommodate and adapt to the person’s SEPAD-related fears, particularly as the anxieties are directed at safeguarding others.13 A pattern of collusion therefore may arise in which the person with SEPAD, the family, and ultimately the clinician, all underestimate the role of SEPAD symptoms as a source of dysfunction in the patient. Diagnostic overlap in symptoms, particularly between agoraphobia and SEPAD, may further confound the picture. SEPAD may also occur in response to the disruptions and losses associated with other severe mental disorders, such as bipolar disorder.14 In these contexts, the mood-related symptoms will often overshadow those of SEPAD, which, as a consequence, will go undetected, even though they add to the person’s overall disability. Severe SEPAD may also present in a variety of ways— for example, as suicidal behavior or stalking in response to actual or threatened separations—which are not indicated in the DSM-5 criteria for the disorder.

In the end, only one of the two developmental models outlined herein, the SA-agoraphobia model and the continuity model, can be valid. Resolution of this issue is not merely one of theoretical importance. SEPAD in adulthood is associated with high levels of disability and signifies a poor response to treatment when conventional pharmacological or cognitive behavioural therapies are used to treat comorbid anxiety disorders.11,12 As a consequence, there may be a substantial cost in disability and suffering by overlooking the diagnosis of adult SEPAD. The critical question, therefore, is whether the DSM-5 reformulation of SEPAD is a turning point that will release SEPAD from its over-attachment to childhood.

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The many faces of narcissism

Although the term narcissism is widely used in psychiatric discourse, there is much confusion about its precise meaning. The term is most often used pejoratively to refer to someone with excessive vanity or an urgent need for validation and praise. There is a continuum of narcissism, and the point where healthy self-esteem ends and pathological narcissism begins is highly arbitrary. A further complication is that some individuals who have elements of pathological narcissism may have sectors of their personalities that are characterized by generosities towards others.

It is unfortunate that a false dialectic between narcissism and altruism is in common usage. The two entities regularly coexist. Vaillant¹, in his longitudinal study of healthy males, found that altruism increases significantly in the second half of life—not simply because we become more selfless as we age, but rather because helping others becomes more rewarding to us. A neuroimaging study² demonstrated that those who are altruistic rather because helping others becomes more rewarding to us. A clinical entity creates challenges for the diagnostician and the psychotherapist. In keeping with the notion that the key to narcissistic personality disorder than in the age group over 65. However, we must question the idea that the current generation is developing such a vastly higher number of narcissists. The overlap between cultural shifts and individual pathology must be more complex than simply following a list of diagnostic criteria. Moreover, the constant connection to social media has also led to altruism in this new generation. Indeed, they are dedicated to service projects, are socially aware and contribute to charity at a higher rate than their elders. Not only do we need to consider the false dialectic between narcissism and altruism in individuals; we must also consider it more broadly in the culture.

In the midst of this confusion, how do we distinguish healthy self-interest from pathological narcissism, usually referred to as narcissistic personality disorder? The time-honored indices of “to love and to work” are problematic in this context, because some of the most successful individuals from an economic perspective are also highly narcissistic. Their narcissistic need for acclaim and recognition may motivate them to succeed. On the other hand, the capacity for mutuality and reciprocity in love relationships may be useful in identifying narcissistic personality disorder. Others are often used up and discarded, existing only to serve the narcissistic individual’s needs.

While problems in human relatedness are central to narcissistic personality disorder, clinicians must be alert to the fact that narcissistic individuals may have considerable variability in their ways of relating to others. There is a spectrum of narcissistic personality disorder, not necessarily reflected in the official nomenclature. Psychoanalytic debates about narcissistic patients stemmed from differences noted by Kohut and Kernberg. While Kohut’s formulation was based on a self-deficit model, causing patients to be highly sensitive to narcissistic injury, Kernberg emphasized the aggressive and destructive aspects of these patients. Further research has documented the existence of two subtypes of narcissistic personality disorder: the grandiose and oblivious variant and the hypervigilant or fragile subtype. More recent research detected a further high-functioning variant, which is outgoing, energetic and articulate, with an exaggerated sense of self-importance.

The fact that narcissistic personality disorder is not a monolithic entity creates challenges for the diagnostician and the psychotherapist. In keeping with the notion that the key to

References:
diagnosis lies in the quality of love relationships, we suggest that a careful examination of modes of relatedness is crucial. As Kohut stressed, some patients who are narcissistically organized tend to idealize others so that they can bask in the reflected glory of an idealized object. They may insist on the most famous psychotherapist or pick a romantic partner purely on his/her looks so that others will be impressed.

Denial of the romantic partner's autonomy may be a central strategy for some narcissists. They are wounded if their love object acts or thinks independently. The fantasy of control serves to defend against ongoing anxiety of losing the one they love. However, it also represents a common problem with narcissistic individuals – namely, they cannot mentalize the internal experience of the other. Hence, they are unable to empathize with the partner's need for agency, autonomy, and freedom from control. Another common mode of relatedness is to deny all pain or conflict in the love relationship, thus turning away from reality.

Narcissistic patients are desperately attempting to manage their vulnerability. Hence denial of dependency, sometimes referred to as “pseudo-self-sufficiency”, is another strategy in their repertoire. If they do not need anyone, then they cannot be hurt by losing someone. Another way that narcissistic individuals will relate to love objects is to see the other as completing the self. It is as though there is a “hole” in their sense of self that requires another person to perform missing functions for them. A common form of this occurs in patients who cannot sooth themselves and need their romantic partner to comfort them, tell them they are wonderful, and provide empathy for their pain. The relationship may end when the partner is not consistent in providing the admiration or praise the patient requires.

Narcissism is pervasive in its normal and pathological variants. While some presentations are quickly apparent in treatment, as in the oblivious subtype, others may take longer to manifest in the clinical relationship. A person with the high functioning variant, who presents with energy, gregariousness and self-importance, may be initially charming to the psychiatrist and hence it takes longer to detect clinically significant narcissism. Only over time does the lack of relatedness and low self-esteem become clear.

Narcissistic patients may feel understood if the clinician focuses on self-esteem struggles and vulnerability beneath the grandiose surface. Some patients may not be able to tolerate any confrontation at first, and may need long periods of empathic validation in order to preserve a therapeutic alliance. A subset of these hypervigilant patients may never be able to tolerate confrontation or rupture, and may instead use the treatment over months and years to shore up a shaky sense of self-esteem and build validation. Timing is everything in making an impact through interventions, and it is advisable to wait for openings in which the patient lets the therapist know that he or she is hurting and yearning for help.

The psychiatrist must be attentive to countertransference issues. Kernberg described that the therapist can feel consigned to a “satellite existence”, which can lead to boredom and distance impacting the therapy. In addition, therapists must be alert to contempt and enactments of judgment and criticism. Finally, patients with narcissistic problems can require some of the longest treatments in a therapist’s caseload. Consultation is recommended in conflicted or difficult cases.

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Time for a global commission on mental health institutions

Concerns about institutional care of people with mental disorders are no longer as prominent as they once were. This is understandable in light of deinstitutionalization and the closure of many psychiatric hospitals in much of the Western world. However, this neglect of old concerns is not excusable. Custodial mental hospitals which are, either directly or indirectly, the legacy of colonial psychiatry remain in many low- and middle-income countries the dominant, if not the only, component of national mental health systems. It is puzzling therefore that, despite the increasing attention to global mental health and the increasing familiarity with the unsatisfactory circumstances of people with mental disorders in such institutions, there is currently little interest in what is happening in those hospitals and other facilities in which people with severe and persistent mental disorders are treated and sometimes confined.

To a great extent, the field of global mental health has relegated the exposure of abuses in mental hospitals and other institutions to news media, non-governmental organizations, and human rights commissions. Hospitals and other institutions are not mentioned in any of the top 25 Grand Challenges in Global Mental Health, although that paper includes a photo of women in a psychiatric hospital in Ukraine.
Moreover, hospitals are not the only sites in which the human rights of people with mental disorders may be violated. For example, in Nigeria, prisons are often where families abandon members who are mentally ill. In Indonesia, the conditions for long-term residents in some social shelters are horrendous and deadly for those mentally ill people who have no other place to live. A report about mental health facilities in Ghana included scathing accounts of abuses in psychiatric hospitals and prayer camps run by spiritual healers. To this list one can add the rapidly growing number of private nursing homes that warehouse patients who have been discharged from mental hospitals.

Unfortunately, it does not seem that reform of these institutions is a priority for global mental health. Instead, development of community and primary care mental health services is overwhelmingly emphasized, with the implicit assumption that such services can meet all requirements of those who need care and treatment for a mental disorder. This is an ill-advised strategy that runs counter to the fact that long-term care options are necessary components of balanced and comprehensive mental health systems. Thus, it is imperative that attention is again directed to the task of transforming existing mental hospitals and other residential care institutions that are plagued by poor physical infrastructure, problematic staff attitudes and practices, the widely prevalent custodial ethos of care, and lack of appropriate discharge options and outreach services. These problems translate into formidable impediments to the creation of comprehensive mental health systems that have at their heart protection of the human rights of persons with mental disorder and disability.

Despite this generally bleak picture, there are examples of mental hospitals that have been transformed into institutions of excellence and repute. Although there is little published evidence of how this is to be done, there is a wealth of accumulated experience of how major changes can be achieved. Just as there is a compelling case to be made for reducing the gap between the number of people in need of care and the number receiving effective treatments, a case must be made for closing the "knowledge and transformation gap" that exists in relation to those institutions that are responsible for the care of persons with mental disorders. Addressing this gap through a combination of internal changes along with the development of integrated community services, in collaboration with service users and local partners from multiple sectors, should become a priority of global mental health.

We propose the establishment of a global commission on mental health institutions. This commission, which would be comprised of mental health professionals, social scientists, representatives of advocacy groups, and legal experts, would develop and carry out a programme of work that would include the following: a) establishing a working definition of "mental health institution"; b) comprehensively mapping mental health institutions in Europe, Asia, the Americas and Africa; c) documenting and understanding the determinants of poor conditions in mental institutions, using instruments such as the Quality Rights Toolkit of the World Health Organization; d) identifying the determinants of long-term stay in such institutions; and e) compiling a comprehensive report on successful strategies for bringing about institutional changes, such as those that have been applied at the National Institute of Mental Health and Neurosciences in Bengaluru, India; Angoda Hospital in Colombo, Sri Lanka; and Yuli Veterans Hospital in Taiwan.

The vision of the United Nations 2030 Agenda for Sustainable Development, adopted by the General Assembly in September 2015, includes "a world with equitable and universal access to quality education at all levels, to health care and social protection, where physical, mental and social well-being are assured" and where "all human beings can fulfill their potential in dignity and equality and in a healthy environment". The conditions in mental hospitals and other institutions for persons experiencing mental illness are an affront to such aspirations. This is the moment to embark on an ambitious program of work to address this problem.

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1. BBC News. Mentally ill patients in Indonesia held in chains. www.bbc.co.uk.
2. Human Rights Watch. "Treated worse than animals": abuses against women and girls with psychosocial or intellectual disabilities in institutions in India. Human Rights Watch, 2014.

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Psychosis as a transdiagnostic and extended phenotype in the general population

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A large body of research indicates that weak expressions of positive psychotic symptoms (“psychotic experiences”) can be measured in the general population, and likely represent the behavioral manifestation of distributed multifactorial (genetic and non-genetic) risk for psychosis. Psychotic experiences are a transdiagnostic phenomenon: the majority of individuals with these experiences have a diagnosis of non-psychotic disorder, particularly common mental disorder, in which psychotic experiences predict greater illness severity and poorer treatment response. Some of the people with common mental disorder and psychotic experiences will present to mental health services meeting criteria for “clinical high risk”. Treatment of the transdiagnostic dimension of psychosis in individuals with common mental disorder who meet “clinical high risk” criteria thus may improve outcome (which cannot be interpreted as prevention of “schizophrenia”). Subthreshold psychotic experiences are transitory in about 80% of individuals, while around 20% go on to develop persistent psychotic experiences and 7% a psychotic disorder, with an annual transition rate of 0.5–1%. Persistence is associated, on the one hand, with environmental exposures, particularly childhood trauma, and, on the other, with network-type dynamic interactions between psychotic experiences themselves (e.g., interactions between hallucinatory experiences and delusional ideation) and between symptom dimensions (e.g., interactions between affective symptoms and psychotic experiences, or interactions between subthreshold negative symptoms and psychotic experiences). The study of psychotic experiences is helping to elucidate the mechanisms by which environmental and genetic influences shape the transdiagnostic expression of psychosis proneness, that is mostly transitory but may first become persistent over time and eventually give rise to transition to a psychotic disorder.

Key words: Psychotic experiences, extended psychosis phenotype, ultra-high-risk states, genetic risk, socio-environmental factors, neuro-cognition, aberrant salience, network models of severity

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While there has been no universal consensus on the concept of “psychosis”, since the term was introduced by Canstatt into the psychiatric literature1, one of the most common uses has been to refer to phenomena such as delusions and hallucinations2. These phenomena have been thought of as key characteristics of psychotic disorders such as schizophrenia for a long time and, somewhat more recently, also referred to as the positive symptom dimension3. However, in recent years, it has become increasingly evident that psychotic experiences are common not only in individuals with psychotic disorder, but also in the general population (i.e., prevalence of ~7%)4. In addition, while subclinical psychotic experiences are transitory in about 80% of individuals, around 20% go on to develop persistent psychotic experiences and 7% a psychotic disorder, with an annual transition rate below 1%4,6.

These findings have been taken to suggest an “extended psychosis phenotype”7, i.e. a phenotype that shares demographic, environmental, familial and psychopathological features7 and is both phenomenologically and temporally continuous with clinical psychotic disorder. In other words, while psychotic experiences are not exclusive to, and can occur independently of, psychotic disorder (“phenomenological continuity”), these experiences can endure over time in some individuals, and may be followed by a psychotic disorder (“temporal continuity”)8.

This continuity of psychotic experiences and psychotic disorder implies that, at all phenomenological and temporal stages of the “extended psychosis phenotype”, individuals may become help-seeking and classified as meeting criteria for an ultra-high-risk (UHR) state7. In UHR individuals, much higher annual transition rates have been reported, which may be explained primarily by selection for the presence of help-seeking behaviour rather than by differences between measures for determining UHR status and presence of psychotic experiences per se9.

There is evidence that the prevalence of psychotic experiences varies according to place and ethnicity. Nuevo et al8, for example, reported considerable variation in the prevalence of psychotic experiences across countries using data from the World Health Organization (WHO) World Health Survey. Also, in a more recent analysis of data from the WHO World Mental Health Surveys, McGrath et al10 found higher lifetime prevalence estimates in middle- and high-income countries than in low-income ones. Furthermore, psychotic experiences have been found to be more common in ethnic minority groups4,10,11.

The method for assessing psychotic experiences does seem to affect prevalence estimates. A recent meta-analysis4 reported markedly higher prevalence estimates of psychotic experiences in studies based on self-report compared with those using interview-based measures. However, no correlation was found between prevalence estimates and the number of items used4.

A TRANSDIAGNOSTIC PHENOTYPE OF PSYCHOTIC SPECTRUM DISORDER

Most individuals with psychotic experiences have a current diagnosis, primarily
one of mood or anxiety disorder\textsuperscript{12-18}, accounting for the association between psychotic experiences and suicidal ideation and behaviour\textsuperscript{19}. Wigman et al\textsuperscript{17} reported a more than two times greater prevalence of psychotic experiences in individuals with depression or anxiety disorder than in people without these disorders. The presence of psychotic experiences in individuals with depression or anxiety disorder is commonly associated with a poorer prognosis and, therefore, early treatment of these experiences (rather than mislabelling as UHR status) requires attention and may be beneficial for the course of psychosis expression\textsuperscript{2}. However, subclinical psychotic experiences are not only common in individuals with depression or anxiety disorder but may also be causally associated with affective disturbance, including anxiety, depressive and hypomanic symptoms\textsuperscript{13,20-24}. In a German prospective cohort community study of 2,524 adolescents and young adults\textsuperscript{24}, a dose-response relationship, suggesting causality, was reported between levels of affective dysregulation (both depression and mania) and psychotic experiences.

There is further evidence that subclinical experiences of negative symptoms are (at least) as prevalent as subclinical experiences of positive symptoms\textsuperscript{25,26}. In addition, subclinical negative and disorganized symptoms have been found to be predictive of, and co-occur with, subclinical positive symptoms, and co-occurrence of subclinical positive, negative and disorganized symptoms seems to predict later functional impairment and help-seeking behaviour\textsuperscript{25}. The evidence therefore suggests that subclinical psychotic experiences represent two underlying constructs: a) a distribution of a specific phenotypic expression of attenuated psychotic phenomena (delusional ideation and hallucinatory experiences) and b) a set of transphenotypic fundamental associations between domains of psychopathology (positive, affective, negative, disorganization).

A similar bimodal set of general, transdiagnostic and specific phenotypic expressions is observed at the level of psychotic disorders. Thus, there is growing evidence for a transdiagnostic psychosis phenotype underlying schizophrenia spectrum and bipolar disorder, with overlapping affective and non-affective psychotic symptoms\textsuperscript{27-29} (Figure 1). This transdiagnostic psychosis phenotype has continuity across subclinical\textsuperscript{24,29,30} and clinical\textsuperscript{27,28} symptom levels and is further supported by the absence of consistent and clear “points of rarity” across psychosis spectrum disorders\textsuperscript{3,31,32}.

There is further evidence that a general, transdiagnostic psychosis dimension is complemented by five specific diagnostic constructs of psychosis (i.e., positive symptoms, negative symptoms, disorganization, mania, depression), which, when used in combination, allow for a

\begin{figure}[h]
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\caption{Schematic representation of transdiagnostic psychosis spectrum encompassing non-affective and affective psychotic experiences}
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more accurate classification of individuals into categorical diagnoses based on dimensional scores.\textsuperscript{3,27,28,32} (Figure 1). This approach draws on bifactor models for generating quantitative scores of a) a general, transdiagnostic psychosis factor and b) specific psychosis factors.\textsuperscript{27,28} Then, it adopts a strategy in which: first, quantitative scores on the general, transdiagnostic psychosis dimension may be used to determine whether to place individuals on the affective or non-affective end of the psychosis spectrum; and, in a second step, based on the profiles for specific symptom dimensions, patients may be classified into specific diagnoses.\textsuperscript{3,27}

What is more, this approach provides directly measurable general, transdiagnostic as well as specific phenotypes for cross-disorder investigations to identify transdiagnostically shared genetic and environmental contributions, as well as non-shared factors contributing to specific symptom dimensions.\textsuperscript{27} Given evidence for a general, transdiagnostic phenotype of psychosis at both the clinical\textsuperscript{27,28} and subclinical\textsuperscript{27,28} level of psychotic experiences, the existence of an “extended and transdiagnostic phenotype” in the general population can be suggested.

**GENETIC AND SOCIOENVIRONMENTAL FACTORS ASSOCIATED WITH THE EXTENDED PSYCHOSIS PHENOTYPE**

Several studies have examined the level of psychotic experiences as an indirect measure of expression of the distributed genetic risk for psychotic disorder. Findings from these studies suggest that subclinical psychotic experiences and schizotypal symptoms in twins from the general population\textsuperscript{33-36} and relatives of patients with psychosis\textsuperscript{37} are influenced by genetic effects. There is also evidence that subclinical psychotic experiences may reflect the transitory developmental expression of genetic risk for psychosis in the general population.\textsuperscript{38}

A Danish birth cohort study reported that subclinical psychotic experiences at age 11-12 years, assessed by clinical inter-view, were strongly associated with a family history of treated psychotic, but not common mental disorder, identified in an unbiased fashion through the national case register.\textsuperscript{39} Further, studies and meta-analyses have consistently reported that socio-environmental risk factors such as ethnicity,\textsuperscript{4,10,11,40-41} urbanicity,\textsuperscript{23,42-45} childhood adversity,\textsuperscript{4,11,44,47} stressful life events,\textsuperscript{21,46,48} and cannabis use\textsuperscript{4,13,21,49-55} are shared across subclinical psychotic experiences and psychotic disorders.

Wigman et al.\textsuperscript{36}, in a general population sample of female twins, showed that childhood trauma and prospectively recorded stressful life events were associated with persistence of psychotic experiences. In addition, psychotic experiences were more likely to persist in monozygotic than in dizygotic twins when persistence occurred in the co-twin.\textsuperscript{36}

Overall, these findings suggest that both genetic and socio-environmental factors are associated with the “extended psychosis phenotype”. However, to date, molecular genetic studies have failed to generate replicated findings on similar associations with a priori selected single-nucleotide polymorphisms,\textsuperscript{56,57} a limited early version of the polygenic risk score,\textsuperscript{57} or genetic variants identified using a genome-wide association approach.\textsuperscript{57}

Cross-disorder investigations and studies using the more powerful recent version of the polygenic risk score are now required for identifying shared genetic and environmental factors (including G × E) of the “transdiagnostic and extended psychosis” phenotype as well as non-shared factors of specific psychosis constructs.

**NEUROCOGNITION, ABERRANT SALIENCE, REASONING BIASES AND THE EXTENDED PSYCHOSIS PHENOTYPE**

Neurocognitive alterations, in particular in processing speed and working memory, have been reported to be more common in individuals with psychotic experiences than in those without these experiences.\textsuperscript{58-62} There is also some evidence of poorer functioning in individuals who report subclinical psychotic experiences, which may potentially in part be due to neurocognitive alterations.\textsuperscript{62}

However, to what degree any association between psychotic experiences and neurocognitive alterations is specific is difficult to examine, as psychotic experiences are strongly associated with a range of non-psychotic mental disorders which in turn are associated with cognitive alterations.\textsuperscript{63} The fact that neurocognitive alterations have been found in siblings of patients with psychotic disorder and, to a lesser extent, in siblings of patients with non-psychotic disorders, suggests transdiagnostic overlap even at the level of what is commonly considered a key marker of genetic risk of schizophrenia.\textsuperscript{7,64}

Not only neurocognitive alterations in processing speed and working memory but also dysregulation in top-down processing such as white noise speech illusion may be relevant to the “extended psychosis phenotype”. An association between a tendency to detect affectively salient speech illusions in random noise with higher levels of positive schizotypy has been previously reported in healthy controls\textsuperscript{65,66} and in patients with a psychotic disorder.\textsuperscript{65,66} Recently, aberrant novelty and salience was also found to be associated with more intense psychotic experiences in daily life in patients with first-episode psychosis, UHR individuals, and healthy controls.\textsuperscript{67} In this experience sampling study, the association between aberrant salience and momentary psychotic experiences was greatest in UHR individuals, which suggests that aberrant salience may be particularly relevant to the development of subclinical and attenuated psychotic experiences.

Another key cognitive process relevant to psychotic experiences across different phenomenological and temporal stages of psychosis is reasoning biases, most prominently, a tendency to jump to conclusions\textsuperscript{68-72}, defined as a bias towards gathering less data to reach decisions. Several studies have reported that the jump to conclusions bias is specifically associated with subclinical and clinical delusional experiences in experimental and virtual reality paradigms.\textsuperscript{73-81}

These findings are consistent with the proposition that responses of aberrant
salience to subtle variations in the environment as well as reasoning biases reflect “microphenotypes” that potentially form part of the core vulnerability of the “extended psychosis phenotype.”

**TRANSDIAGNOSTIC AND NETWORK MODELS OF SEVERITY**

Several studies have reported that exposure to childhood trauma is associated with both occurrence and persistence of psychotic experiences. For example, in a recent study, individuals with childhood trauma reported higher levels of psychotic experiences both at baseline and at 3-year follow-up than those without childhood trauma, suggesting that childhood trauma creates a vulnerability for psychotic experiences to persist over time.

If, as van Os and Linscott proposed, psychotic experiences persist over a prolonged period of time under the influence of genetic factors, this may increase the risk for initial onset and sustained expression of psychotic disorder, as demonstrated by Dominguez et al. in a repeated measures study of psychotic experiences in the general population spanning more than 10 years.

In addition, van Nierop et al. reported that childhood trauma increases in particular the likelihood of co-occurrence of hallucinations and delusions (rather than either symptom alone), which has, in turn, been shown to be associated with greater symptom severity and familial risk of psychotic disorder. Since a similar pattern is evident for other socio-environmental factors, such as cannabis use and urbanicity, as well as for increased likelihood of co-occurrence of psychotic experiences with other symptoms including affective and anxiety symptoms, it has been proposed that a transdiagnostic model of severity may apply, in which coexistence of psychotic experiences, affective and anxiety symptoms reflects greater severity, socio-environmental risk and poorer functioning.

This may be complemented by, and combined with, a network model of severity (Figure 2), in which symptoms of the transdiagnostic psychosis phenotype do not vary independently, but impact on each other over time, and connectivity of symptoms increases as socio-environmental load increases.

In this model, as a result of elevated connectivity, more symptoms are recruited and severity of states increased further, which, in the event of exposure to further...
socio-environmental adversity, leads to an increased probability of clinical transition to psychotic disorder95-97.

CONCLUSIONS AND FUTURE PROSPECTS

In recent years, research has revealed a phenomenological and temporal continuity of psychotic experiences with psychotic disorder, as well as the co-occurrence and overlap of psychotic experiences with affective and anxiety symptoms and disorder, which, taken together, suggests an “extended and transdiagnostic psychosis phenotype” in the general population. Evidence suggests the existence of a general, transdiagnostic factor as well as five specific psychosis factors, which are measurable and best represented by a dimensional bifactor model of psychosis. A bifactor “general” and “specific” model of psychosis may substantially enhance classification accuracy of categorical diagnoses based on dimensional scores.

While there is evidence that subclinical psychotic experiences and psychotic disorder are associated with similar socio-environmental and genetic variables, cross-disorder investigations are now required for identifying shared genetic and socio-environmental variables (including G × E) underlying the transdiagnostic psychosis factor, as well as non-shared variables underlying specific psychosis factors. Transdiagnostic overlap may be present even at the level of what are commonly considered core markers of genetic risk of schizophrenia such as neurocognitive alterations. Co-presence of neurocognitive alterations, alterations in salience attribution, and reasoning biases may be particularly relevant on the pathway from persistence of psychotic experiences to initial onset and, ultimately, sustained expression of psychotic disorder.

Initial evidence on transdiagnostic and network models of severity now needs to be strengthened further through prospective studies into the dynamic nature of the “extended psychosis phenotype” cutting across boundaries of diagnostic categories of current classification systems.

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REFERENCES

29. Shevlin M, McElroy E, Murphy J. The psychosis continuum: testing a bifactor model of psy-


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Whether “psychosis” is best conceptualized as a continuum or in categories is an empirical, practical and political question

van Os and Reininghaus¹ argue for the existence of an “extended and transdiagnostic phenotype” of psychosis in the general population. They assert that research has revealed a phenomenological and temporal continuity of psychotic experiences with psychotic disorder, as well as the co-occurrence and overlap of psychotic experiences (delusions and hallucinations) with affective and anxiety symptoms and disorders. They also make a clinical proposal that “first, quantitative scores on the general, transdiagnostic psychosis dimension may be used to determine whether to place individuals on the affective or non-affective end of the psychosis spectrum; and, in a second step, based on the profiles for specific symptom dimensions, patients may be classified into specific diagnoses”. In so doing, they raise important issues about our scientific approach to understanding psychosis, how it is best managed in clinical practice, and how those affected are viewed.

Empirically, it is difficult if not impossible to prove that psychotic experience is on a continuum with normal experience, and whether or not some psychotic disorders are qualitatively distinct remains “not proven”². For sure, there are many clinical, genetic, neuroimaging and cognitive similarities and overlaps between schizophrenia and bipolar disorder and severe depression, and so on, but there are also important distinctions which are at least statistically significant³,⁴. van Os and Reininghaus acknowledge that genetic studies thus far do not really support their arguments. Moreover, while some cognitive disturbances are commonly associated with psychotic experiences in the general population, no study I am aware of has yet associated these experiences with the processing speed impairments which are the most severe deficit in schizophrenia⁵. Meanwhile, our age-old descriptive category of “schizophrenia” continues to be scientifically serviceable – for example, with more success in genome-wide association studies than many medical diagnoses⁶ – and new biomedical and psychosocial insights continue to accrue.

In the absence of an identifiable biomarker to distinguish psychotic disorders, we should bear in mind that, as R. Kendell wrote more than 40 years ago, “in attempting to choose between categorical and dimensional schemata in any given situation, it is important to realise that in principle both are available”⁷. In other words, there is no statistical method of deciding whether or not a continuum or categorical approach is “correct”. He continued: “The appropriate question is always which is more useful or more appropriate, and the answer may well vary with the purpose in mind”⁷. From that wise perspective, the main concern is what works best in a particular situation.

From a practicing clinician’s viewpoint, our current diagnostic system does reasonably well. That’s why we use it. We differentiate, amongst others, brief psychoses which usually do not require treatment, bipolar disorder which has some specific therapeutic implications (such as lithium), and schizophrenia. To overturn current practice would require convincing proof or at least some persuasive evidence that the psychosis continuum approach adds something in clinical settings²,⁸. But very little evidence has been marshalled. van Os and Reininghaus state that a general, transdiagnostic factor (affective/developmental) and five specific psychosis factors (depression, mania, psychosis, disorganization, negative) “may substantially enhance classification accuracy of categorical diagnoses based on dimensional scores”⁸, but none of the references they cite actually compare classification accuracy, let alone show an enhancement. What the studies tend to show is that psychosis factor scores are statistically associated with some measures of illness severity.

Of course, adding symptom factor scores and/or other continuous measurements to our current diagnostic categories could enhance some aspects of clinical practice. Indeed, we have recently proposed exactly this⁸. This does have some empirical support, in that adding symptom factor scores to diagnostic categories has been shown to significantly increase the amount of variability explained in predicting, among other things, duration of untreated psychosis⁹. The reverse approach, of adding categories to continua, as van Os and Reininghaus seem to propose, fared less well.

And then there is the issue of measurement. Continuous measures are routinely employed in the rest of medicine (e.g., blood pressure, blood glucose) when they can be simply and reliably assessed in one dimension. Even then, for ease of use, categorical thresholds for treatment are imposed, often informed by clinical trials. We do not have such simple or readily used measurement in psychosis research or practice. The prevalence of psychotic experiences differs according to the instrument used. The standard measure of psychotic symptom severity is the Positive and Negative Syndrome Scale, which can be time consuming to use and demands training and regular monitoring to sustain adequate reliability. The idea that busy clinicians might use that and then adopt five factor scores to guide management seems impractical. Precious clinician time with patients might well be better spent using briefer scales, measuring symptom duration and/or aspects of cognition⁸.

This scientific and clinical justification of current diagnostic practice is not to deny that our extant classificatory systems are works in progress, with far from perfect reliability and validity, and that many patients find our diagnostic labels – or at least the process of getting them – stigmatizing⁹. These issues are paramount when people are in their first episode, when sub-grouping within the psychotic disorder rubric may not be possible and when establishing a therapeutic relationship is arguably critical. The use of vague terms
like “psychosis” may be the most appropriate diagnosis at these times, but when people meet diagnostic criteria for a specified disorder, then they should get the appropriate diagnosis. Where such categories apply, it is up to clinicians to demonstrate the benefits of these (such as clinical trial evidence) to patients. Schizophrenia, in particular, has been misrepresented as a condition which usually has a poor outcome and for which treatment is at best ameliorative, whereas most patients can be treated successfully if services are adequate, and the outcome is good in up to 50% of cases10.

To sum up, van Os and Reininghaus make a reasonable scientific case, but much more evidence is required before revolutionizing clinical practice could be justified. It is more practical to improve clinical practice by building upon it, whilst trying to bring our patients and their representatives with us8.

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Epistemological error and the illusion of phenomenological continuity

van Os and Reininghaus’ paper on the transdiagnostic “extended psychosis phenotype” attempts to present an exhausting framework for the nosology and pathogenesis of psychiatric and especially psychotic disorders1. We have there the genes, gene-environment interactions, an emphasis on the role of childhood trauma (resurrected after a period of skepticism about psychoanalytic theories and reluctance to ascribe independent causal role to retrospectively ascertained events), and a dimensional approach to phenotypic manifestations. There is also a theory of symptomatic dimensions and their combinations to yield a few categorical entities of “psychotic disorders”.

Since the paper aspires to break a new ground and radiates an air of recency and novelty, it seems relevant to mention that a somewhat similar dimensional approach was tried out on a sample of psychiatric inpatients already around the time of World War II2. Those hand-made calculations, prior to factor analysis, revealed three main psychotic “dimensions”: the paranoid (positive), the heboid (disorganized) and the schizoid (negative). The dimensional approach was then pursued through the creative contributions of P. Meehl and the scales by the Chapmans3. Despite some useful information, this line of research has not resulted in a radically new understanding of mental disorders.

The multiple scales on subthreshold psychotic symptoms, applied in the studies to which the authors refer, are not a product of original research into the life-world of psychosis but rather a reflection-based attenuation of DSM criteria for schizophrenia – formulated at a very high chronicity level – in order to be applicable to young, first-contact patients with a schizophrenia spectrum disorder4. Such simplification is certainly amplified by conceptual ambiguities. For example, the authors seem to use the notions of “weak expressions of positive psychotic symptoms”, “psychotic experiences”, and “psychotic symptoms” more or less equivalently, without explaining their relations or, more basically, what makes a symptom “psychotic”5.

The fundamental problem is of an epistemological kind. Since the creation of DSM-III, the symptom is considered a thing-like object, existing in itself, i.e. independently of other symptoms, larger Gestalts, and structures of consciousness. For example, a phenomenon of self-reference is considered as such independently of whether it is caused by melancholic guilt feelings, insecurity after a panic attack, or a sense of being the center of the universe in incipient schizophrenia.

This simplification of the concept of symptom, with a complete absence of holistic, contextual and gestaltic considerations, has contributed to a situation in which diagnoses are assigned on the basis of accidental recombination of criteria, with a neglect of differential-diagnostic considerations6. This is well illustrated by the authors’ reference to common mental disorders like anxiety with psychotic experiences as anteceding a full-fledged psychosis. These patients already having psychotic experiences should have not fallen into the category of “common mental disorders” in the very first place, and their anxiety may be fundamentally different from “common” anxiety.

The fundamental epistemological problem of operationalism results in a homogenization, trivialization, and non-specificity of mental symptoms, which invites an illusion of “phenomenological continuity”. Feeling that other people stare at one, because one is the center of the universe, is not the same as feeling that others have noticed one’s panic attack. In a very important work, Stanghellini et al7 demonstrated that “hallucinatory experiences” in a non-clinical population are qualitatively different from hallucinations in schizophrenia (see also Henriksen et al8). Similarly, Schultz-Zutter et al9 documented that self-reported “psychotic-like experiences”
are simply uncorrelated with the clinician-assessed “attenuated psychotic symptoms”.

Another example of the metaphysical reification of symptoms, implicit in van Os and Reininghaus’ paper, is their claim that, under pressure of traumatic experiences, hallucinations and delusions amplify each other because of increased “connectivity” of symptoms (presumably a connectivity between the networks responsible for single symptoms). We are not offered any psychological or phenomenological considerations of higher-level interactions between the psychotic phenomena.

Blankenburg\textsuperscript{10} emphasizes that many patients with a schizophrenia spectrum disorder initially present with vague or unpecific complaints, for instance of fatigue, feeling unmotivated or having problems with occupational performance. Through a phenomenological interview, he demonstrates that these seemingly “non-specific” complaints often are shorthand for much more “specific” ones. For example, one patient reports: “The situation is that I do not feel a genuine drive. I always come so rapidly to the dead point. My patience is then almost run out…”\textsuperscript{10} He feels “exhausted”; everything “gets on his nerves”\textsuperscript{10}. While these complaints may seem “non-specific”, the patient’s further utterances testify to their embeddedness in a much more recognizable, “specific” clinical Gestalt of schizophrenia spectrum: he complaints of “lacking distance to his surroundings”, of only perceiving “the front” of things, and “of a failing approach to everyday life, to the reality of ordinary life”\textsuperscript{10}. Consequently, even the simplest task is felt as a burden, requiring massive cognitive efforts on his behalf, and partly so because he is unable to take for granted what others consider obvious or self-evident (i.e., “lack of common sense” and hyper-reflectivity)\textsuperscript{11}.

Early diagnostic assessment requires not only a superficial symptomatic screening but also an insight into the life-world of the patient, implying considerable psychopathological knowledge. Moreover, it is unwarranted to perceive a symptom (e.g., a “psychotic experience”) in abstraction from other symptoms, larger Gestalts, and structures of consciousness. We are certainly able to build up scales trivializing symptoms into phenomenological continua, but in this move the symptoms are emptied of their clinical validity.

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### Causal narratives and psychotic phenomena

In their detailed and well-argued exposition, van Os and Reininghaus\textsuperscript{1} identify and substantiate major problems in the intellectual structures that underpin psychiatry. In particular, by reviewing the recent great advances in our knowledge of psychotic conditions, they raise important questions about the relationship between psychiatric phenomena and defined diagnostic categories. They propose a solution that involves a radical remodelling of this relationship. I have considerable sympathy with their position and their arguments, so this commentary is by way of providing additional conceptual context and setting out the implications for advances in research strategies.

The lay concept of madness is common to virtually every society and language group. Thus, certain individuals may be identified by consensus as being in consistent, persistent and idiosyncratic error, often linked to actions perceived as incomprehensible or deeply inappropriate. The recognition that such people required help rather than exorcism or punishment meant that the phenomena of madness gradually came to be seen as the province of physicians, leading to important and enduring changes in the way these phenomena were studied. Specific aspects of madness became codified as the key symptoms of delusions (erroneous thinking) and hallucinations (erroneous perceptions), and these came to be seen as signs of one or more diseases.

Because it encapsulates the idea of disease, diagnostic classification is the central feature of the medical approach. As a branch of medicine, psychiatry was similarly built around the formulation of diagnostic categories. The division of ill-health into categories is based on the belief that this will ultimately enable the rational allotment of treatments. Disease classes (syndromes) are constructed when diligent observation identifies groups of people whose ill-health is associated with consistent and distinguishable features, that is, specific symptoms and signs. In this view, disease classes are theoretical constructs which then provide the basis for testing theories of aetiology, pathology, treatment, course and outcome\textsuperscript{2}. When the theories based on them are corroborated (as they often have been in general medicine), the aetiology or pathology associated with the syndromes may consequently take over as classifiers.
The construction of a disease category creates a conceptual shift. The category is thereby held to reflect an underlying disease process and so comes to be accorded an implicit causal function: it becomes the cause of the symptoms by which it is recognized. The disease process in turn is held to be the result of some fundamental cause, which may be extraneous (e.g., microbial, toxic or other physical factors) or constitutional (genetic, or genetic-environmental). This transposition in scientific focus is seen equally in physical and mental disorders. While it is a rational strategy, its success is not guaranteed.

However, disease classes are hostage to empirical evidence: their acceptance should therefore always be tentative, and they may be revised or abandoned in the light of new information (for this reason it is dangerous to accord them an intrinsic reality3,4). The revision of disease categories has been a particular characteristic of psychiatric classification. Indeed, the emergence of psychosis as a preferred term in research over the last 20 years reflects dissatisfaction with narrower categorizations: affective psychosis, schizoaffective disorder and schizophrenia. This was particularly driven by the realization that virtually all psychotic disorder involves affective changes and, quite probably, similar affective mechanisms. While to purists the term psychosis may appear like an imprecise catch-all, the flexibility it allows has certainly contributed to an increased knowledge of the conditions covered.

Once categories are agreed, the process of diagnosis depends on categorical judgements that individuals meet or fail to meet the requirements for membership. In psychiatry, our continuing ignorance of any causal correlates sufficient to justify an aetiology-based classification means that we are left defining classes in terms of symptoms. This is what creates the situation addressed by van Os and Reininghaus1. In particular, a hierarchical element has traditionally been central to psychiatric classification. Thus, schizophrenic disorders are defined in terms of the presence, at some stage, of psychotic symptoms. In their absence, the diagnosis cannot be made; in their presence, the diagnosis will be made irrespective of other psychological symptoms. Schneider’s first rank symptoms of schizophrenia are much vaunted in clinical psychiatry, but their significance lies in the fact that they are regarded as prima facie indicators of schizophrenia, whatever the other psychiatric symptoms individuals might have. We choose to place schizophrenia at the apex of the psychiatric diagnostic hierarchy, for the perfectly good reason that it corresponds to the layperson’s idea of madness, the psychiatric problem associated with most distress and dysfunction.

However, although it is reasonably straightforward to identify key symptoms like delusions and hallucinations, problems do arise. In particular, there are dimensional issues even with categorically defined symptoms. Thus, there is a (rational) reticence to diagnose a psychotic disorder if the psychotic symptoms are only experienced rarely, or occur singly, especially if the person is undisturbed by them and has insight. Thus, psychotic symptoms may sometimes be identified in people who fall below diagnostic thresholds, what van Os and Reininghaus call the extended phenotype. In practice, many people have a few symptoms, while only a few have many5.

As van Os and Reininghaus demonstrate in their review, a minor degree of psychotic symptomatology may be present in a range of other disorders, most notably affective disorder. In their terminology, these psychotic symptoms are transdiagnostic. To some extent, transdiagnostic symptomatology is an inevitable consequence of the rules placing psychosis high in the diagnostic hierarchy. It is well established that affective symptoms are widespread in the general population6, thus they are at least equally likely to appear in people with a diagnosis of psychosis. However, the interesting point, well substantiated by van Os and Reininghaus, is that the level of affective disturbance in people with psychosis is far higher than in the general population.

All in all, the evidence therefore suggests that there is no such thing as an event horizon in psychosis, and this must be taken into account in attempts to determine its causation. In fact, it encourages a productive paradigm shift, away from the idea that disorders cause symptoms. It fosters a view of transdiagnostic symptoms and associated psychological attributes as elements in potential causal chains, possibly linking external experience with the emergence of particular psychotic symptoms7. It then becomes possible to examine the interrelationship of social environmental factors and the internal features of psychosis. This endeavour is furthered by analysing symptoms in terms of correlates that are likely to influence them in distinctive ways. There is good evidence of this sort of multiple influence in paranoia, which is characteristically associated with a worry thinking style, negative thoughts about the self, increased interpersonal sensitivity, anomalous internal experiences, insomnia, and various anomalous styles of reasoning8-10. As a consequence, transdiagnostic symptoms provide rational targets for psychological therapy in psychosis.

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Psychosis as a continuous phenotype in the general population: the thin line between normality and pathology

van Os and Reininghaus\(^1\) provide a compelling overview of evidence suggesting that psychosis may be perceived as an extreme expression of continuously distributed quantitative traits in the general population, where minor psychotic symptoms, similar but less severe than those observed in affected individuals, can be found in proportions of up to 7%. The concept of the extended psychosis phenotype offers a number of unique opportunities. Firstly, recognizing the psychosis phenotype as a gradual infusion of quantitative traits into clinical syndromes provides an elegant explanation for variation in the degree of severity of psychosis-like experiences. Secondly, as highlighted by the authors, the extended psychosis phenotype is transdiagnostic in nature, implying that it is not restricted to any specific psychotic disorder but rather represents a continuous expression across the psychosis spectrum. This may explain the overlap in psychopathological presentation observed across mental disorders and therefore provides a foundation for cross-disorder analyses. The latter in turn would tackle the indistinctness of current diagnostic categories, that are marked by lack of clear boundaries between themselves and with normality\(^2\). While considering psychopathology in terms of a transdiagnostic psychosis dimension with five specific constructs may still be perceived as agnostic with respect to traditional diagnostic systems, using these two approaches in combination may allow for a more accurate classification of affected individuals.

The transdiagnostic approach may also have important advantages for scientific research. In research carried out by our group employing the transdiagnostic psychosis dimension, a degree of specificity was found in the relationships between different types of childhood trauma and psychosis symptom dimensions in adulthood, suggesting that distinct pathways may be involved in the relationship between the childhood trauma and psychosis\(^3\). Eventually, these findings might feed into interventions targeting high-risk children. Similarly, Jones et al\(^4\) have shown the importance of the transdiagnostic psychosis dimension in exploring how an increased genetic risk for schizophrenia expresses during early teens among the general public. Building on these findings, future studies may shed some light on the pathways between the genetic liability for schizophrenia and the phenotypical expression of this illness in childhood, adolescence and throughout adulthood.

It is asserted that 20% of those who report subclinical psychotic symptoms make the transition to persistent psychosis. If these estimates are accurate, then detecting individuals with subclinical psychotic experiences from the general public would offer a unique opportunity to reduce the duration of untreated psychosis, which in turn has been linked to poor treatment response, increased risk for relapse and overall poorer prognosis\(^5\). It would also enable early interventions ultimately resulting in diminishing symptom severity from the onset, deferring or preventing the onset of psychosis and reducing the financial and emotional liabilities associated with the lifetime burden of the illness.

Are these estimates accurate? Identification of individuals with subclinical psychotic experiences is reliant on help-seeking behaviour. However, young individuals with an early onset of psychosis are less likely to engage in such behaviour\(^6\). The likelihood of help-seeking is dependent on the awareness and insight of the earliest manifestations of psychotic symptoms, and even more so on availability of supportive families and strong social networks around at-risk young individuals\(^5\). Another issue relevant to the calculation of so-called transition rates is the drawing of distinctions between the emergence of psychotic symptoms (marking the onset of the period of untreated psychosis) and the onset of psychotic disorder. The claim that early intervention services reduce the duration of untreated psychosis in comparison to generic clinical services\(^7\) is critically dependent on whether the time between the earliest report of symptoms and the intervention of the former services is taken as the “duration of untreated psychosis” or whether the beginning of “duration of untreated psychosis” is “reset” after such an intervention until the individual is in the unlucky minority and subsequently develops a first episode of full-blown psychosis. Furthermore, preliminary work from our clinic indicates that, when we look back at the journey that first episode psychosis patients took before arriving at generic catchment area clinical services, we find that there are very few who come via prodromal services, suggesting that the scope for reducing or postponing the onset of psychosis is limited. Some people have an onset that is too rapid and severe, while others have an onset that is so insidious that they escape the notice even of services whose philosophy is not at all tied to diagnostic categories and who embrace the dimensional approach\(^8\).

Finally, it has also been argued that subclinical psychotic experiences are more likely to occur in adolescence – the phase in young people’s lives that is frequently marked by experimenting with substances or rebellious behaviour\(^2\). This issue is exacerbated by differing approaches used to elicit psychotic experiences, some of which exclude clinical judgement and others seem to lead the respondent into endorsing such experiences (see David\(^9\) for a discussion). These methodological issues probably contribute to the wide range of estimates of psychotic experiences in the general population.

Evidence suggests that neurocognitive alterations, dysregulation in top-down processing and reasoning biases may be particularly relevant to the development of psychotic experiences even in non-help seeking populations, and sophisticated imaging analysis techniques may be used to uncover them\(^10\). These may yet serve as important markers for illness onset. However, it is too early to say how specific these sorts of findings are to psychotic spectrum disorders and to what extent they apply to other mental disorders.
Certainly, the evidence based on family studies suggests that subclinical psychotic experiences are influenced by genetic risk factors. In theory this may offer a unique prospect to develop a screening test based on genetic composition. Indeed, similarly to the asserted nature of the extended psychosis phenotype, the genetic risk for psychosis is distributed on a continuum at the highest end of which are affected individuals followed by their healthy relatives. Although these results support the premise of being able to detect those at risk based on their genetic make-up, recent attempts of linking genetic risk score for schizophrenia to an intermediate phenotype in non-clinical populations have so far been contradictory.

The importance of the transdiagnostic and extended psychosis phenotype in relation to diagnosis, aetiology, prevalence and outlining the future direction for research is indeed noteworthy. However, without a clearly established and scientifically validated threshold defining pathology, as well as markers indicative of susceptibility to the illness, the borderline between normality and psychopathology will remain contested.

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Psychotic experiences and their significance

The term “psychotic experiences” generally refers to subthreshold forms of hallucinations and delusions. However, this term is used inconsistently, sometimes referring to psychotic symptoms (i.e., full threshold positive phenomena), at other times including both sub- and full threshold positive symptoms. van Os and Reininghaus use the term “subclinical psychotic experiences” to discuss their views on psychotic experiences along the extended psychosis phenotype. Here we present a clinical perspective from the ultra high risk (UHR) paradigm, that aims to identify people at high risk of psychotic disorder by the presence of genetic risk factors. In theory this may offer a unique prospect to develop a mood or anxiety disorder than a psychotic disorder, these phenomena actually predict psychotic disorders far more strongly. This is because mood and anxiety disorders are much more common than psychotic disorders and frequently occur in the absence of psychotic experiences. Consistent with this, as van Os and Reininghaus note, evidence from a Danish birth cohort study showed that psychotic experiences at age 11–12 years were strongly associated with a family history of psychotic disorder, but not of common mental disorder. Thus, just as the UHR state is relatively specific to psychotic disorders (compared to non-psychotic disorders), this is also the case with psychotic experiences in the general population.

So, how are we to understand these psychotic experiences? It is important to recognize that not all positive psychotic symptoms are the same. Previous research has identified four factor (persecution, bizarre experiences, hallucinations, and paranoid beliefs/magical thinking) and five factor (hallucinations, delusions, paranoia, grandiosity, paranormal beliefs) models of psychotic experiences. Persecution, bizarre experiences and...
hallucinations are more likely to be associated with distress and disability than paranoid beliefs/magical thinking. Further, the type of experience may play a role in determining if an individual develops psychotic disorder or more common mental disorder. The finding that most individuals with psychotic experiences have no mental disorder may be because they have the more benign paranormal beliefs/magical thinking. This remains to be investigated.

There are other factors which are likely to be significant predictors of whether an individual develops a clinical disorder or not, and whether that disorder is schizophrenia, another psychotic disorder or common mental disorder. These include the intensity, persistence and frequency of symptoms, related distress, attributional style, the presence of negative symptoms and cognitive dysfunction, history of childhood maltreatment, demographic features (such as social deprivation), and genetic risk. These factors are likely to influence each other.

Consistent with this, van Os and Reininghaus postulate that some psychotic experiences are associated with and are risk factors for psychotic disorder (the "specific extended psychosis phenotype"), while some are non-specific and are risks for both psychotic and non-psychotic disorders (the "transdiagnostic psychosis phenotype"). This is similar to a model we have previously described, where we posited three groups. We proposed that: a) some psychotic experiences may indicate underlying vulnerability to schizophrenia (psychosis-specific); b) some may be “incidental” to common mental disorders such as anxiety and depression (similar to the “transdiagnostic phenotype”); and c) some may not be associated with any clinical disorder and may never come to clinical attention. This third group accounts for the finding that many individuals with psychotic experiences have no clinical disorder.

It is important to also account for the dynamic nature of symptoms. Individuals with psychotic experiences and common mental disorder may still be at risk of psychotic disorder. Mood and anxiety symptoms are common in the prodrome of schizophrenia, and individuals who meet the UHR criteria often have concurrent mood and/or anxiety disorder. In the UHR population, mood and/or anxiety disorders may persist over time, often in the presence of continued psychotic experiences, without the individual ever developing frank psychotic disorder. This suggests that the psychotic experiences are part of these “neurotic” illnesses (the “transdiagnostic” or “incidental symptoms” group). For those with both psychotic experiences and mood/anxiety disorders, it is not possible to determine the direction of causality.

People with psychotic experiences that co-occur with mood and anxiety symptoms may seek help, and van Os and Reininghaus claim that these people will be “mislabelled as UHR”. We do not agree with this. These individuals will meet UHR criteria and are at high risk of full-blown psychotic disorder. They are also at risk of persistent or recurrent mood and anxiety disorder, of impaired psychosocial functioning and of persistent psychotic experiences. It is also true that they may not be at risk of any disorder, and symptoms and functioning might resolve over time. We acknowledge that the UHR group is heterogeneous. The clinical approach to treating this group is to manage current symptoms and reduce distress. Cognitive behavioural therapy is useful both to manage mood and anxiety symptoms and assist people to better deal with psychotic experiences. It can therefore be seen as a “transdiagnostic” treatment, where therapy focuses on the issues that the clients themselves identify as being important targets.

Understanding more about the UHR group and what predicts different trajectories is an ongoing challenge for research in this area. Negative symptoms and cognitive dysfunction appear to predict poor long-term functioning in the UHR group. Similarly, in the general population, negative symptoms and worse cognition are associated with poor functioning in those with psychotic experiences. Ultimately, we need to be able to distinguish these and other risks in both the general population and those in the UHR group, regardless of whether the outcome is a psychotic or non-psychotic disorder.

General population and UHR sampling approaches can complement each other in examining psychotic experiences, their aetiopathology, associations with possible mediating factors (such as negative symptoms, cognition, childhood maltreatment and substance use), and their clinical significance. van Os and Reininghaus’ paper stimulates thought in this area, and robust, ongoing debate and discussion are to be welcomed.

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High time for a paradigm shift in psychiatry

There is no doubt that several people, especially during their childhood and adolescence, have some sort of psychotic-like experiences, and that only a minority of them go on to develop a serious psychiatric disease. We completely agree on this
with van Os and Reininghaus\(^1\), although the prevalence of psychotic-like experiences in the population is still not clear, because it strongly depends on methodological issues, such as the definition of these experiences, the type of prevalence (e.g., annual or lifetime) reported, the representativeness of the study sample and the age group investigated, the method of assessment (usually self-rating questionnaires or standardized interviews administered by laypersons, which do not allow for checking alternative explanations for the psychotic experiences or for assessing the grade of certainty), and the consideration of influencing factors such as cannabis abuse\(^2,3\).

The “continuity” of psychosis is not an exception in medicine. We know quite well that many people are sometimes depressed or anxious without ever developing a depressive or anxiety disorder, and that many people sometimes have a cough without developing a serious lung disease.

Regarding the continuity of psychosis, G. Huber\(^4\) already in the 1980s described the Vorpostensymptome (“outpost symptoms”), basic and prodromal symptoms preceding the outbreak of frank psychosis, and we later replicated these findings in a large representative sample with Häfner and others\(^5\).

Based on these findings and P. McGorry’s initiative of assessing this insidious onset of psychosis prospectively, early detection of psychosis was established\(^6\). Thus, acknowledging the continuity of psychosis has opened the door for its early detection. Many centers in the world have in the meantime shown that transition to frank psychosis can be predicted with a relatively high accuracy by carefully assessing these early signs and symptoms in help-seeking individuals: about 37% of those fulfilling the risk criteria develop psychosis within three years, mainly schizophrenia spectrum disorders\(^6,7\), although psychotic transition was most likely prevented in some patients by caring for them in the early intervention services.

The big question, however, always was: when do psychotic-like experiences really predict later transition to psychosis, when are they symptoms of another mental disorder, and when are they just harmless, transient phenomena?

Early detection research has established quite an elaborate set of criteria for this prediction and is continuously trying to refine them\(^6-8\). the individuals or one of their significant others need to be distressed and help-seeking; they have to belong to an age group at risk; they concurrently have to display psychotic-like experiences such as attenuated hallucinations, unusual thought content or suspiciousness above a certain threshold of severity; or they must have had full-blown psychotic symptoms for less than one week; or they have to show a genetic risk in combination with a recent marked social decline, or, in some studies, with newly developed unspecific prodromal signs\(^9\); and, most importantly, risk assessment is based on thorough examinations by specifically trained, specialized psychiatrists and psychologists. More and more, additional predictors are included, such as (subclinical) negative symptoms or neurocognitive decline.

Well aware of the fact that psychotic experiences can be “transdiagnostic” phenomena, patients in early detection services are usually diagnosed according to the criteria they fulfil (mainly as having depressive or anxiety disorders) and, in addition to that, they are educated about their potential risk of going on to develop some sort of psychotic disorder. So, there is not a “mislabelling as ultra-high risk status”, as stated by van Os and Reininghaus\(^1\), but the transdiagnostic nature of psychotic-like experiences is taken into account, which is exactly what van Os and Reininghaus demand. Fortunately, about two thirds of these individuals do not develop frank psychosis and some of them recover completely. In these cases, early treatment may have been beneficial not only for their psychotic-like symptoms, but also for the other symptom dimensions.

Acknowledging continuity also offers a chance for destigmatization. Educating patients, their significant others and the general population about the continuity of mental health problems often brings great relief and opens the door for the “coming out” of those concerned and a better understanding by those not (or not yet) concerned. At the same time, it is a step away from an old patriarchal psychiatry in which patients were not educated about their diagnoses and risks.

However, if we acknowledge that mental (not only psychotic) symptoms are often continuous – temporally as well as phenomenologically – and cross the borders of traditional categories, does that really mean that we need new diagnostic approaches?

Clearly defined, reliable diagnostic categories brought great progress into psychiatry – research and clinic – some decades ago. But are these categories really valid entities? We suppose we have to admit that they are not. What was a progress some decades ago is not satisfying anymore, because research in psychiatry has made significant progress in the meantime, enabling us to enter a process which other medical specialties such as internal medicine have entered much earlier. Our colleagues there are well beyond deriving diagnoses from the presenting symptoms only, such as different sorts of coughing, aspects of sputum etc., but have learned to also use the “biomarkers” of their patients by means of X-rays, bacteriological analyses etc., and thereby learned that one and the same symptom can have completely different aetiologies, which is the basis for their diagnoses (e.g., pneumonia, tuberculosis or lung cancer).

Psychiatry in the meantime also has developed this potential of identifying disorders based on aetiology or at least suspected pathogenetic mechanisms rather than only on presenting symptoms. The challenge is now to use emerging research findings for identifying new, valid, aetologically defined disease entities. To this end, data from genetics, neuroimaging, neurocognition, neurophysiology, neuroendocrinology, immunology etc. should be used, but also data on psychosocial pathogenetic influences such as environmental stressors and triggers\(^9\).

In order to derive such new, aetologically valid entities, research has to be free from preconceived assumptions and specifications and should be purely data-driven in a first step. All the above-mentioned assessment modalities have to
be integrated. Dimensional rather than categorical approaches should be used in a first step, in order to avoid loss of data. Furthermore, data have to be derived from large populations with mental problems and not from specific, pre-defined traditional and to some extent artificial categories of patients. Thinking in silos has rarely brought progress.

New statistical methods, e.g. latent variable mixture models or unsupervised machine learning, could allow for such new transdiagnostic, assumption-free, multi-domain approaches, which are not just based on psychopathology but mainly on aetiological factors – neurobiological as well as psychosocial ones.

Thus, expanding on van Os and Reininghaus’ suggestions, we propose an even more radical paradigm shift in psychiatry. Hopefully, our discipline and our patients can, in the future, benefit from such new approaches in many ways: a) in the general population, a more dimensional concept of mental symptoms would foster destigmatization and early detection; b) in research, more valid, aetiological defined disease entities could be identified; c) in the clinic, these new entities would hopefully allow for more causal therapies.

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Conceptualizing psychotic disorders: don’t throw the baby out with the bathwater

“Everything should be made as simple as possible, but not simpler.” (A. Einstein)

Since its introduction two centuries ago, the term “psychosis” has been conceptualized in a variety of ways, but is generally defined by impaired reality testing characterized by delusions, hallucinations and/or disordered thinking. There are several limitations in our current conceptualization of psychoses, including:

a) unclear boundaries between disorders (e.g., between psychotic bipolar disorder, schizoaffective disorder and schizophrenia);

b) enormous unexplained clinical heterogeneity within individual psychotic disorders;

c) the frequent co-occurrence of mood and psychotic symptoms; and
d) poorly described relationships between subclinical psychotic phenomena in the general population and defined psychiatric disorders.

In an effort to address these challenges, van Os and Reininghaus synthesize findings from various fields and propose that psychosis is best conceptualized as a continuous phenotype that includes subclinical psychotic-like experiences in the general population (extended phenotype) and is continuous across the Kraepelinian dichotomy (transdiagnostic phenotype), and that this transdiagnostic continuity is seen at both clinical and subclinical levels. They claim further support for their proposition by citing shared aetiological factors (most notably childhood trauma) across this transdiagnostic, extended phenotype. A careful scrutiny of the tenets of their hypothesis and its implications is warranted.

There are three premises on which this hypothesis rests: a) psychosis-like experiences in the general population are analogous to and both phenomenologically and temporally continuous with true psychotic phenomena in individuals with a defined psychotic disorder; b) since psychotic symptoms co-vary with depression and anxiety symptoms in both clinical and general populations, they represent a single phenotype; and c) there are shared aetiological factors across the breadth of the extended, transdiagnostic phenotype, thereby validating it.

Each one of these postulates is based on an uncritical reading of the literature. The assertion that psychosis-like phenomena detected in the general population are similar to psychotic experiences in the clinical setting ignores distinctions between imagery and hallucinations, or between overvalued ideas and delusions. This premise is further undermined by the fact that data in the general population are generally collected by inexperienced interviewers using imprecise instruments such as the Composite International Diagnostic Interview (CIDI). Using the CIDI to reliably evaluate depression in the general population is similarly problematic.

Jumping to the conclusion that co-occurrence of mood and psychotic symptoms across a range of psychiatric disorders implies that all these disorders are part of a singular “general psychosis syndrome” is unwarranted and runs counter to the vast amounts of data indicating the utility of current diagnostic categories. Furthermore, the authors ignore their own note of caution that “evidence on a general psychosis dimension remains restricted to the here studied schizophrenia spectrum disorders” and that “we did not find evidence that would justify replacing specific diagnostic constructs of psychosis with a general psychosis syndrome.”

The assertion about aetiological factors being common across the breadth and
depth of the extended transdiagnostic phenotype rests on an overly selective citation of the literature. For example, genetic risk for schizophrenia is poorly correlated with psychosis-like experiences in the general population. Also, sharing some risk factors does not denote a singular clinical entity.

As noted by one of the authors, there was a significant effort in the development of DSM-5 to address the limitations in our current characterization of psychotic disorders. Relevant revisions in DSM-5 include the elimination of the classic subtypes of schizophrenia, the addition of unique psychopathological dimensions, the provision of a scale to measure each of these dimensions across all psychotic disorders, a more precise definition of the boundary between schizophrenia and schizoaffective disorder, and the addition of a new category of “attenuated psychosis syndrome” as a condition for further study in Section 3 of the manual.

There was, in fact, a vigorous debate among members of the Psychotic Disorders Work Group about the merits of including a "general psychosis syndrome" in DSM-5, and a substantial majority found an insufficient basis to do so. The group recognized that there are individuals in the general population who exhibit subclinical psychotic or psychosis-like symptoms and that a subset of these individuals is at high risk of developing a psychotic disorder. A definition of attenuated psychosis syndrome was found to best define this group at “substantially higher risk”, and data continue to support the validity and utility of this construct.

In line with the multi-dimensional nature of psychotic disorders, the most important change in DSM-5 was the delineation of distinct symptom domains across all psychotic disorders: reality distortion (delusions, hallucinations), negative symptoms, disorganization, cognitive impairment, motor symptoms (e.g., catatonia), and mood symptoms (depression, mania). Measuring the relative severity of these symptom dimensions through the course of illness in the context of treatment can provide useful information to the clinician about the nature of the illness in a particular patient and in assessing the specific impact of treatment on different aspects of the patient’s illness. A 0-4 rating scale with anchor points for each of the eight items (delusions, hallucinations, negative symptoms, cognitive impairments, disorganization, catatonia, depression, and mania) to rate these six dimensions is provided in Section 3 of the DSM-5 manual. As a simple rating scale, it should encourage clinicians to explicitly assess and track changes in the severity of these dimensions in each patient with schizophrenia and use this information to guide measurement-based, collaborative treatment.

The article by van Os and Reininghaus prompts a critical re-examination of our conceptualization of psychotic disorders. The specific premises and implications of their model of “psychosis as a transdiagnostic and extended phenotype in the general population”, however, do not stand up to scrutiny. While our current construct of the psychosis syndrome is inadequate, we do not want to throw the baby out with the bathwater. Replacing an imperfect but useful construct with one that is more flawed and less valid is a retrograde step. Changes in DSM-5 (revisions in ICD-11 are likely to be similar) appear to represent our best foot forward: they enhance clinical utility while providing a more useful platform in integrating emerging genetic and other neurobiological information.

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Population-based analysis of health care contacts among suicide decedents: identifying opportunities for more targeted suicide prevention strategies

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The objective of this study was to detail the nature and correlates of mental health and non-mental health care contacts prior to suicide death. We conducted a systematic extraction of data from records at the Office of the Chief Coroner of Ontario of each person who died by suicide in the city of Toronto from 1998 to 2011. Data on 2,835 suicide deaths were linked with provincial health administrative data to identify health care contacts during the 12 months prior to suicide. Sub-populations of suicide decedents based on the presence and type of mental health care contact were described and compared across socio-demographic, clinical and suicide-specific variables. Time periods from last mental health contact to date of death were calculated and a Cox proportional hazards model examined covariates. Among suicide decedents, 91.7% had some type of past-year health care contact prior to death, 66.4% had a mental health care contact, and 25.3% had only non-mental health contacts. The most common type of mental health contact was an outpatient primary care visit (54.0%), followed by an outpatient psychiatric visit (39.8%), an emergency department visit (31.1%), and a psychiatric hospitalization (21.0%). The median time from last mental health contact to death was 18 days (interquartile range 5-63). Mental health contact was significantly associated with female gender, age 25-64, absence of a psychosocial stressor, diagnosis of schizophrenia or bipolar disorder, past suicide attempt, self-poisoning method and absence of a suicide note. Significant differences between sub-populations of suicide decedents based on the presence and nature of their health care contacts suggest the need for targeting of community and clinical-based suicide prevention strategies. The predominance of ambulatory mental health care contacts, often close to the time of death, reinforce the importance of concentrating efforts on embedding risk assessment and care pathways into all routine primary and specialty clinical care, and not only acute care settings.

Key words: Suicide, health care contacts, population-based analysis, outpatient primary care, mental health care, suicide prevention strategies

(World Psychiatry 2016;15:135–145)

At least 800,000 people worldwide die from suicide each year, at an estimated rate of 11.4 per 100,000 per year. Suicide results in devastating personal and societal loss, with immense emotional and economic costs. There is no singular profile of a person who dies by suicide, and many interconnected factors may lead to this tragic outcome, but mental illness is often at the core, being present among >90% of cases. The absolute risk of suicide in people with a lifetime contact with specialty mental health services is estimated at 6-7% among men and 4-5% among women.

Within the health care system, there are a variety of different potential points of contact prior to suicide death. Mental health care may be accessed through primary care, ambulatory psychiatric services, emergency departments or inpatient care settings. Extant data suggest that <50% of people who die by suicide have mental health care contact during the year prior to death, with specialized mental health services being the most common access point among those with mental health care contact.

There is a paucity of comprehensive data on factors associated with any mental health contact or with specific mental health contact types. Furthermore, while the most common type of any health care contact during the year prior to suicide death is with primary care physicians, only a portion of visits involve an assessment of the patients’ safety or have a documented mental health focus, and there are limited data examining the role of primary care providers in the care of individuals at risk of suicide. Women and older adults have been reported to be more likely to have had contacts with a primary care physician or mental health services prior to suicide, but most other possible demographic and clinical factors have not received sufficient study.

There are a large group of people who die by suicide without having any recent mental health care contact. This group is even less well understood, with available data describing and comparing contact and non-contact groups limited by small sample size and non-representative samples. By definition, studies of this group must rely on population-based datasets for identification of suicide decedents, since health care administrative databases such as those from health maintenance organizations or other similar sources are not designed to sufficiently capture data on people not in treatment. Population-based groups that differ based on the presence, type, frequency and recency of health care contacts prior to
suicide represent potentially different suicide risk populations that would require different suicide prevention strategies. A better understanding of the socio-demographic, clinical and suicide-related differences between these groups can serve to inform the implementation and evaluation of targeted suicide prevention strategies.

We examined a large, population-based sample of suicide decedents in order to detail the nature and correlates of mental health and non-mental health care contacts prior to suicide death. We sought to address a number of limitations in the literature by utilizing population-based data sources that combined detailed person-related information on suicide decedents with health care administrative data that captured all types of mental health and non-mental health care contacts (where there is no contact) within primary and specialty care.

METHODS

Data from the Office of the Chief Coroner of Ontario

The Office of the Chief Coroner of Ontario (OCC) investigates all suicide deaths in Toronto, Canada. We conducted a systematic extraction of data from records at the OCC of each person who died by suicide in the city of Toronto (approximate population 2.5 million) from 1998 to 2011 (3,091 suicide deaths).

The OCC becomes involved in all sudden or unexpected deaths, and conducts an investigation to determine the cause, which can include suicide, according to a standard of a high degree of probability. Coroner charts compile all relevant information into an investigation report and search for confluence from multiple, independent sources, including a police report, evidence from the scene (e.g., a suicide note), death certificate, post-mortem examination (pathology report), toxicology report (for self-poisoning deaths only), collateral information gathered from interviews with family or others, physician/clinical records, and in some cases a full inquest. OCC data are not available for approximately two years after the death, while full investigations are completed.

A standardized data extraction procedure was used, collecting data on: a) socio-demographics, including age, gender, marital status, and living circumstances; b) recent stressors, including employment/financial, interpersonal conflict, relationship breakup, immigration, medical/health, police/legal, and bereavement; c) clinical variables, including diagnosis of bipolar disorder or schizophrenia, past suicide attempts, and presence of any comorbid medical condition; and d) suicide details, including method, place of death and presence of a suicide note. More than one method of suicide could be recorded, if there was more than one independent cause of death identified (e.g., self-poisoning and asphyxia). Details regarding intent of prior suicidal behavior were not systematically available in coroner data; therefore we had to rely on the coroner determination of a past suicide attempt without clarity as to whether the behavior should have been better characterized within the notion of deliberate self-harm, non-suicidal self-injury, or other descriptors of suicidal behavior.

Two study investigators (MS and AS) provided onsite training to research staff and were in continuous contact to address any questions and reach consensus regarding coding for more complex cases. Socio-demographic data and details of the suicide were available in >99% of investigation reports. Information on clinical and stressor variables are primarily collected by the coroner to aid the investigation of the cause and details of the death; as such these variables are subject to missing information which may or may not be associated with prior mental health contact. We included them in the analyses, but interpret the results cautiously. Previous studies using coroner data on bipolar disorder or schizophrenia have suggested adequate reliability of diagnosis, but we chose to not include other diagnoses (e.g., depression, anxiety, personality disorders) because of reliability concerns as a result of non-specific information in the coronary records.

Health administrative data

Provincial health administrative data maintained at the Institute for Clinical Evaluative Sciences (ICES) provide accurate and complete information on residents of Ontario (except the prison population and Aboriginal residents on reserve) and their contact with physicians in the health care system, including outpatient physician visits, emergency department visits, and inpatient hospitalizations.

Datasets that were accessed for this study included: a) registered persons database for basic personal information; b) Ontario Health Insurance Plan for physician visits and billing codes (including specific mental health codes for primary care) and for emergency department visits prior to 2002; c) National Ambulatory Care Reporting System for emergency department visits since 2002; d) Canadian Institute for Health Information – Discharge Abstract Database for hospitalizations with a mental health primary discharge diagnosis; and e) Ontario Mental Health Reporting System for psychiatric hospitalizations subsequent to October 2005. These datasets allowed for a one-year look back for all years in the study.

A number of mental health and non-mental health related service contacts were defined a priori. Mental health related primary care physician visits were defined as any Ontario Health Insurance Plan claim with a mental health/addiction diagnostic code, or a fee code for primary mental health care or psychotherapy made by a physician designated as a family physician in the ICES physician database. This definition utilized an existing algorithm validated at ICES, which results in 96.1% sensitivity and 93.1% specificity when compared with chart abstracted data. All other primary care physician Ontario Health Insurance Plan claims were defined as non-mental health related. An outpatient psychiatric contact was defined by a standard outpatient
Ontario Health Insurance Plan claim made by a psychiatrist (defined by ICES physician database main specialty).

A mental health related emergency department visit was defined in one of three ways: a) prior to 2002, as an Ontario Health Insurance Plan claim with a mental health/addiction diagnostic code or mental health service code billed in the emergency department setting; b) since 2002, within National Ambulatory Care Reporting System, as an emergency department visit with a mental health/addiction diagnostic code (ICD-9 codes 290-319 or ICD-10 codes F00-F99); c) since 2002, as an emergency department visit that involved suicide-related behavior based on National Ambulatory Care Reporting System coding of self-inflicted poisoning or injury (ICD-9 codes E950-9 or ICD-10 codes X60-X84)\textsuperscript{33,34}. All other emergency department visits that did not meet the above criteria were defined as non-mental health related.

Mental health related hospitalization was defined as any Canadian Institute for Health Information – Discharge Abstract Database record with a mental health/addiction diagnostic code (ICD-9 codes 290-319 or ICD-10 codes F00-F99), or any Ontario Mental Health Reporting System discharge record after October 2005. All other hospitalizations were defined as non-mental health related.

### Linking data from the OCC and ICES

These datasets were linked using unique, encoded identifiers and analyzed at ICES. For each person who died by suicide, we attempted to link via probabilistic matching of name, gender, date of birth, date of death, and home postal code (first three characters) since the OCC charts do not contain health card numbers that are the basis for identification within health administrative data. Unsuccessful linkage occurs when there is insufficient information on the key linkage variables from either dataset to establish a definitive match.

Successful linkage was obtained for 94.7% of cases. The linkage rate showed a weak increasing trend over years ($R^2=0.335$, $p=0.031$), with a range from 88.7% to 97.7%. A further 3.0% of cases were excluded from analysis after quality check because of discrepancies between ICES and coroner data on age (by $>3$ years), gender, or date of death (by $>2$ days), or because the date of death was prior to a recorded health care contact. This resulted in an analyzable sample of 2,835 suicide deaths (91.7% of total suicide deaths).

A comparison of the analysis and excluded groups was conducted. Decedents under age 25 years ($p=0.031$), and those with an immigration stressor ($p=0.001$), a bipolar disorder diagnosis ($p=0.046$), a past suicide attempt ($p=0.002$) and a medical diagnosis ($p=0.001$) were significantly more likely to be excluded.

### Mental health and non-mental health care contacts

A mental health care contact in the 12 months prior to the date of suicide was defined as one or more of the following: a) a mental health related primary care outpatient physician contact; b) an outpatient psychiatric contact; c) a mental health related emergency department visit; or d) a mental health related hospitalization. Each of these mental health contacts was also examined separately.

A non-mental health contact was defined as one or more of the following: a) a non-mental health related primary outpatient physician contact; b) a contact with an ICES physician database-defined specialty other than primary care or psychiatry; c) a non-mental health related emergency department visit; or d) a non-mental health related hospitalization. Emergency department visits or hospitalizations that included a component of both non-mental health and mental health care were considered to be mental health related.

### Statistical analysis

Among the analyzable sample of 2,835 suicide deaths, the proportion of subjects with a mental health care contact, only a non-mental health care contact, or neither type of contact within the 12 months prior to suicide was described. Bivariate analyses compared socio-demographics, clinical variables, recent stressors and suicide details between subjects with any mental health contact, only non-mental health contact and no contact.

Multivariate logistic regression for any past-year mental health contact was then conducted using generalized estimating equation models to test associations of any mental health contact in the year prior to suicide. Variables tested included age, gender, marital status, living circumstances, recent and past suicide attempt, diagnosis of bipolar disorder, diagnosis of schizophrenia, recent medical diagnosis, method of death, place of death, and presence of a suicide note. Models were run with and without year of death to test for a secular trend in the results, and crude and adjusted odds ratios were obtained for the independent variables.

The proportion of subjects with each specific type of mental health care contact within the past 12 months prior to suicide was also described. Mental health contacts were then categorized as either acute (emergency department visit or hospitalization) or ambulatory (outpatient psychiatric or primary care visits), and bivariate analyses compared subjects with any acute mental health care versus those with only ambulatory mental health care. Further secondary analyses compared four subgroups of subjects who had: a) a mental health inpatient or emergency department visit; b) mental health emergency department visit(s), but no hospitalization; c) outpatient psychiatric or mental health primary care visits, but no acute care; or d) only outpatient mental health primary care visits.

For those with any prior mental health care contact, mean, median and categorical time periods from last mental health contact to date of death were calculated for any and each type of mental health contact. A time-to-event curve was generated for any and each type of mental health contact. We structured...
Table 1  Comparison of people who died by suicide by type of health care contact in prior year in Toronto, Canada, 1998-2011

<table>
<thead>
<tr>
<th>Socio-demographics</th>
<th>Any mental health contact (N=1883)</th>
<th>Only non-mental health contact (N=716)</th>
<th>No contact (N=236)</th>
<th>Test value (F/\chi^2)</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, years± SD)</td>
<td>47.0 ± 16.5</td>
<td>50.4 ± 20.5</td>
<td>41.0 ± 14.7</td>
<td>27.19</td>
<td>2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 24 years</td>
<td>7.4</td>
<td>12.4</td>
<td>14.8</td>
<td>109.23</td>
<td>4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>25-64 years</td>
<td>77.4</td>
<td>60.6</td>
<td>80.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>15.2</td>
<td>27.0</td>
<td>4.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>64.9</td>
<td>79.6</td>
<td>84.7</td>
<td>79.12</td>
<td>2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Marital status (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single/no status available</td>
<td>54.6</td>
<td>49.6</td>
<td>65.3</td>
<td>25.46</td>
<td>4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Divorced, separated or widowed</td>
<td>20.8</td>
<td>19.3</td>
<td>17.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married, including common law</td>
<td>24.5</td>
<td>31.1</td>
<td>17.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living circumstances (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>44.2</td>
<td>37.8</td>
<td>48.3</td>
<td>22.54</td>
<td>4</td>
<td>0.0002</td>
</tr>
<tr>
<td>Family/friends</td>
<td>49.1</td>
<td>58.1</td>
<td>44.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>6.6</td>
<td>4.1</td>
<td>6.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent stressors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bereavement (%)</td>
<td>5.6</td>
<td>5.3</td>
<td>6.8</td>
<td>0.74</td>
<td>2</td>
<td>0.6915</td>
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<tr>
<td>Employment/financial (%)</td>
<td>15.7</td>
<td>21.4</td>
<td>31.4</td>
<td>39.51</td>
<td>2</td>
<td>&lt;0.0001</td>
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<tr>
<td>Bipolar disorder diagnosis (%)</td>
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<td>1.4</td>
<td>x</td>
<td>55.28</td>
<td>2</td>
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</tr>
<tr>
<td>Schizophrenia diagnosis (%)</td>
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<td>68.28</td>
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<td></td>
</tr>
<tr>
<td>Method of death (%)</td>
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<td></td>
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<tr>
<td>Hanging</td>
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<td>133.67</td>
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<td>8.5</td>
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</tr>
<tr>
<td>Fall/jump from height</td>
<td>23.5</td>
<td>22.8</td>
<td>25.4</td>
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<td></td>
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<td>Subway/train/car collision</td>
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<td>4.1</td>
<td>5.1</td>
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<td></td>
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<tr>
<td>Other asphyxia</td>
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<td>11.9</td>
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<td></td>
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<td>Shooting</td>
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<tr>
<td>Other</td>
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<td>8.5</td>
<td>7.6</td>
<td></td>
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<tr>
<td>Place of death (%)</td>
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<td>Own home</td>
<td>61.7</td>
<td>68.4</td>
<td>64.8</td>
<td>34.81</td>
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<td>Other residence</td>
<td>2.7</td>
<td>2.4</td>
<td>5.1</td>
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<tr>
<td>Outdoors</td>
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<td>11.0</td>
<td>16.1</td>
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</table>
this similarly to data by Ahmedani et al.8 to facilitate comparison across datasets.

We then examined time from last mental health contact (any type) to suicide death among subjects with at least one contact. The relationship between baseline covariates and the time from last mental health contact of any type until suicide was modeled using a Cox proportional hazards model to obtain both crude and adjusted hazard ratios. The proportional hazards assumption was tested, and time dependent variables were added to the basic model for medical diagnosis, diagnosis of schizophrenia, living circumstances and method of death. Both adjusted and unadjusted hazard ratios were obtained for the baseline covariates. This model was also run with year of death as a covariate.

For those with prior contact, the frequency of each type of mental health care contact was also reported as mean, median and range.

**Ethical approval and privacy**

The OCC granted approval to this study and provided full access to their records for the purposes of completing this study. The study was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre, Toronto, Canada. Strict privacy procedures utilized by the OCC and ICES were fully adhered to.

**RESULTS**

Of the 2,835 people who died by suicide, a total of 91.7% had some type of health care contact during the year prior to suicide death. The majority (66.4%) had a mental health contact, with 25.3% having only non-mental health related contacts.

Table 1 summarizes the bivariate analyses across three groups based on contact during the year prior to suicide death: a) subjects with a mental health contact; b) subjects with only a non-mental health contact; and c) subjects with no mental health or non-mental health contact.

All significant variables were entered in a multivariate logistic regression for any past-year mental health contact. Table 2 displays the significant findings from this regression. Past-year mental health contact was significantly associated with female gender, age 25-64, absence of an identified psychosocial stressor, diagnosis of schizophrenia, diagnosis of bipolar disorder, past suicide attempt, self-poisoning method of suicide, and the absence of a suicide note. There were no major secular trends associated with any mental health contact, except for an effect for year 2001 vs. 1998 (adjusted OR=1.86, 95% confidence interval (CI) 1.09-3.16).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Multivariate logistic regression for any past-year mental health contact in persons who died by suicide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio, adjusted</td>
</tr>
<tr>
<td>Gender: male vs. female</td>
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</tr>
<tr>
<td>Age at death: 10 to 24 vs. 25 to 64</td>
<td>0.5639</td>
</tr>
<tr>
<td>Age at death: 65 and over vs. 25 to 64</td>
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<tr>
<td>Any stressor: yes vs. no</td>
<td>0.6636</td>
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<tr>
<td>Bipolar disorder diagnosis: yes vs. no</td>
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<tr>
<td>Schizophrenia diagnosis: yes vs. no</td>
<td>6.6147</td>
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<tr>
<td>Past suicide attempt: yes vs. no</td>
<td>3.6598</td>
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<tr>
<td>Method of death: self-poisoning vs. hanging</td>
<td>1.575</td>
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<tr>
<td>Note left: yes vs. no</td>
<td>0.8214</td>
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</table>

Significant differences are highlighted in bold prints.
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<thead>
<tr>
<th>Socio-demographics</th>
<th>Accessed acute mental health care (N=882)</th>
<th>Accessed only ambulatory mental health care (N=1001)</th>
<th>No contact (N=952)</th>
<th>Test value ($F/\chi^2$)</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, years±SD)</td>
<td>44.5 ± 15.6</td>
<td>49.2 ± 16.9</td>
<td>48.1 ± 19.6</td>
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<td>≤ 24 years</td>
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<td>75.6</td>
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<td>≥ 65 years</td>
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<td>Gender (% male)</td>
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<td>Marital status (%)</td>
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<td>Single/no status available</td>
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<td>Divorced, separated or widowed</td>
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<td>Married, including common law</td>
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<td>27.8</td>
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<td>Living circumstances (%)</td>
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<td>44.3</td>
<td>40.4</td>
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<td>54.8</td>
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<td>4.7</td>
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<td>Recent stressors</td>
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<td>37.91</td>
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<tr>
<td>Police/legal (%)</td>
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<td>6.8</td>
<td>6.8</td>
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<tr>
<td>Bipolar disorder diagnosis (%)</td>
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<td>6.7</td>
<td>1.5</td>
<td>68.64</td>
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<tr>
<td>Schizophrenia diagnosis (%)</td>
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<td>6.4</td>
<td>1.4</td>
<td>103.72</td>
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<tr>
<td>Past suicide attempt (%)</td>
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<td>25.3</td>
<td>11.3</td>
<td>336.68</td>
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<td>Medical diagnosis (%)</td>
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<td>Method of death (%)</td>
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<td>Hanging</td>
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<td>12.4</td>
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<td></td>
</tr>
<tr>
<td>Fall/jump from height</td>
<td>25.7</td>
<td>21.6</td>
<td>23.4</td>
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<tr>
<td>Subway/train/car collision</td>
<td>11.8</td>
<td>6.1</td>
<td>4.3</td>
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<td>Other asphyxia</td>
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<td>8.6</td>
<td>9.3</td>
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<td>Cutting/stabbing</td>
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<tr>
<td>Other</td>
<td>5.3</td>
<td>7.9</td>
<td>12.7</td>
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<tr>
<td>Place of death (%)</td>
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<tr>
<td>Own home</td>
<td>52.7</td>
<td>69.6</td>
<td>67.5</td>
<td>87.73</td>
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<tr>
<td>Outdoors</td>
<td>13.6</td>
<td>10.6</td>
<td>12.3</td>
<td></td>
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</table>
CI: 1.14-3.03, \( p = 0.014 \), which was likely accounted for by a change in data source for emergency department visits in year 2000.

Within the group that had a mental health contact, the most common type of contact was a mental health outpatient primary care visit (54.0%), followed by an outpatient psychiatric visit (39.8%), a mental health emergency department visit (31.1%), and a mental health hospitalization (21.0%).

Mental health contacts were also divided into acute care (emergency department visits and hospitalizations) and ambulatory care (outpatient psychiatric or primary care visits). Table 3 shows the comparison between subgroups who accessed any acute mental health care (\( N = 882 \)), those who accessed only ambulatory mental health care (\( N = 1001 \)), and those with no mental health contact of any type (\( N = 952 \)). The acute care subgroup was younger, less likely to be married or to have an identified psychosocial stressor, more likely to have a major mental illness or past suicide attempt, and less likely to die at home or produce a suicide note.

The number of mental health contacts and the categorized time from last mental health contact (any, and by type) to suicide death are shown in Table 4. The cumulative weekly percentages of subjects receiving mental health care (any, and by type) in the year prior to suicide death are shown in Figure 1. Cox proportional hazards model found that time from last contact to suicide death was significantly longer among males (adjusted hazard ratio, HR = 0.785, 95% CI: 0.708-0.871, \( p < 0.0001 \)), people aged 10-24 years (adjusted HR = 1.426, 95% CI: 1.183-1.720, \( p = 0.0002 \)), and suicide decedents without an identified psychosocial stressor (adjusted HR = 0.759, 95% CI: 0.634-0.908, \( p = 0.003 \)).

A shorter time from last contact to suicide death was identified for those with a bipolar disorder diagnosis (adjusted HR = 1.935, 95% CI: 1.634-2.291, \( p < 0.0001 \)), a schizophrenia diagnosis (adjusted HR = 1.531, 95% CI: 1.270-1.846, \( p < 0.0001 \)), a past suicide attempt (adjusted HR = 1.768, 95% CI: 1.596-1.958, \( p < 0.0001 \)), and those who died in hospital (adjusted HR = 1.891, 95% CI: 1.168-3.060, \( p = 0.0095 \)).

### Table 3 Comparison of people who died by suicide by type of mental health contact (acute vs. ambulatory care) in prior year (continued)

<table>
<thead>
<tr>
<th></th>
<th>Accessed acute mental health care (( N = 882 ))</th>
<th>Accessed only ambulatory mental health care (( N = 1001 ))</th>
<th>No contact (( N = 952 ))</th>
<th>Test value (( F/\chi^2 ))</th>
<th>df</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subway/railway</td>
<td>10.5</td>
<td>5.3</td>
<td>3.9</td>
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</tr>
<tr>
<td>Other</td>
<td>20.3</td>
<td>12.0</td>
<td>13.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suicide note (% yes)</td>
<td>24.6</td>
<td>33.6</td>
<td>35.1</td>
<td>27.13</td>
<td>2</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Significant differences are highlighted in bold prints

### Table 4 Number of mental health contacts and timing of last mental health contact in persons who died by suicide

<table>
<thead>
<tr>
<th></th>
<th>Outpatient primary care visit (( N = 1531 ))</th>
<th>Outpatient psychiatric visit (( N = 1127 ))</th>
<th>Emergency department visit (( N = 690 ))</th>
<th>Inpatient visit(^a) (( N = 596 ))</th>
<th>Any mental health contact(^b) (( N = 1883 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of mental health care contacts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>6.5 ± 9.9</td>
<td>11.4 ± 15.1</td>
<td>2.4 ± 2.8</td>
<td>1.9 ± 1.4</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>3 (1-153)</td>
<td>6 (1-134)</td>
<td>1 (1-24)</td>
<td>1 (1-12)</td>
<td></td>
</tr>
<tr>
<td>Time from last mental health contact to death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean time, days (SD)</td>
<td>87.3 (94.8)</td>
<td>66.5 (86.4)</td>
<td>87.4 (99.1)</td>
<td>99.9 (98.7)</td>
<td>52.6 (77.4)</td>
</tr>
<tr>
<td>Median time, days (IQR)</td>
<td>47 (14-134)</td>
<td>26 (8-86)</td>
<td>42 (9-138)</td>
<td>62.5 (16.5-168.5)</td>
<td>18 (5-63)</td>
</tr>
<tr>
<td>0 to 24 hrs, N (%)</td>
<td>12 (0.8)</td>
<td>14 (1.2)</td>
<td>26 (3.8)</td>
<td>31 (5.2)</td>
<td>65 (3.5)</td>
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<tr>
<td>1 to 7 days, N (%)</td>
<td>219 (14.3)</td>
<td>246 (21.8)</td>
<td>127 (18.4)</td>
<td>76 (12.8)</td>
<td>541 (28.7)</td>
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<tr>
<td>8 to 30 days, N (%)</td>
<td>390 (25.3)</td>
<td>337 (29.9)</td>
<td>138 (20.0)</td>
<td>103 (17.3)</td>
<td>561 (29.8)</td>
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<tr>
<td>31 to 90 days, N (%)</td>
<td>383 (25.0)</td>
<td>256 (22.7)</td>
<td>156 (22.6)</td>
<td>144 (24.2)</td>
<td>357 (18.9)</td>
</tr>
<tr>
<td>&gt;90 days, N (%)</td>
<td>527 (34.4)</td>
<td>274 (24.3)</td>
<td>243 (35.2)</td>
<td>242 (40.6)</td>
<td>359 (19.1)</td>
</tr>
</tbody>
</table>

\(^a\)Hospitalizations that immediately followed an emergency department visit were excluded if the main diagnosis was non-mental health related and/or if it appeared to be directly related to the suicide event

\(^b\)Uses the type of visit that has the shortest period prior to death
DISCUSSION

To our knowledge, this is the largest study to date that comprehensively reports on the nature and correlates of mental health and non-mental health care contacts prior to suicide death in a population-based sample. A key finding is that, among the 2,835 suicide decedents, 66.4% had a mental health care contact during the year prior to death. A mental health focus within a primary care physician contact was identified as the most common specific type of contact (54.0%), followed in descending order by an outpatient psychiatric visit (39.8%), a mental health emergency department visit (31.1%), and a mental health hospitalization (21.0%). There were a number of socio-demographic, clinical and suicide-specific differences associated with the presence, type and timing of health care contacts prior to suicide.

The likelihood of any mental health care contact was considerably higher in this study than previous estimates. This may be best accounted for by our inclusion of a validated method for identifying a mental health care focus within a primary care physician contact, especially as this type of contact was the most common. As well, our sample derived exclusively from an urban setting with limited barriers within a universal health care model that promotes the centrality of primary health care delivery. Any mental health contact was significantly and positively correlated with female gender, age at death of 25-64 years, absence of an identified recent psychosocial stressor, bipolar disorder diagnosis, schizophrenia diagnosis, past suicide attempt, method of suicide being self-poisoning, and the absence of a suicide note being left. The age, gender, and schizophrenia effects replicate prior findings, and overall the results expand our understanding of factors that are associated with treatment contact prior to suicide.

These findings have a number of implications. First, the fact that a substantial majority of people received some form of more broadly-defined mental health care argues for the great opportunity inherent in clinically-based suicide prevention interventions. Second, the better characterization of the sub-population that received mental health care allows for potentially better targeting of clinically-based suicide prevention interventions. Mental health treatment has been clearly shown to lower suicide risk; however, a stronger basis for targeted clinical interventions can be provided by better characterization of groups distinguished by type, frequency and recency of mental health care contacts prior to suicide.

Third, our finding that the most common types of contact occur in ambulatory care strongly reinforces the importance of designing and integrating suicide prevention strategies into routine clinical care rather than viewing suicide prevention strategies as only being relevant in high-risk, acute care environments. Such strategies should include evidence-based guidance on most appropriate screening for suicide risk in ambulatory settings and care pathways for different levels of risk.

Our results indirectly support Finnish data indicating that the prominence of outpatient psychiatric services is a key mental health system variable associated with lower suicide risk.
rates\textsuperscript{39}. The challenge, however, is the perception and reality that suicide remains a rare outcome, so that, while many people who die by suicide sought care in ambulatory settings, the majority of people receiving ambulatory care are not going to die by suicide. We found the group of suicide decedents who accessed only ambulatory mental health care to be older, more likely to be single and to have a medical health stressor or comorbid medical diagnosis, which may drive a more medical focus to outpatient psychiatric service visits.

There is broad consensus that comprehensive suicide prevention efforts benefit from both community-based and clinically-based interventions\textsuperscript{36,47}. For the 33.6\% of people that had no past-year mental health treatment contact, community-based measures such as public education, anti-stigma campaigns, online self-help, gatekeeper training, crisis lines, and broad-based means restriction are paramount\textsuperscript{40,47}. If specific groups such as men, youth, and older adults are significantly less likely to access mental health treatment prior to suicide, then community-based interventions should consider these specific demographic groups as critically important target populations.

We also found that approximately one quarter of all suicide decedents only had a non-mental health physician contact, which could include a primary care visit without a mental health focus, or contact with other medical specialties. People who only had a non-mental health contact were significantly older (27\% above age 65 years), and more likely to be male, married, living with others, and to have a recent medical stressor or any type of identified stressor. The presence of such a large group that was only seen in the context of non-mental health care highlights the importance of gatekeeper training and general medical education on identification of suicide risk through simple screening measures\textsuperscript{1,46}. The finding that not only medical stressors, but also psychosocial stressors were associated with non-mental health contact highlights the powerful link between stress and physical symptomatology that is directing people towards physicians, but not necessarily with their mental health needs as a stated or identified priority.

An examination of time from last mental health contact until date of death found a fairly even proportion of persons having their last contact during the week prior to death, the month prior to death, and one to twelve months prior to death. The median time from any type of last mental health contact until death was 18 days. Therefore, while the suicide rate is clearly highest during the period soon after a treatment contact, and is significantly correlated with a number of clinical factors such as diagnosis, past suicide attempt and age, the time to event analyses reveal a sizeable number that have a clear gap between date of last contact and their death. Among the specific types of mental health care contacts, the longest median time from last contact to death was for inpatient hospitalizations (62.5 days), with 64.8\% of deaths occurring >30 days after the last inpatient contact, similar to other studies\textsuperscript{10}. Inpatient hospitalizations are the least frequent type of contact, and frequency was inversely associated with time from last contact until death, but nonetheless these results highlight the importance of not exclusively focusing on the relevance of very recent hospitalizations, which identify high risk periods but are least common.

The results of this study should be interpreted in the context of some limitations. First, the precise nature of the clinical care delivered during various types of treatment contacts was not known, and therefore we do not know if patients had been identified as being at higher risk of suicide and if any interventions were utilized. Similarly, we do not know if the absence of care was as a result of system issues related to lack of access, or whether care was not sought by the individual\textsuperscript{7}. Our study should, therefore, be understood as a descriptive analysis that must be followed up by studies that enhance the delivery and content of care.

Second, coroner data were used to identify suicides. While this provides detailed information on suicide, determination of suicide as the cause of death is inherently complex and may be influenced by the presence of mental health contacts, with a small proportion of deaths likely to be misclassified in each direction. Previous coroner data validation studies have identified that under-reporting of suicide is greater than over-reporting, and that the overall rates are quite low, suggesting that the results are likely highly valid but may not be representative of 100\% of suicides\textsuperscript{46,49}.

Similarly, health administrative data maintained at ICES have been extensively utilized for many mental health studies, with the main limitation being successful linkage with external data sources. Our analysis cohort was comprised of 91.7\% of all suicide deaths, which is well within the acceptable range, but does indicate that numerous suicide deaths were not included in our analysis. Decedents under age 25 years and those with an immigration stressor were significantly more likely to be excluded from our analyses, and comprise small but important subgroups that are less well presented in our data.

Third, ICES data only captured physician-based clinical services, and thus we have no information on other important sources of mental health care provided by psychologists, social workers, the educational system, community agencies, and others. While this is clearly a gap, the nature of the Canadian health care system is that physician-based services are covered through universal health care, while the other sources must be paid for out of pocket, through employer-based insurance plans, or by institutions such as schools or universities. The typical pathway of care delivery would be for any person identified with significant mental health care needs or any indication of suicide risk to be referred to some form of physician-based services.

Finally, the study only examined suicides among people living in the city of Toronto, a large urban centre with ample mental health resources. It is unknown whether the results would be applicable in other non-Canadian or rural settings.

In conclusion, two thirds of people who died from suicide had mental health care contacts during the year prior to death, most commonly primary and specialty outpatient care. Our data suggest that clinically-based suicide prevention strategies should adjust to the predominance of opportunities within ambulatory care. For the one third of decedents who do not
have any mental health care contact, and who are more likely to be male and youth or older adults, community-based suicide prevention opportunities are a key source of suicide prevention and should be designed and delivered with those at highest need in mind. Overall, understanding the factors that influence the likelihood and nature of mental health care provided prior to suicide can aid in developing evidence-based care delivery and suicide prevention interventions.

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REFERENCES

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Does menopausal transition really influence mental health?
Findings from the prospective long-term Zurich study

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In the prospective long-term Zurich study, we re-examined the hypothesized association between mental health problems in women and the transition through menopausal stages. One hundred sixty-eight women from a population-based Swiss community cohort were prospectively followed up from age 21 to 50. At age 50, the occurrence of hot flushes/night sweats and sleep disturbances was significantly more frequent in peri- and post-menopausal women. Irritability/nervousness was increased only in peri-menopausal women, but that association was accounted for by neuroticism trait scores at age 30. Transitions to peri- or post-menopause were not related to changes in either the prevalence rates of DSM major depressive episode or anxiety disorders, or the course of psychopathological syndromes as assessed by the Symptom Checklist 90 - Revised. The null associations held when adjusting for duration of reproductive period or age at menopause. Preceding mental health problems between ages 21 and 41, increased neuroticism trait scores at age 30, and concurrent psychosocial distress were significantly related to mental health problems occurring between ages 41 and 50. Depending upon the cut-off point that was chosen, the arbitrary dichotomization of a continuous depression outcome produced spurious associations with the menopausal transition. We conclude that mental health problems between ages 41 and 50 are probably not directly related to the menopausal transition, and that previously reported associations could be false positives due to inadequate dichotomizations, reporting bias, undisclosed multiple adjustments or overfitting.

Key words: Menopause, depression, psychopathology, false positives, neuroticism, psychosocial distress

(World Psychiatry 2016;15:146–154)

The menopausal transition typically begins in the mid-forties and lasts on average up to five years. The mean age at final menstrual period (menopause) in Western countries is approximately 50 years1.

The menopausal transition is a time in a woman’s life that can be marked by various physical and psychological changes2. The fluctuations and decline in levels of ovarian hormones can cause physical symptoms such as hot flushes, night sweats, urogenital atrophy with incontinence, vaginal dryness, sexual dysfunction, osteoporosis, and metabolic changes.

It has been thought that the menopausal transition is also a time of increased risk for mental health problems, especially depression3,4. Although most prospective cohort studies failed to find statistically and practically significant associations between menopausal transitions and mental health problems5-9 (see also Vesco et al10), some recent investigations have suggested that a relationship does exist. These longitudinal studies, all performed in the U.S., have reported that the menopausal transition entails an increased risk not only for depressive symptoms11-13, but also for major depressive disorder14.15. Although the rise in depressive symptoms might seem to be associated with hormonal changes during the menopausal transition, especially the falling and fluctuating levels of estradiol and corresponding increases in levels of follicle-stimulating hormone (FSH) and luteinizing hormone15, some well-conducted longitudinal studies have found no correlation with female sex hormones15,16. Thus, at present, the literature indicates no consistent relationship between circulating estradiol/FSH levels and depression14,17.

An increase in mood symptoms has been partly attributed to the manifold psychosocial changes that often occur in women’s lives during that time span, such as alterations in family structure, losses and role transitions, stressful life events, and a lack of social support6,10,18,19. Furthermore, the relationship between the menopausal transition and depression seems to be strongly influenced by preceding mental disorders5,12,14. This implies that depressive symptoms during the menopausal transition could represent the re-occurrence of pre-existing disorders or reflect a general vulnerability to develop mental health problems during stressful life events1. In this respect, although the personality trait of neuroticism has been repeatedly reported to be a crucial risk factor for mental health problems and psychosocial dysfunction20-22, no study on the psychopathology-menopause association has included that trait thus far.

Most studies conducted to date on this issue have suffered from major limitations. In particular, all the longitudinal studies which reported a significant impact of menopausal transition on depressive symptoms treated depression as a dichotomous outcome (i.e., absent versus present), even though the evidence is compelling that depression23,24, and psychopathology in general25, are continuously distributed in nature. Moreover, many studies focused exclusively on depression, and covered only short intervals (i.e., 5-10 years) that did not allow one to address the question of preceding mental health problems. Furthermore, to the best of our knowledge, no investigation has tested the prospective effect of neuroticism on mental health problems ascribed to the menopausal transition.
We used data from the Zurich study, a longitudinal community study that spanned a 30-year period and included participants beginning at age 20. The following questions were addressed: a) Does the severity of psychopathological syndromes increase during the menopausal transition? b) Is there an increase in prevalence rates of DSM-diagnosed major depressive episode or anxiety disorders? c) If a change in mental health does occur during the menopausal transition, is it related to a pre-existing vulnerability to psychopathology, a personality trait of neuroticism, concurrent psychosocial distress, or advancing age? d) Can treating depression as a dichotomous outcome produce false positive results?

METHODS

Sampling and procedure

The Zurich Study comprised a cohort of 4,547 subjects (2,201 males and 2,346 females) representative of the canton of Zurich in Switzerland, who were screened in 1978 by the Symptom Checklist 90 - Revised (SCL-90-R)26 when they were 19 years old (if males) or 20 years old (if females).

Male and female participants were sampled with different approaches. In Switzerland, every male person must undertake a military screening test at the age of 19. With the consent of military authorities, but independent of their screening procedure, we randomly screened 50% of all male conscripts of the canton of Zurich in this age group. The refusal rate was 0.3%. Female participants were identified from the complete electoral register of the canton of Zurich. Again, 50% of them were randomly selected and received questionnaires by mail; 75% responded.

We selected a sub-sample of 591 subjects for interview, with two-thirds consisting of high scorers (defined by the 85th percentile or more of the global severity index of the SCL-90-R) and one-third consisting of a random sample of those with scores below the 85th percentile. Altogether, seven interview waves were conducted: in 1979 (292 males and 299 females), 1981 (220 males and 236 females), 1986 (225 males and 232 females), 1988 (200 males and 224 females), 1993 (192 males and 215 females), 1999 (162 males and 205 females), and 2008 (144 males and 191 females).

For the present study, we included only women who had participated consistently through 2008 (at age 50) and who were still menstruating in 1999 (at age 41), to exclude cases of premature menopause. This produced a final sample size of 168 subjects.

Instruments and measures

All information about menstruation and menopause was obtained during the interviews in 1999 and 2008, when participants were 41 and 50 years old, respectively. Interviews were conducted according to the Structured Psychopathological Interview and Rating of the Social Consequences of Psychological Disturbances for Epidemiology (SPIKE)27. This semi-structured interview, developed for epidemiological surveys in psychiatric research, assesses data about socio-demography, psychopathology, substance use, medication, health services use, impairment, and social activity. Its reliability and validity have been reported elsewhere28.

Menopause status was comprehensively assessed in the last interview in 2008. We defined as post-menopausal those women whose last menstruation had occurred more than 12 months before. We defined as peri-menopausal those women whose last menstruation had occurred within the past 12 months and who had not menstruated in the preceding two months, and those whose last menstrual cycle had occurred less than one month before and who reported menstrual irregularities. We defined as pre-menopausal those women whose most recent menstruation had occurred within the past month and who had experienced no menstrual irregularities during the past 12 months.

The following symptoms were assessed by the SPIKE during the 2008 interviews, and were included in our analysis: hot flushes and/or night sweats, sleep disturbances, depressed mood, irritability and/or nervousness, anxiety and/or panic, physical and mental tiredness, sexual problems, urinary incontinence, vaginal dryness, and joint pain. Participants rated distress related to each of these symptoms using a five-point Likert scale ranging from 1 ("not at all") to 5 ("extremely").

We also assessed psychopathology through the SCL-90-R, in which distress from each symptom is rated according to a five-point Likert scale ranging from 1 ("not at all") to 5 ("extremely"). We covered the most recent four-week period at each interview. The 90 items of the checklist were grouped into nine subscales (anxiety, depression, hostility, interpersonal sensitivity, obsessive-compulsivity, paranoid ideation, phobic anxiety, psychoticism, and somatization), with the score on each subscale calculated as the average of the scores on the corresponding items (thus ranging from 1 to 5). Psychopathological vulnerability was evaluated using the mean SCL-90-R global severity index of each individual between 1979 and 1999. The SCL-90-R has shown good internal consistency and test-retest reliability29,30.

Personality was assessed by the Freiburg Personality Inventory31 in 1988, when the women were 30 years old. We utilized an empirically derived subscale of neuroticism consisting of 16 items, which has been found to have good validity and reliability32,33.

At each interview, the 12-month prevalence of major depressive episode and anxiety disorders was assessed on the basis of the information provided by the SPIKE. The criteria for major depressive episode, agoraphobia, social phobia, specific phobia and obsessive-compulsive disorder were those of the DSM-III-R, whereas the criteria for generalized anxiety disorder and panic disorder were those of the DSM-III (see Angst et al34 for further information).
The assessment of psychosocial distress was based on participants' perceived discontent, expressed using a five-point Likert scale ranging from 1 (“not at all”) to 5 (“extremely”), with six psychosocial domains: employment, financial situation, friendships, health, partnership, and family. Because the intercorrelation of these six variables was high, we used a single variable obtained by computing the mean score across the six domains.

Statistical analysis

We conducted a series of ordinal logistic regression analyses with the various five-point-scaled menopause symptoms entered separately as the dependent variable and menopause status considered the predictor variable. Estimates of variance explained were reported according to Nagelkerke's pseudo $R^2$.

All other associations were analyzed longitudinally, using variables measured in 1999 (age 41) and 2008 (age 50). For this purpose we used a series of generalized estimating equations. These analyses were introduced to fit regression models that account for within-subject correlations, which is an inherent part of longitudinal studies that rely on repeated measures. Psychopathology and mental disorders were entered as the dependent variable. Owing to the right-skewed distribution of the continuous SCL-90-R psychopathology syndromes, a gamma distribution with a log link-function best fitted our data. Models with dichotomous dependent variables (i.e., diagnoses of major depressive episode and anxiety disorders) were fitted with a binomial distribution and logit link-function. To reduce the effects of influential observations, we used a robust estimator of the parameter estimate covariance matrix.

Menopause status was entered as the predictor variable.

For all generalized estimating equations, in addition to adjusting for within-subject correlations, time was included as a between-subject effect to account for the influence of aging as participants progressed from 41 to 50 years old. This is a common procedure in longitudinal data analysis when outcomes are assumed to increase or decrease over time. Finally, to test for the effects of intervening variables such as psychosocial distress and psychopathological vulnerability, we fitted a series of multiple predictor models in which all interesting predictors were entered simultaneously as main effects. The analyses examining the effect of dichotomization were weighted to compensate for power loss.

All statistical analyses were performed with SPSS version 20 for Macintosh.

RESULTS

Of the 168 women who were still regularly menstruating at age 41 in 1999, 54 (32.1%) were considered in 2008 (at age 50) to be pre-menopausal, 65 (38.7%) peri-menopausal, and 45 (26.8%) post-menopausal. The remaining four women (2.4%) could not be assigned to any of these groups because of missing data.

At age 50, when menopause status was assessed, the 12-month prevalence rates of major depressive episode in pre-, peri-, and post-menopausal women were 18.5%, 13.8%, and 11.1%, respectively, while the 12-month prevalence rates of anxiety disorders were 24.1%, 23.1%, and 22.2%, respectively. The lifetime prevalence rates in pre-, peri-, and post-menopausal women were 53.7%, 55.4%, and 42.2%, respectively, for major depressive episode, and 63.0%, 63.1%, and 60.0%, respectively, for anxiety disorders. None of the differences in prevalence rates across the three groups reached statistical significance according to Pearson $\chi^2$ tests (all $p>0.10$).

Cross-sectional associations between menopause symptoms and menopause status at age 50 are presented in Table 1. The occurrence of hot flushes and/or night sweats was significantly increased in women classified as peri- and post-menopausal (OR=2.79 and OR=3.04, respectively) when compared with pre-menopausal women. Sleep disturbances were also more common in peri- and post-menopausal women (OR=2.26 and OR=2.58, respectively), while irritability and/or nervousness were significantly increased only in pre-
menopausal women (OR=2.34). Vaginal dryness was significantly increased only in post-menopausal women (OR=2.86). Estimates of explained variance in these outcomes ranged from 3.9% for vaginal dryness to 6.7% for hot flushes/night sweats (corresponding to small-to-medium effect sizes). Neither depressed mood nor anxiety/panic (both $R^2=0.005$) was related to menopause status.

When neuroticism was added to the analysis, the transition to peri-menopause was no longer related to irritability and/or nervousness, while neuroticism was (for one standard deviation increase in neuroticism: OR=1.67, 95% CI: 1.16-2.39, $p=0.006$). Thus, neuroticism as assessed at age 30 fully explained the association between the transition to peri-menopause and irritability and/or nervousness at age 50. In contrast to menopause status, neuroticism at age 30 also strongly predicted the occurrence of depressed mood (OR=1.94, 95% CI: 1.33-2.82, $p=0.001$) and anxiety/panic (OR=1.81, 95% CI: 1.15-2.83, $p=0.010$) at age 50.

Longitudinal associations between menopause status and the prevalence of mental disorders between ages 41 and 50 are shown in Table 2. No association reached statistical significance. In other terms, increases or decreases in prevalence rates of major depressive episode or anxiety disorders between 41 and 50 did not differ between women who remained pre-menopausal over time and those who transitioned from pre- to peri- or from pre- to post-menopause. That null association held when adjusting for preceding psychopathological vulnerability, duration of reproductive period, or age at menopause. In contrast, sensitivity analyses revealed that the personality trait of neuroticism as assessed at age 30 significantly predicted increases in the prevalence of major depressive episode (OR=1.37, $p=0.045$) and anxiety disorders (OR=1.93, $p<0.001$).

Longitudinal associations between menopause status and psychopathological syndromes are outlined in Table 3. No syndrome score increased or decreased significantly over time in relation to menopause status. These null findings were not merely due to a lack of statistical power, because the effect sizes were also practically insignificant (all $d<0.2$). The null associations held after adjusting for duration of reproductive period or age at menopause.

Longitudinal associations among menopause status, important covariates and course of psychopathology over time as participants aged from 41 to 50 years are shown in Table 4. Again, changes in menopause status were not related to the course of psychopathology. In contrast, preceding psychopathological vulnerability, i.e. the severity of preceding psychopathological syndromes between ages 21 and 41, was significantly associated with all syndromes. When neuroticism as assessed at age 30 was included in the analysis, it similarly accounted for significant increases in all psychopathological syndromes between 41 and 50 years (all $p<0.001$). Concurrent

### Table 2: Longitudinal associations between menopause status and change in prevalence rates of DSM-III-R/DSM-III mental disorders over time as participants aged from 41 to 50

<table>
<thead>
<tr>
<th>Menopause status</th>
<th>1999</th>
<th>2008</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major depression episode</td>
<td>Pre</td>
<td>Pre</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>Peri</td>
<td>0.71 (0.34, 1.51)</td>
<td>0.375</td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>0.57 (0.24, 1.37)</td>
<td>0.209</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>Pre</td>
<td>Pre</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>Peri</td>
<td>1.10 (0.55, 2.20)</td>
<td>0.788</td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>0.92 (0.43, 1.97)</td>
<td>0.824</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Menopause status</th>
<th>1999</th>
<th>2008</th>
<th>b (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>Pre</td>
<td>Pre</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>Peri</td>
<td>0.027 (−0.157, 0.210)</td>
<td>0.774</td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>−0.091 (−0.283, 0.101)</td>
<td>0.352</td>
</tr>
<tr>
<td>Depression</td>
<td>Pre</td>
<td>Pre</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>Peri</td>
<td>0.090 (−0.131, 0.311)</td>
<td>0.426</td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>0.000 (−0.220, 0.220)</td>
<td>0.998</td>
</tr>
<tr>
<td>Hostility</td>
<td>Pre</td>
<td>Pre</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>Peri</td>
<td>0.052 (−0.086, 0.191)</td>
<td>0.460</td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>−0.071 (−0.187, 0.045)</td>
<td>0.228</td>
</tr>
<tr>
<td>Interpersonal sensitivity</td>
<td>Pre</td>
<td>Pre</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>Peri</td>
<td>0.051 (−0.146, 0.248)</td>
<td>0.612</td>
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<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>−0.003 (−0.226, 0.221)</td>
<td>0.982</td>
</tr>
<tr>
<td>Obsessive-compulsivity</td>
<td>Pre</td>
<td>Pre</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>Peri</td>
<td>0.029 (−0.182, 0.240)</td>
<td>0.789</td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>−0.045 (−0.271, 0.182)</td>
<td>0.700</td>
</tr>
<tr>
<td>Paranoid ideation</td>
<td>Pre</td>
<td>Pre</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>Peri</td>
<td>−0.005 (−0.199, 0.189)</td>
<td>0.958</td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>−0.063 (−0.268, 0.141)</td>
<td>0.543</td>
</tr>
<tr>
<td>Phobic anxiety</td>
<td>Pre</td>
<td>Pre</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>Peri</td>
<td>0.026 (−0.085, 0.137)</td>
<td>0.644</td>
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<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>−0.005 (−0.139, 0.128)</td>
<td>0.937</td>
</tr>
<tr>
<td>Psychoticism</td>
<td>Pre</td>
<td>Pre</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>Peri</td>
<td>−0.009 (−0.140, 0.121)</td>
<td>0.887</td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>−0.031 (−0.163, 0.102)</td>
<td>0.651</td>
</tr>
<tr>
<td>Somatization</td>
<td>Pre</td>
<td>Pre</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>Peri</td>
<td>0.066 (−0.084, 0.217)</td>
<td>0.388</td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>−0.066 (−0.253, 0.120)</td>
<td>0.486</td>
</tr>
</tbody>
</table>

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psychosocial distress was also related to the course of all syndromes over time, except for phobic anxiety. The progression in age was significantly associated with the course of hostility, interpersonal sensitivity, and paranoid ideation.

Table 5 shows how selection of particular cut-off scores for dichotomous depression could influence the odds ratios. Relative to pre-menopause, we found a significant effect of transition to peri-menopause ($OR = 1.57$, $p = 0.033$) only when the SCL-90-R depression cut-off was set at $\geq 2.0$. For all other cut-off points (i.e., $\geq 1.5$, $\geq 2.5$, and $\geq 3.0$), no statistically significant positive association with transition to peri-menopause was detected. Actually, when the cut-off was set at $\geq 3.0$, the odds

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Wald $\chi^2$ (df)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopause status (41-50)</td>
<td>0.185 (2)</td>
<td>0.912</td>
</tr>
<tr>
<td>Psychopathological vulnerability (21-41)</td>
<td>71.854 (1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Psychosocial distress (41-50)</td>
<td>8.956 (1)</td>
<td>0.003</td>
</tr>
<tr>
<td>Effects of aging (41-50)</td>
<td>0.023 (1)</td>
<td>0.880</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopause status (41-50)</td>
<td>1.648 (2)</td>
<td>0.439</td>
</tr>
<tr>
<td>Psychopathological vulnerability (21-41)</td>
<td>52.741 (1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Psychosocial distress (41-50)</td>
<td>46.843 (1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Effects of aging (41-50)</td>
<td>1.784 (1)</td>
<td>0.182</td>
</tr>
<tr>
<td>Hostility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopause status (41-50)</td>
<td>1.137 (2)</td>
<td>0.566</td>
</tr>
<tr>
<td>Psychopathological vulnerability (21-41)</td>
<td>30.656 (1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Psychosocial distress (41-50)</td>
<td>12.277 (1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Effects of aging (41-50)</td>
<td>6.120 (1)</td>
<td>0.013</td>
</tr>
<tr>
<td>Interpersonal sensitivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopause status (41-50)</td>
<td>0.351 (2)</td>
<td>0.839</td>
</tr>
<tr>
<td>Psychopathological vulnerability (21-41)</td>
<td>72.042 (1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Psychosocial distress (41-50)</td>
<td>24.688 (1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Effects of aging (41-50)</td>
<td>13.010 (1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obsessive-compulsivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopause status (41-50)</td>
<td>0.064 (2)</td>
<td>0.968</td>
</tr>
<tr>
<td>Psychopathological vulnerability (21-41)</td>
<td>90.216 (1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Psychosocial distress (41-50)</td>
<td>12.735 (1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Effects of aging (41-50)</td>
<td>0.055 (1)</td>
<td>0.814</td>
</tr>
<tr>
<td>Paranoid ideation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopause status (41-50)</td>
<td>1.072 (2)</td>
<td>0.585</td>
</tr>
<tr>
<td>Psychopathological vulnerability (21-41)</td>
<td>61.703 (1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Psychosocial distress (41-50)</td>
<td>10.777 (1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Effects of aging (41-50)</td>
<td>4.300 (1)</td>
<td>0.038</td>
</tr>
<tr>
<td>Phobic anxiety</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopause status (41-50)</td>
<td>0.017 (2)</td>
<td>0.992</td>
</tr>
<tr>
<td>Psychopathological vulnerability (21-41)</td>
<td>77.636 (1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Psychosocial distress (41-50)</td>
<td>3.205 (1)</td>
<td>0.073</td>
</tr>
<tr>
<td>Effects of aging (41-50)</td>
<td>0.027 (1)</td>
<td>0.869</td>
</tr>
<tr>
<td>Psychoticism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopause status (41-50)</td>
<td>1.299 (2)</td>
<td>0.522</td>
</tr>
<tr>
<td>Psychopathological vulnerability (21-41)</td>
<td>40.104 (1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Psychosocial distress (41-50)</td>
<td>14.828 (1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Effects of aging (41-50)</td>
<td>1.113 (1)</td>
<td>0.292</td>
</tr>
<tr>
<td>Somatization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopause status (41-50)</td>
<td>2.044 (2)</td>
<td>0.360</td>
</tr>
<tr>
<td>Psychopathological vulnerability (21-41)</td>
<td>22.973 (1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Psychosocial distress (41-50)</td>
<td>14.773 (1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Effects of aging (41-50)</td>
<td>2.704 (1)</td>
<td>0.100</td>
</tr>
</tbody>
</table>

SCL-90-R – Symptom Checklist 90 - Revised
ratio was negative for the transition to post-menopause when compared with the pre-menopause phase (OR=0.29, p=0.032), indicating that those who became post-menopausal had a lower risk for depression. As indicated above, when depression was modelled as a continuous variable, no differences were found (p=0.255). Moreover, all mean differences among menopause phases were practically insignificant (all d<0.1), indicating that a lack of statistical significance was not merely a result of insufficient power, but rather a clear null result of no practical significance37.

**DISCUSSION**

This is the first prospective community study spanning 30 years and focusing on a broad range of psychopathological, psychosocial and physical problems putatively associated with the menopausal transition.

At age 50, hot flushes/night sweats and sleep disturbances were more common in peri- and post-menopausal women than in pre-menopausal ones, whereas irritability and/or nervousness were heightened only in peri-menopausal women. However, the association between irritability/nervousness and peri-menopause was fully explained by neuroticism at age 30, suggesting that the symptom was triggered by that personality vulnerability.

Our longitudinal analyses further revealed that changes in menopause status were not related to either the course of psychopathological syndromes or the prevalence of major depressive episode or anxiety disorders between ages 41 and 50. However, the course of psychopathological syndromes was related to psychopathological vulnerability prior to age 41 as well as to concurrent psychosocial problems. This finding emphasizes the importance of adjusting for these covariates when studying the effect of menopause on mental health. Notably, when neuroticism as assessed at age 30 was included in the analysis, it also significantly predicted increased psychopathology between ages 41 and 50. This result suggests that neuroticism is a reliable marker of persistent vulnerability to psychopathology22,38 and is in line with emergent evidence that neuroticism has a substantial genetic overlap with depression, internalizing disorders, and even general psychopathology39-41.

Some recent longitudinal studies have reported that the occurrence of depression is associated with the transition from pre- to peri-menopause11,13,15,42. Two studies have also identified more symptoms in the post- versus pre-menopausal phase11,14. On the other hand, several other longitudinal studies have found no statistically and practically significant increase in mental health symptoms in relation to the menopausal transition5-9,43,44. Methodological factors probably best explain these discrepancies across studies.

First, and most importantly, all recent longitudinal studies that have described positive associations between depression and menopause status used dichotomous or dichotomized outcomes, that is, depressed versus not depressed12,15,42. When psychopathology is reduced to present versus absent, one cannot account for increases or decreases in symptom

### Table 5 Effect of dichotomization and choice of arbitrary cut-offs for SCL-90-R depression, adjusted for preceding psychopathological vulnerability

<table>
<thead>
<tr>
<th>Cut-off on a scale from 1.0 to 5.0</th>
<th>Menopausal status</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression ≥ 1.5</td>
<td>Post-menopausal</td>
<td>0.85</td>
<td>0.60, 1.22</td>
<td>0.382</td>
</tr>
<tr>
<td></td>
<td>Peri-menopausal</td>
<td>1.05</td>
<td>0.74, 1.50</td>
<td>0.770</td>
</tr>
<tr>
<td></td>
<td>Pre-menopausal</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression ≥ 2.0</td>
<td>Post-menopausal</td>
<td>1.54</td>
<td>0.94, 2.54</td>
<td>0.089</td>
</tr>
<tr>
<td></td>
<td>Peri-menopausal</td>
<td>1.57</td>
<td>1.04, 2.38</td>
<td>0.033</td>
</tr>
<tr>
<td></td>
<td>Pre-menopausal</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression ≥ 2.5</td>
<td>Post-menopausal</td>
<td>1.11</td>
<td>0.58, 2.10</td>
<td>0.754</td>
</tr>
<tr>
<td></td>
<td>Peri-menopausal</td>
<td>1.29</td>
<td>0.78, 2.12</td>
<td>0.319</td>
</tr>
<tr>
<td></td>
<td>Pre-menopausal</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression ≥ 3.0</td>
<td>Post-menopausal</td>
<td>0.29</td>
<td>0.10, 0.90</td>
<td>0.032</td>
</tr>
<tr>
<td></td>
<td>Peri-menopausal</td>
<td>0.79</td>
<td>0.43, 1.46</td>
<td>0.452</td>
</tr>
<tr>
<td></td>
<td>Pre-menopausal</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Continuously</th>
<th>Menopausal status</th>
<th>Mean score</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression scale from 1.0 to 5.0</td>
<td>Post-menopausal</td>
<td>1.78</td>
<td>1.67, 1.89</td>
<td>0.255</td>
</tr>
<tr>
<td></td>
<td>Peri-menopausal</td>
<td>1.81</td>
<td>1.70, 1.91</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre-menopausal</td>
<td>1.74</td>
<td>1.64, 1.86</td>
<td></td>
</tr>
</tbody>
</table>
severity over time. Furthermore, because psychopathology is dimensional by nature, treating it categorically produces a severe bias both on methodological and conceptual grounds. As demonstrated by our data, dichotomizing continuous variables can produce severe flaws and should therefore be avoided. Most researchers and clinicians are probably not aware that, when dichotomization occurs at the low end of an underlying continuous construct (which is typically the case when continuous screening instruments are dichotomized), the resulting odds ratios can be severely inflated.

Another important limitation of some previous studies is that they inferred the first onset of binary depression from a single retrospective assessment of history of lifetime depression. Since it is now well established that retrospective lifetime assessments grossly underestimate the true lifetime prevalence of mental disorders, we suggest that this estimation of “first onset” may be biased, and that many women classified as having no history of depression at the outset of the study were already in fact experienced unrealled or denied depressive episodes (see also Andrews et al).

Further biases were apparently involved in previous studies. For example, Freeman et al reported that the transition to peri-menopause was positively related to dichotomized scores on the Center for Epidemiologic Studies Depression Scale (CES-D) (OR=2.89, p=0.01), but by tendency negatively related to the diagnosis of major depression (OR=0.24, p=0.21). This is surprising, because high CES-D scores should indicate probable major depression diagnoses. Moreover, in their bivariate analysis, early (OR=1.33, p=0.10) and late (OR=1.79, p=0.10) perimenopausal transitions were not significantly related to depression. Instead, after multiple adjustments and probable overfitting of their regression analyses, they achieved the significance level of p<0.05 for both early (OR=1.55, p=0.03) and late transitions (OR= 2.89, p=0.01). On the other hand, in their re-analysis of data restricted to women with no history of depression, these authors referred to the unadjusted bivariate analysis (OR= 2.50, p=0.01), omitting to discuss that the adjusted multivariate analysis would have produced no significant result for a diagnosis of major depression (OR=1.60, p=0.34). Similarly, Cohen et al stated that the menopausal transition significantly increased the risk for dichotomized depression only after they adjusted for age at study entry and adverse life events, but did not show unadjusted associations in their report.

Moreover, studies reporting positive findings should also provide compelling evidence for their practical significance. With large samples (e.g., N>400), statistical significance may easily be achieved even for trivial effects. One example of a small effect size that yielded statistical significance in a very large sample (N=67,434) can be found in a recent meta-analysis which reported a protective effect of later age at menopause with regard to depression, attributed to longer exposure to endogenous estrogens. In this meta-analysis, the odds ratio for a two-year increment was only 0.98 (95% CI: 0.96-0.99), which is a difference in the odds of only 2%. This effect size is practically irrelevant, and its statistical significance is likely to be merely a result of the huge sample size.

Several authors have postulated that a lifetime history of depression is the strongest predictor of depression during the menopausal transition. Our results suggest that, while a preceding psychopathological vulnerability as expressed through high scores on neuroticism is an important predictor of psychopathology between ages 41 and 50, menopausal stages per se are not. Persons who score high on neuroticism are more susceptible to the negative effects of daily stress and critical life events. Consequently, if negative affective symptoms occur during the menopausal transition, they might reflect the difficulties that vulnerable women have in coping with and adapting to the developmental changes that accompany this transition. Accordingly, it has been argued that psychopathological symptoms during menopause might be triggered by psychosocial strains such as stressful life events rather than by hormonal changes. Our data support this notion, revealing that concurrent psychosocial distress from ages 41 to 50 is strongly related to higher psychopathology during this time period, regardless of menopausal stage or preceding psychopathological vulnerability.

We recognize some limitations of our study. First, our sample size was initially moderate and was then further reduced through attrition. Second, the Zurich study was not designed specifically to examine the menopausal transition in women. Thus, we could not provide a fine-grained assessment of that transition. Furthermore, the information on psychopathological or psychosocial outcomes that was applied in the present study relied on measurements made in 1999 and 2008. The time gap between those interviews was wide and menopause status was evaluated only twice. Third, no hormonal assessments were made.

Nevertheless, in line with three comprehensive reviews, our data indicate that mental health problems between ages 41 and 50 are not directly related to the menopausal transition. All the longitudinal studies that did find associations between psychopathology and the menopausal transition used binary or dichotomized outcomes, which is problematic from a methodological and conceptual point of view. As demonstrated by our data, a dichotomization of continuous variables may produce spurious positive or negative associations.

We suggest that the relationship between psychopathology and menopause should be reconsidered carefully. Future research should incorporate not only previous history of mental disorders and current stressors, but also the personality trait of neuroticism, because this trait is likely to influence the risk of psychopathological symptoms occurring during the age of the menopausal transition.

ACKNOWLEDGEMENT

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REFERENCES

3. Freeman EW. Associations of depression with the transition to menopause. Menopause 2010;17:823-7.
menopause: a systematic review and meta-analysis. JAMA Psychiatry 2016;73:139-49.


57. Hengartner MP, Van der Linden D, Bohleber L et al. Big Five personality traits and the General Factor of Personality as moderators of stress and coping reactions following an emergency alarm on a Swiss university campus. Stress Health (in press).


60. Judd FK, Hickey M, Bryant C. Depression and midlife: are we overpathologising the menopause? J Affect Disord 2012;136:199-211.

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The CHANGE trial: no superiority of lifestyle coaching plus care coordination plus treatment as usual compared to treatment as usual alone in reducing risk of cardiovascular disease in adults with schizophrenia spectrum disorders and abdominal obesity

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Life expectancy in patients with schizophrenia is reduced by 20 years for men and 15 years for women compared to the general population. About 60% of the excess mortality is due to physical illnesses, with cardiovascular disease being dominant. CHANGE was a randomized, parallel-group, superiority, multi-centre trial with blinded outcome assessment, testing the efficacy of an intervention aimed to improve cardiovascular risk profile and hereby potentially reduce mortality. A total of 428 patients with schizophrenia spectrum disorders and abdominal obesity were recruited and centrally randomized 1:1:1 to 12 months of lifestyle coaching plus care coordination plus treatment as usual (N=138), or care coordination plus treatment as usual (N=142), or treatment as usual alone (N=148). The primary outcome was 10-year risk of cardiovascular disease assessed post-treatment and standardized to age 60. At follow-up, the mean 10-year risk of cardiovascular disease was 8.4 ± 6.7% in the group receiving lifestyle coaching, 8.5 ± 7.5% in the care coordination group, and 8.0 ± 6.5% in the treatment as usual group (p=0.41). We found no intervention effects for any secondary or exploratory outcomes, including cardiorespiratory fitness, physical activity, weight, diet and smoking. In conclusion, the CHANGE trial did not support superiority of individual lifestyle coaching or care coordination compared to treatment as usual in reducing cardiovascular risk in patients with schizophrenia spectrum disorders and abdominal obesity.

Key words: Schizophrenia, abdominal obesity, CHANGE trial, lifestyle coaching, care coordination, cardiovascular risk, cardiorespiratory fitness, physical activity

(WORLD Psychiatry 2016;15:155–165)

The gap in life expectancy between patients with schizophrenia and the general population – twenty years shorter for men and fifteen years shorter for women1,2 – is a major challenge to public health. About 60% of the premature mortality in schizophrenia is due to physical diseases3, with cardiovascular disease explaining the majority4.

Several factors contribute to the early and frequent development of cardiovascular disease in this population, including genetic vulnerability5, metabolic adverse effects of antipsychotics6,7, insufficient treatment of somatic comorbidity8, and unhealthy lifestyle9. Of these risk factors, medication with antipsychotic drugs can be considered partly modifiable, as reducing doses or switching prescriptions only leads to moderate improvement of metabolic risk factors10,11. Insufficient treatment of somatic comorbidity and unhealthy lifestyle are potentially fully modifiable and, if they are properly targeted, life expectancy for patients with schizophrenia might improve.

Several clinical trials12-14 have reported an effect of lifestyle modification in this population, indicating that weight reduction and smoking cessation are possible. However, there are still gaps in the current knowledge. Selecting the optimal outcome for trials aiming to reduce cardiovascular risk remains a challenge: weight reduction or weight gain prevention is the most used outcome, but the correlation between weight loss and mortality remains questionable15. To overcome this, composite surrogate outcomes assessing the risk of cardiovascular disease have been proposed16. Moreover, since the pathogenesis of cardiovascular disease is multifactorial, strategies to reduce multiple, concurrent risk behaviours are needed17. Interventions with long-term follow-up are also warranted, since there are no reasons to believe that changes in metabolic risk factors occur faster in patients with severe mental disorders than the general population18. Equally important are follow-ups after the intervention has ended, as the effect of lifestyle modification tends to vanish, and an intentional weight loss may be followed by an unhealthy weight gain in the majority of participants in behavioural trials19. Finally, it is crucial to evaluate the external validity of trials, which might be compromised by the recruitment of patients with a higher readiness to change and a lower degree of barriers to lifestyle modifications – such as cognitive impairment, anxiety or substance abuse – than the clinical population with severe mental illness as a whole. This can be minimized by pragmatic designs, with few exclusion criteria20.

The CHANGE trial was designed to address the above-mentioned gaps. We conducted a randomized, pragmatic trial exploring if 12-month lifestyle coaching plus care coordination plus treatment as usual, compared to care coordination plus treatment as usual and to treatment as usual alone, could reduce the 10-year risk of cardiovascular disease in patients with schizophrenia spectrum disorders and abdominal obesity.
METHODS

Study design and participants

CHANGE was an investigator-initiated, independently funded, randomized, parallel-group, superiority, multi-centre trial with blinded outcome assessment. Patients were recruited from well-defined catchment areas in two major Danish cities (Aarhus and Copenhagen). The trial protocol was published in 2015 with no changes made to the original version21.

Patients were eligible if aged 18 or older, receiving a diagnosis of schizophrenia (F20), schizoaffective disorder (F25) or persistent delusional disorder (F22) according to ICD-10 – as ascertained by the Schedules for Clinical Assessment in Neuropsychiatry (SCAN)22 – and having a waist circumference (measured between the iliac crest and the lowest rib) above 88 cm for women and 102 cm for men23.

Eligible patients were verbally informed by the usual carer and, if accepting, referred to CHANGE research staff by phone or e-mail. An initial meeting was arranged at the research centre, the outpatient clinic, or patient’s home. Verbal and written information on the trial was provided to all patients. Patients reporting current pregnancy or unable to provide informed consent were excluded. If the patient accepted participation in the trial, an informed consent form was signed and an appointment for collection of baseline data was made.

The Danish Ethical Committee (H-4-2012-051) and the Danish Data Protection Agency (referral number 01689 RHP-2012-007) approved the trial.

Recruited patients were randomized with a 1:1:1 ratio to lifestyle coaching plus care coordination plus treatment as usual (CHANGE intervention), or care coordination plus treatment as usual, or treatment as usual alone. Randomization was stratified according to site (Copenhagen/Aarhus), gender, and a baseline high/low risk of cardiovascular disease. High risk was defined according to cut-off points from a Danish population study24, using the Copenhagen risk score16 with age standardized to 60 years.

The randomization was centralized and carried out by the Copenhagen Trial Unit using a computerized sequence with alternating block sizes (9, 12 and 15) unknown to the investigators. After the inclusion of a patient in the trial, one of the lifestyle coaches (see below) contacted the Copenhagen Trial Unit with a unique patient identifier plus stratification variables and in return received the patient allocation. Outcome assessors, statisticians and all investigators involved in the trial were blinded to patient allocation, but patients and the health professionals providing the interventions were not.

Interventions

Lifestyle coaching

Lifestyle coaching was defined as affiliation to a CHANGE team member, offering a tailored, manual-based intervention targeting physical inactivity, unhealthy dietary habits and smoking, and facilitating contact to the patient’s general practitioner to secure medical treatment of somatic comorbidities. The theoretical framework of the lifestyle coaching was based on the theory of stages of change25, motivational interviewing26 and an assertive approach adapted from the assertive community treatment27. Motivational interviewing is a method to help patients elicit their own wishes to change; the assertive approach allows the staff to be respectfully active and persistent in follow-up, and implement short message services, phone calls, home visits and meetings in the local area. These methods were incorporated into four manuals with detailed descriptions of the interventions addressing four tracks: care coordination, smoking cessation, healthy diet, and physical activity. Manuals are provided in the paper describing the trial protocol21.

The coach offered home visits with systematic exploration of possibilities for physical activity in daily life, which were realistic and attractive to the patient. Dietary changes involved concrete examination of the patient’s dietary habits, food purchases and cooking practices, and identification of economically realistic, easy and attractive possibilities for change. During home visits, the coach took part in the activities (e.g., physical activity or food purchases), if requested by the patient, to support lifestyle changes. Personal and professional networks were included if possible in individual plans. The smoking cessation program was adapted from that published by the Danish Cancer Society28, and tailored to each patient in order to elicit and enhance motivation and maintain smoking cessation.

The patients were offered affiliation with the team member for one year, with at least one weekly personal meeting of variable duration, often one hour. Further support could be provided by text messages, phone calls and e-mail messages. The coach to participant ratio was 1:15.

Each participant was encouraged to choose if focus should be on one or more of the four possible tracks, and the lifestyle coach supported the patient in setting individual goals. The staff had access to baseline results regarding cardiorespiratory fitness, forced expiratory volume, anthropometric measures and metabolic variables, and used these in their first consultation with each patient to plan the further course.

The lifestyle coaches performed written registration of all contacts with patients including cancellations. All coaching sessions were classified, according to the focus area of each consultation, into care coordination, smoking cessation, healthy diet or physical activity.

Lifestyle coaches were health professionals (occupational therapists, physiotherapists or dieticians) with clinical experience in psychiatry. They received a 5-day course in motivational interviewing, a 5-day course in smoking cessation, a 1-day course in examination and treatment of lifestyle disorders, and a 2-day course in healthy dieting, all based on the Danish Health Authority guidelines. During the trial, lifestyle coaches had weekly sessions with supervision to ensure program fidelity. In addition to the intervention described above,
the patients in the CHANGE group were offered care coordination (see below) and continued treatment as usual.

**Care coordination**

Care coordination was incorporated in the CHANGE group and implemented as add-on to treatment as usual in the care coordination group. The intervention was manual-based. The care coordinator, a trained psychiatric nurse, facilitated contact to primary care in order to ensure that the patients received optimal treatment of physical health problems. Each care coordinator had 30–40 participants assigned at a time. Affiliation to the care coordinator was offered for one year.

The care coordinators’ contact with patients comprised personal meetings, phone calls and text messages. The frequency of contact was adjusted according to the individual need. The first meeting with the patient consisted of a general health talk about physical well-being and an evaluation of test results from the physical examination performed at baseline. Special attention was paid to symptoms of obstructive pulmonary disease, diabetes and cardiovascular disease. The care coordinator used a decision tree to plan the further course. In addition to the care coordination described above, the patients in this group continued treatment as usual.

**Treatment as usual**

All three groups of patients received treatment as usual for obese patients with schizophrenia. In Denmark all persons have a general practitioner and can consult her/him for free when needed. Patients in secondary mental health services stay affiliated with their general practitioner, who is responsible for treating abnormal results from the mandatory yearly screening of metabolic risk factors. No formalized extra effort was made regarding lifestyle counselling or treatment of physical disorders in the treatment as usual group. Results from the baseline assessment were available if requested by the patient or the usual carer and, if any of the results was a matter of urgent consideration, the CHANGE research team contacted staff at the psychiatric outpatient clinic.

**Outcome assessments**

The primary outcome was the 10-year risk of cardiovascular disease, evaluated post-treatment and standardized to age 60 years. We used the Copenhagen risk score, which is based on data from two large epidemiological studies in the Copenhagen area\(^1\), and is recommended by the European Society of Cardiology for screening of cardiovascular risk\(^2\). This composite measure incorporates non-modifiable and modifiable factors. The non-modifiable factors include: gender, family history of cardiovascular disease (defined as parents suffering from a fatal or non-fatal cardiovascular event before the age of 55 years for fathers or 60 years for mothers), and prior heart disease (defined as myocardial infarction or verified atherosclerosis of coronary arteries). The modifiable factors include: smoking (defined as daily smoking, yes/no), diabetes mellitus (defined as either haemoglobin A1c >48 mmol/mol or receiving antiglycaemic drugs due to earlier confirmed diagnosis, yes/no), total cholesterol, high density lipoprotein (HDL) cholesterol, systolic blood pressure, and body mass index. Absolute risk was defined as the probability of a clinical event (ischaemic heart disease, myocardial infarction, stroke or death) happening to a person within 10 years. We calculated the risk for each patient, independent of age, as if age was 60, an approach recommended by the European Guidelines on Cardiovascular Disease Prevention in Clinical Practice\(^3\) to assess risk in young individuals.

The key secondary outcome was cardiorespiratory fitness (the patient’s maximal oxygen uptake was measured using a bicycle cardiopulmonary exercise test). Further secondary outcomes included: forced expiratory volume (measured with Easy-one\(^4\) spirometer), waist circumference, systolic blood pressure (average of three values measured on the right upper arm in a sitting position after 10 minutes of rest, and before the bicycle test), resting heart rate, haemoglobin A1c, HDL and non-HDL cholesterol, and self-reported moderate and vigorous physical activity (using the Physical Activity Scale\(^5\)).

The exploratory outcomes included: weight, body mass index, triglycerides, high sensitivity C-reactive protein, self-reported time spent sedentary\(^6\), daily smoking (using the Fagerström Test for Nicotine Dependence\(^7\)), diet (using the Dietary Quality Score\(^8\)), positive and negative symptoms (assessed using the Scale for the Assessment of Positive Symptoms\(^9\) and the Scale for the Assessment of Negative Symptoms\(^10\)), cognition (assessed by the Brief Assessment of Cognition in Schizophrenia\(^11\)), quality of life (evaluated by the Manchester Short Assessment of Quality of Life\(^12\) and the EuroQOL Five Dimensions Questionnaire\(^13\)), psychosocial functioning (explored by the Global Assessment of Functioning\(^14\)), perceived health\(^15\), and perceived stress\(^16\).

**Statistical analysis**

We expected the experimental interventions to reduce the Copenhagen risk score by 2.5% in the CHANGE group compared with the care coordination group, and by 2.5% in the care coordination group compared with the treatment as usual group. As we planned to compare all three groups, we reduced our alpha level to 0.05/3 = 0.0167. Allowing a power of 90%, we estimated to recruit 150 participants to each intervention group, a total of 450 participants. This calculation was based on a standard deviation of 5.9% of the Copenhagen risk score as found in the Inter99-trial\(^17\).

The primary outcome analysis was an intention-to-treat one. Multiple imputation was used to handle missing data. The imputations were based on a linear regression model with 100 imputations and 20 iterations. As predictors in the imputation
model, we selected variables from a predefined list (age, gender, Global Assessment of Functioning score, duration of illness, daily dose of antipsychotic medication in chlorpromazine equivalents, and research centre) if they were significant predictors of the outcome variable or predictors of dropout \( (p < 0.05 \) in a univariable model). These variables were, together with the baseline value of the variable and the randomization group, used as predictors for all imputations, if they had less than 5% missing values. Predictor variables with missing values were then simultaneously imputed along with the outcome variables. For the primary outcome, the composite values were imputed.

Analysis of covariance (ANCOVA) was used to calculate any significant differences between the three intervention groups, using the baseline value of each measure and the three stratification variables (gender, research centre and baseline risk of cardiovascular disease) as covariates. All distributions were assessed for normality using visual inspection of histograms and Q-Q plots. If not normally distributed, variables were log transformed, and if unsuccessful, a non-parametric test was used. For dichotomous outcomes, we performed multiple logistic regressions with treatment as usual as reference and stratification variables as covariates after having imputed missing values using a logistic regression model.

All tests were two-tailed. For the primary outcome, the \( p \) values were Bonferroni-adjusted (alpha level \( = 0.05/3 = 0.0167 \)). We had several secondary and exploratory outcomes, and further Bonferroni correction would have been too conservative, as this approach demands an assumption of independency between outcomes, which was not reasonable in our study. Therefore, \( p \) values for secondary and exploratory outcomes are presented unadjusted, and interpreted as follows: no effect of the experimental intervention if \( p \geq 0.05 \); a possible positive effect if \( p < 0.05 \) but \( > 0.001 \); a strong indication of a positive effect if \( p < 0.001 \).

Sensitivity analyses included an analysis of complete cases, removal of outliers (defined as standardized residuals greater than three standard deviations), a per-protocol analysis defining participants not having a single contact as violating the protocol, and a second per-protocol analysis including participants with at least 50% of intended personal meetings in the CHANGE group. This second per-protocol analysis is likely to cause severe selection bias, as the CHANGE group would include the participants with the highest level of motivation.

Figure 1 Flow diagram showing the process of recruiting and follow-up
Therefore, it was only considered meaningful to report negative results from this analysis.

**RESULTS**

Figure 1 illustrates the flow of patients through the trial. Between December 2012 and May 2014, 428 participants were assigned to receive the CHANGE intervention (N = 138), or care coordination plus treatment as usual (N = 142), or treatment as usual alone (N = 148). According to the protocol, we ought to include 450 participants, but had to stop before, due to lack of referrals.

Retention proportion was 86.0% for the sample as a whole. There was no difference in the dropout rates among the three groups (p = 0.68). 365 participants (85.3%) provided information enabling a calculation of the primary outcome at follow-up. The dropouts did not differ from completers regarding baseline metabolic or psychometric characteristics or pattern of medication, except for a smaller proportion of the former receiving antidepressant treatment (30.0% vs. 46.0%).

Table 1 shows the baseline socio-demographic and clinical characteristics of the patients. We included slightly more women, and the average age was 38.6 ± 12.4 years. Most patients were diagnosed with schizophrenia (88.0%). The majority were unemployed (92.0%), and a small proportion...
lived in supported housings (13.8%). There were 52.1% daily smokers and 15.0% had a diagnosis of diabetes. There were no differences between the intervention groups, apart from a higher proportion of participants living in supported housings (16.9% vs. 8.7%) and a smaller proportion having diabetes (9.5% vs. 18.6%) in the treatment as usual group compared with the CHANGE group.

In the CHANGE group, the mean number of personal meetings was 24.6 ± 14.5; 60.0% of the participants attended 21 or more of the intended 42 personal meetings; 97.8% had at least one personal meeting with their coach. The 73 daily smokers allocated to the CHANGE group received a mean of 11.2 ± 9.3 sessions focusing on smoking cessation. For the group as a whole, there was a mean of 19.5 ± 13.1 meetings focused on physical activity, 6.3 ± 6.6 on care coordination and 15.8 ± 11.2 on healthy dieting.

Results for primary and secondary outcomes are shown in Table 2. The mean age-standardized 10-year risk of

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<tr>
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<th>CHANGE</th>
<th>CARE</th>
<th>TAU</th>
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</tr>
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<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
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<tr>
<td>10-year risk of CVD (%)</td>
<td>8.4 ± 6.7</td>
<td>8.5 ± 7.5</td>
<td>8.0 ± 6.5</td>
<td>1.04</td>
<td>0.41</td>
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<td>8.3 ± 0.3</td>
<td>8.6 ± 0.3</td>
<td>8.1 ± 0.3</td>
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<tr>
<td><strong>Secondary outcomes</strong></td>
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<tr>
<td>Cardiorespiratory fitness (ml O2/min/Kg)</td>
<td>18.1 ± 5.5</td>
<td>18.0 ± 6.8</td>
<td>18.2 ± 6.7</td>
<td>0.86</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>18.1 ± 0.4</td>
<td>17.9 ± 0.4</td>
<td>18.3 ± 0.4</td>
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<tr>
<td>Forced expiratory volume (l/sec)</td>
<td>3.1 ± 0.8</td>
<td>3.1 ± 0.8</td>
<td>3.0 ± 1.0</td>
<td>0.23</td>
<td>0.26</td>
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<td>3.0 ± 0.04</td>
<td>3.1 ± 0.04</td>
<td>3.1 ± 0.04</td>
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<td>Waist circumference (cm)</td>
<td>113.9 ± 16.8</td>
<td>115.8 ± 16.3</td>
<td>115.0 ± 15.0</td>
<td>0.26</td>
<td>0.79</td>
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<td>114.8 ± 0.7</td>
<td>115.1 ± 0.7</td>
<td>114.8 ± 0.6</td>
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<td>Systolic blood pressure (mm Hg)</td>
<td>128.7 ± 13.9</td>
<td>127.6 ± 13.8</td>
<td>129.1 ± 14.1</td>
<td>1.12</td>
<td>0.39</td>
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<td></td>
<td>129.3 ± 1.1</td>
<td>127.4 ± 1.0</td>
<td>128.7 ± 1.0</td>
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<tr>
<td>Resting heart rate (beats/min)</td>
<td>86.4 ± 14.9</td>
<td>87.5 ± 15.5</td>
<td>86.0 ± 14.1</td>
<td>0.56</td>
<td>0.61</td>
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<tr>
<td></td>
<td>86.9 ± 1.0</td>
<td>86.9 ± 1.0</td>
<td>85.9 ± 1.0</td>
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<tr>
<td>HbA1c (mmol/mol)</td>
<td>38.4 ± 9.7</td>
<td>38.7 ± 10.6</td>
<td>36.7 ± 6.9</td>
<td>3.65</td>
<td>0.07</td>
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<td></td>
<td>37.8 ± 0.5</td>
<td>38.7 ± 0.5</td>
<td>37.2 ± 0.4</td>
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<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.2 ± 0.4</td>
<td>1.2 ± 0.4</td>
<td>1.2 ± 0.4</td>
<td>1.24</td>
<td>0.34</td>
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<tr>
<td></td>
<td>1.2 ± 0.02</td>
<td>1.2 ± 0.02</td>
<td>1.2 ± 0.02</td>
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<tr>
<td>Non-HDL cholesterol (mmol/l)</td>
<td>3.8 ± 1.1</td>
<td>3.9 ± 1.2</td>
<td>3.8 ± 1.1</td>
<td>0.29</td>
<td>0.77</td>
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<tr>
<td></td>
<td>3.8 ± 0.1</td>
<td>3.8 ± 0.1</td>
<td>3.8 ± 0.1</td>
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<tr>
<td>Moderate-vigorous physical activity (hours/week)</td>
<td>2.5 ± 4.0</td>
<td>3.1 ± 4.4</td>
<td>2.5 ± 4.0</td>
<td>0.99</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>2.6 ± 0.4</td>
<td>3.0 ± 0.4</td>
<td>2.4 ± 0.3</td>
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</tbody>
</table>

CARE – Care coordination, TAU – treatment as usual, HDL – high density lipoprotein, HbA1c – haemoglobin A1c

*after multiple imputation; †adjusted for gender, research center and baseline risk of cardiovascular disease
<table>
<thead>
<tr>
<th>Table 3</th>
<th>Results for exploratory outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CHANGE</td>
</tr>
<tr>
<td>Weight (Kg)</td>
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</tr>
<tr>
<td>Mean±SDa</td>
<td>103.1 ± 23.8</td>
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<tr>
<td>Adjusted mean±SEb</td>
<td>102.2 ± 0.7</td>
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<tr>
<td>Body mass index</td>
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<tr>
<td>Mean±SDa</td>
<td>33.9 ± 5.9</td>
</tr>
<tr>
<td>Adjusted mean±SEb</td>
<td>33.9 ± 0.2</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
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<tr>
<td>Mean±SDa</td>
<td>2.0 ± 1.2</td>
</tr>
<tr>
<td>Adjusted mean±SEb</td>
<td>2.0 ± 0.1</td>
</tr>
<tr>
<td>Hs-CRP (mg/l)</td>
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<tr>
<td>Mean±SDa</td>
<td>3.1 ± 2.7</td>
</tr>
<tr>
<td>Adjusted mean±SEb</td>
<td>3.2 ± 0.3</td>
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<tr>
<td>Time spent sedentary (hours/day)</td>
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<tr>
<td>Mean±SDa</td>
<td>9.9 ± 3.6</td>
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<tr>
<td>Adjusted mean±SEb</td>
<td>10.1 ± 0.3</td>
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<tr>
<td>Daily smoking (yes/no)</td>
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<tr>
<td>%a</td>
<td>49.0</td>
</tr>
<tr>
<td>% (adjusted)b</td>
<td>49.0</td>
</tr>
<tr>
<td>Intake of fruit (g/week)</td>
<td></td>
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<tr>
<td>Mean±SDa</td>
<td>393.1 ± 268.5</td>
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<tr>
<td>Adjusted mean±SEb</td>
<td>394.8 ± 20.0</td>
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<tr>
<td>Intake of vegetables (g/week)</td>
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<tr>
<td>Mean±SDa</td>
<td>507.5 ± 338.8</td>
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<td>Adjusted mean±SEb</td>
<td>518.2 ± 28.0</td>
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<tr>
<td>Intake of fish (g/week)</td>
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<tr>
<td>Mean±SDa</td>
<td>138.1 ± 14.5</td>
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<tr>
<td>Adjusted mean±SEb</td>
<td>136.2 ± 12.3</td>
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<tr>
<td>Intake of saturated fat (yes/no)</td>
<td></td>
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<tr>
<td>%a</td>
<td>52.0</td>
</tr>
<tr>
<td>% (adjusted)b</td>
<td>55.0</td>
</tr>
<tr>
<td>Positive symptoms (SAPS global score)</td>
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</tr>
<tr>
<td>Mean±SDa</td>
<td>1.7 ± 1.6</td>
</tr>
<tr>
<td>Adjusted mean±SEb</td>
<td>1.6 ± 0.1</td>
</tr>
<tr>
<td>Negative symptoms (SANS global score)</td>
<td></td>
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<tr>
<td>Mean±SDa</td>
<td>2.1 ± 1.2</td>
</tr>
<tr>
<td>Adjusted mean±SEb</td>
<td>2.1 ± 0.1</td>
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<tr>
<td>Cognition (BACS composite score)</td>
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<tr>
<td>Mean±SDa</td>
<td>244.3 ± 50.1</td>
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<tr>
<td>Adjusted mean±SEb</td>
<td>238.8 ± 2.2</td>
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<tr>
<td>Quality of life (MANSA score)</td>
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<tr>
<td>Mean±SDa</td>
<td>4.7 ± 0.8</td>
</tr>
<tr>
<td>Adjusted mean±SEb</td>
<td>4.7 ± 0.07</td>
</tr>
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</table>
cardiovascular disease was 8.4 ± 6.7% in the CHANGE group, 8.5 ± 7.5% in the care coordination group, and 8.0 ± 6.5% in the treatment as usual group ($F_{2,428}=1.04, p=0.41$).

The sensitivity analyses of the primary outcome using complete cases, or removing outliers, did not change the results. When analyzing complete cases, we found that the mean age-standardized 10-year risk of cardiovascular disease was 8.5 ± 7.0% in the CHANGE group, 8.6 ± 7.8 in the care coordination group and 7.4 ± 5.3% in the treatment as usual group ($p=0.46$). After removing outliers, we found that it was 7.9 ± 5.2% in the CHANGE group, 7.6 ± 4.9% in the care coordination group and 7.1 ± 4.1% in the treatment as usual group ($p=0.18$). After removing CHANGE participants who had less than half of the intended 42 sessions, we found that the mean risk was 8.6 ± 7.7% in the CHANGE group, 8.6 ± 7.8% in the care coordination group and 7.4 ± 5.3% in the treatment as usual group ($p=0.65$). Equally, the per-protocol analysis removing the three participants with no contact at all to the coach did not change the results.

There were no differences between the three groups for any of the secondary outcomes. The means for cardiorespiratory fitness, our key secondary outcome, were 18.1 ± 5.5 ml O2/min/Kg in the CHANGE group, 18.0 ± 6.8 ml O2/min/Kg in the care coordination group, and 18.2 ± 6.7 ml O2/min/Kg in the treatment as usual group ($F_{2,428}=0.86, p=0.54$).

The analyses revealed no significant differences between the three groups on any exploratory outcomes (Table 3). For weight, the means were 103.1 ± 23.8 Kg in the CHANGE group, 103.7 ± 21.2 Kg in the care coordination group, and 102.9 ± 21.7 Kg in the treatment as usual group ($F_{2,428}=1.91, p=0.18$). The proportion of daily smokers was 49.0% in the CHANGE group, 49.0% in the care coordination group, and 50.0% in the treatment as usual group (CHANGE group vs. treatment as usual group: $p=0.65$; care coordination group vs. treatment as usual group: $p=0.79$).

Five patients died during the trial. The distribution can be seen in the flow diagram (Figure 1). The causes of death were cancer (N=2), suicide (N=1), and unexplained (N=2). Psychiatric hospitalizations amounted to 18.8% in the CHANGE group, 33.8% in the care coordination group and 24.3% in the treatment as usual group; the difference between the care coordination and the CHANGE group was statistically significant ($p=0.004$). Somatic hospitalizations amounted to 12.3% in the CHANGE group, 17.6% in the care coordination group and 16.2% in the control group ($p=0.40$).

**Table 3  Results for exploratory outcomes (continued)**

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<tr>
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<th>CHANGE</th>
<th>CARE</th>
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<tbody>
<tr>
<td>Quality of life (EuroQOL score)</td>
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<tr>
<td>Mean±SD</td>
<td>1.4 ± 0.3</td>
<td>1.4 ± 0.3</td>
<td>1.3 ± 0.3</td>
<td>1.14</td>
<td>0.36</td>
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<tr>
<td>Adjusted mean±SE</td>
<td>1.4 ± 0.03</td>
<td>1.4 ± 0.03</td>
<td>1.3 ± 0.03</td>
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<tr>
<td>GAF total score</td>
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<tr>
<td>Mean±SD</td>
<td>49.4 ± 11.2</td>
<td>47.6 ± 9.8</td>
<td>47.8 ± 9.4</td>
<td>1.19</td>
<td>0.35</td>
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<tr>
<td>Adjusted mean±SE</td>
<td>49.0 ± 0.8</td>
<td>48.1 ± 0.8</td>
<td>47.6 ± 0.8</td>
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<tr>
<td>Perceived health</td>
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<tr>
<td>Mean±SD</td>
<td>2.8 ± 1.0</td>
<td>2.8 ± 0.9</td>
<td>2.7 ± 0.8</td>
<td>0.33</td>
<td>0.74</td>
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<tr>
<td>Adjusted mean±SE</td>
<td>2.7 ± 0.1</td>
<td>2.8 ± 0.1</td>
<td>2.7 ± 0.1</td>
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<tr>
<td>Perceived stress</td>
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</tr>
<tr>
<td>Mean±SD</td>
<td>26.8 ± 7.8</td>
<td>27.0 ± 7.4</td>
<td>25.5 ± 7.4</td>
<td>1.68</td>
<td>0.26</td>
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<tr>
<td>Adjusted mean±SE</td>
<td>27.1 ± 0.6</td>
<td>26.5 ± 0.6</td>
<td>25.7 ± 0.6</td>
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CARE = care coordination, TAU = treatment as usual, Hs-CRP = high sensitivity C-reactive protein, SAPS = Scale for the Assessment of Positive Symptoms, SANS = Scale for the Assessment of Negative Symptoms, BACS = Brief Assessment of Cognition in Schizophrenia, MANSQ = Manchester Short Assessment of Quality of Life, GAP = Global Assessment of Functioning

*aafter multiple imputation; *adjusted for gender, research center and baseline risk of cardiovascular disease

DISCUSSION

We hypothesized that a tailored, multi-domain intervention, delivered by personal coaching in a community setting, would lead to a meaningfully reduced risk of cardiovascular disease in patients with schizophrenic spectrum disorders and abdominal obesity. However, the findings of this trial suggest that neither the CHANGE intervention nor care coordination were superior to standard treatment in reducing the 10-year risk of cardiovascular disease.

CHANGE is the first trial, to our knowledge, to evaluate the effect of lifestyle interventions on a composite score estimating the risk of cardiovascular disease in patients with...
schizophrenic spectrum disorders. One U.S. study had explored the impact of care coordination in patients with severe mental illness, using a composite cardiovascular risk score, finding a significant effect\(^{44}\). Our negative results might be explained by better access to primary care in Denmark. Few of our participants had baseline values of lipids or blood pressure indicating a need for change in medication, according to the current guidelines for cardiovascular prevention\(^{45}\), and only two had haemoglobin A1c values above the cut-off for diabetes without having being diagnosed and treated beforehand. This might be the result of a successful mandatory examination of blood lipids in the Danish Schizophrenia database, encouraging all clinicians across the three intervention groups to treat risk factors. Thus, the generalizability of results of care coordination might be limited to countries with similar health care systems. Also, we cannot exclude that selecting a subgroup with more severe somatic comorbidities might have changed our results in favour of care coordination or CHANGE intervention.

For our key secondary outcome, cardiorespiratory fitness, few studies have evaluated the effect of lifestyle interventions in patients with schizophrenia, but they reported promising findings\(^{43,45}\). Trials evaluating the effect of behavioural interventions in reducing metabolic risk factors have shown mixed results\(^{17}\). Weight reduction is the most used outcome\(^{46-56}\) and the evidence is reported to be favourable\(^{17}\), although long-term trials are missing\(^{18}\). Trials exploring the effect of behavioural interventions frequently use dyslipidaemia\(^{46,47,49,52}\), haemoglobin A1c\(^{46,56}\) and blood pressure\(^{46,49,52,56,57}\) as secondary outcomes, and the evidence is currently low or inadequate\(^{17}\). Thus, our results are not in line with previous trials regarding weight reduction and cardiorespiratory fitness, which might be explained by the clinical characteristics of our sample and the type of intervention.

The clinical characteristics of the sample we recruited reflect our inclusion and exclusion criteria. Our sample might differ from previous trials, as we aimed to optimize the external validity by having as few exclusion criteria as possible, being assertive in the process of recruitment, and offering an intervention without mandatory elements, in order to avoid exclusion of the severely ill (many trials exclude patients with somatic comorbidity, substance abuse or suicidal ideation) and volunteer bias.

The methods used to intervene reflect the chosen outcome variables. As cardiovascular disease is multifactorial, we thought that complex interventions should be the right approach. However, a majority of earlier trials have focused on single risk behaviours, such as diet or smoking or physical inactivity. Our intervention was heterogeneous, as every patient was free to choose the focus area for the intervention in dialogue with the coach. This might have limited our possibility to show an effect on single metabolic outcomes, thus reducing our power.

In spite of a high retention proportion (86.0%), the per-protocol analysis showed that only 60.0% of patients randomized to the CHANGE group attended at least half of the intended weekly meetings, indicating that offering a higher frequency of sessions or a lower caseload would doubtfully have led to different results.

The CHANGE trial had several strengths. First, the design had central randomization; blinded outcome assessments, data management and data analysis; and independent funding. Second, we planned our sample size to avoid substantial type II errors. Third, we used a manual-based, well-described and evidence-based theoretical framework. Fourth, we implemented a high-intensity intervention, offering an assertive approach with at least weekly personal contact. Fifth, we had a multifaceted method, allowing the staff to work on all the known risk factors. Sixth, our composite outcome measure integrated the results even though they might be heterogeneous. Seventh, by comparing lifestyle coaching with care coordination, we were able to differentiate between the effect of lifestyle changes and that of sufficient monitoring and treatment of somatic comorbidities. Eighth, all contacts with patients were registered. Ninth, the intervention was developed to be sustainable, using low-budget possibilities in the neighbourhood.

The ideal outcome measures for trials aiming to reduce mortality from cardiovascular disease are obviously hard ones like death. However, waiting for survival analyses is too time consuming and expensive for most studies, leaving surrogate outcomes as the second best choice. Currently there is no gold standard for surrogate outcomes in trials aiming to improve cardiovascular health, and the outcomes we chose for this trial have strengths and limitations. Strengths are that we used a composite score including several well-known risk factors. The score consisted of both modifiable and non-modifiable risk factors. This may be seen as a weakness, since it means that an intervention could affect all the modifiable risk factors, yet not affect the composite outcome measure. This was not an issue in the CHANGE trial, as there were no indications of significant reductions even in the separate modifiable risk factors. Conversely, we view our choice of primary outcome measure as a strength, as constructing a risk score without non-modifiable risk factors would not yield an accurate estimate of risk. A weakness, though, is the lack of validation of the surrogate measure in a population with schizophrenia. In fact, research published after the initiation of this trial has questioned the generalizability of cardiovascular risk scores to people with severe mental illness\(^{58}\).

As we did not succeed in recruiting the planned number of participants (we recruited 428 patients, while 450 were expected), we cannot exclude a risk of being underpowered, increasing the risk for type II errors. However, we find it unlikely that including 22 further participants would have changed our results substantially, and we still have a power of 87.2% regarding our primary outcome, which seems an acceptable one compared to most trials.

The lack of effect on individual risk behaviours should be interpreted with caution, due to insufficient power. Furthermore, existing tools measuring lifestyle changes have not been validated in a population with schizophrenia, where cognitive impairment and psychotic symptoms might compromise the validity. As self-reporting might be subject to both recall
problems (introducing random errors and thus increasing the risk of type II errors) and social desirability bias (leading to systematic errors), more direct measurements like actigraphs would have been preferable, but they were not considered in this study due to logistic reasons.

In conclusion, the CHANGE trial provides evidence that a manual-based individual lifestyle coaching intervention does not reduce the 10-year risk of cardiovascular disease, compared with treatment as usual, in patients with schizophrenia spectrum disorders and abdominal obesity. Offering lifestyle interventions to this group might seem like a moral imperative, but, seen in the light of the lack of beneficial results and moderate compliance with weekly meetings with the coaches, it is just as imperative to ask whether this is the right approach to improve life for patients with schizophrenia. The general population, and even more, a vulnerable population like this one, is facing major barriers to making healthy choices and powerful pressures to select the unhealthy. We suggest that future research should focus on environmental/structural changes rather than individually anchored health interventions, taking into account the special needs of patients with schizophrenia.

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REFERENCES


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Diabetes mellitus in people with schizophrenia, bipolar disorder and major depressive disorder: a systematic review and large scale meta-analysis

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Type 2 diabetes mellitus (T2DM) is highly predictive of cardiovascular diseases and can have particularly deleterious health impacts in people with severe mental illness (SMI), i.e. schizophrenia, bipolar disorder or major depressive disorder. This meta-analysis aimed: a) to describe pooled frequencies of T2DM in people with SMI; b) to analyze the influence of demographic, illness and treatment variables as well as T2DM assessment methods; and c) to describe T2DM prevalence in studies directly comparing persons with each specific SMI diagnosis to general population samples. The trim and fill adjusted pooled T2DM prevalence among 438,245 people with SMI was 11.3% (95% CI: 10.0%-12.6%). In antipsychotic-naive participants, the prevalence of T2DM was 2.9% (95% CI: 1.7%-4.8%). There were no significant diagnostic subgroup differences. A comparative meta-analysis established that multi-episode persons with SMI (N=133,470) were significantly more likely to have T2DM than matched controls (N=5,622,664): relative risk, RR=1.85, 95% CI: 1.45-2.37, p<0.001. The T2DM prevalence was consistently elevated in each of the three major diagnostic subgroups compared to matched controls. Higher T2DM prevalences were observed in women with SMI compared to men (RR=1.43, 95% CI: 1.20-1.69, p<0.001). Multi-episode (versus first-episode) status was the only significant predictor for T2DM in a multivariable meta-regression analysis (r²=0.52, p<0.001). The T2DM prevalence was higher in patients prescribed antipsychotics, except for aripiprazole and amisulpride. Routine screening and multidisciplinary management of T2DM is needed. T2DM risks of individual antipsychotic medications should be considered when making treatment choices.

Key words: Diabetes mellitus, severe mental illness, schizophrenia, bipolar disorder, major depressive disorder, antipsychotics

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People with severe mental illness (SMI) – defined as schizophrenia, bipolar disorder or major depressive disorder (MDD) – have a two to three times higher risk for premature death than the general population.1,2 This mortality gap translates to a 10-20 year shortened life expectancy3,4 and appears to be widening5. The most important cause for this shortened life expectancy is cardiovascular disease (CVD)6. Major risk factors include antipsychotic medication use and an unhealthy lifestyle7, and these risks are compounded by obstacles in access to medical care8-12.

Type 2 diabetes mellitus (T2DM) is a major risk factor for CVD. It confers about a two-fold excess risk for coronary heart disease, major stroke subtypes, and deaths attributed to other vascular causes13,14. Prevention and treatment of T2DM demand careful consideration in clinical practice, particularly in populations with an increased risk for CVD and associated premature mortality15,16.

Recent meta-analyses17-20 demonstrated that all diagnostic SMI subgroups have a higher risk for developing T2DM than the general population. However, meta-analytic data comparing T2DM risks across different psychiatric diagnoses are currently lacking. Furthermore, there are no meta-analytic data that combine all major diagnostic SMI subgroups, and information on the prevalence of T2DM among people with SMI prescribed different antipsychotic medication classes is insufficient.

Large-scale pooled analyses in the SMI population are relevant, as they enable investigation of risk factors across large numbers of studies and participants, distinguishing risk factors for T2DM associated with specific SMIs from those independent of these illnesses. Pooling data across major diagnostic categories allows for investigation of the effect of demographic variables (gender, age, illness duration, study setting, geographical region) and treatments (particularly mood stabilizers and antipsychotics prescribed for psychotic and non-psychotic conditions). If risk stratification is observed, this could potentially guide clinicians in monitoring and treatment.

Given the aforementioned gaps within the literature, we conducted a large scale systematic review and meta-analysis of pooled T2DM prevalences in people with schizophrenia or related psychotic disorders, bipolar disorder or MDD. We aimed to: a) describe pooled T2DM frequencies in people with SMI; b) analyze the influence of demographic, illness and treatment variables as well as T2DM assessment methods; and c) describe T2DM prevalence in studies directly comparing persons with each specific SMI diagnosis to general population samples.
METODS

Inclusion and exclusion criteria

This systematic review was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines21 and in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard22. We included observational studies (cross-sectional, retrospective and prospective studies) and randomized controlled trials in adults with a psychiatric diagnosis of schizophrenia or related psychotic disorders, bipolar disorder or MDD according to the DSM-IV-TR or the ICD-10, irrespective of clinical setting (inpatient, outpatient or mixed, community setting), that reported study-defined T2DM prevalences.

We excluded studies restricted to patients with or without cardiovascular diseases. When required, we contacted the primary or corresponding authors of studies to confirm eligibility, and to obtain the data needed for analysis if they were not available in the published paper.

Search criteria, study selection and critical appraisal

Two independent reviewers (DV, BS) searched Medline, PsycARTICLES, Embase and CINAHL from database inception to August 1, 2015, without language restrictions. Key words used were “diabetes” OR “glucose” AND “severe mental illness” OR “serious mental illness” OR “schizophrenia” OR “psychosis” OR “bipolar disorder” OR “depression” OR “depressive disorder” in the title, abstract or index term fields. Manual searches were also conducted using the reference lists from recovered articles and recent systematic reviews.

After the removal of duplicates, the reviewers screened the titles and abstracts of all potentially eligible articles. They both applied the eligibility criteria, and a list of full text articles was developed through consensus. Next, the two reviewers considered the full texts of these articles and the final list of included articles was reached through consensus. A third reviewer (CC) was available for mediation throughout this process. Methodological appraisal included evaluation of bias (confounding, overlapping data, publication bias).

Statistical analyses

Due to anticipated heterogeneity, a random effects meta-analysis was employed. Heterogeneity was measured with the Q statistic (which is always presented at the end of the description of the results as a second or final p-value).

We calculated the relative risk (RR) to investigate the T2DM prevalence within and across SMI subgroups, the latter only in those studies directly comparing diagnostic subgroups. Moreover, we compared the prevalence of T2DM between people with schizophrenia, bipolar disorder and MDD and general population control groups that were matched on age and gender, using data from studies in which they were directly compared. In both analyses, only comparisons of specific SMI groups or a SMI group with a matched general population group were included that had been performed within the same study, in order to minimize variability of T2DM frequencies due to different sampling and assessment procedures.

Furthermore, in the entire dataset, we conducted subgroup analyses to investigate differences between the three main diagnostic subgroups, first-episode versus multi-episode illness, males versus females, population based versus non-population based studies, and differences across medication classes (antipsychotics, antidepressants, mood stabilizers) and geographical regions. In order to reduce heterogeneity, we did not calculate diagnostic and gender differences across studies, but pooled only data of studies that compared these differences on a patient level. Further, we conducted meta-regression analyses to investigate potential moderators (age, percentage of males, illness duration, smoking prevalence, and T2DM assessment methods) with Comprehensive Meta Analysis (version 3).

Publication bias was tested using the Egger’s regression method23 and Begg-Mazumdar test24, with a p-value <0.05 suggesting the presence of bias. When we encountered publication bias, we conducted a trim and fill adjusted analysis25 to remove the most extreme small studies from the positive side of the funnel plot, and recalculated the effect size iteratively, until the funnel plot was symmetrical around the (new) effect size.

RESULTS

Search results and included participants

After excluding duplicates and irrelevant hits, our search yielded 323 publications, of which 118 (including 135 T2DM prevalences) met inclusion criteria (Figure 1). A list of the included and excluded studies (with reasons) is available upon request from the first author.

The final sample comprised 438,245 unique persons with SMI and 5,622,664 matched controls. Sample sizes ranged from 12 to 143,943 participants, with a median sample size of 270. The mean age of participants with SMI was 44.3 years (range 23.1-77.6 years); 56.8% were male (range 0-100); 69% were Caucasian (range 0-100; 37 studies). Mean illness duration was 16.1 years (range 0-35 years; 29 studies). Thirty-one studies (N=77,028) reported smoking frequencies, and 44.5% (95% CI: 29.2%-60.4%) of the included participants smoked.

T2DM prevalence

The estimated weighted mean prevalence of T2DM among 438,245 people with SMI was 10.2% (95% CI: 9.1%-11.4%; Q=14228.7, p<0.001). The Begg-Mazumdar (Kendall’s tau=0.15,
Subgroup analyses and predictors of T2DM

Study setting and design

The pooled prevalences across different treatment settings (inpatients, outpatients, community patients, mixed settings), study designs (cross-sectional, retrospective and prospective studies, and population versus non-population based), median year of data collection (before or after the year 2000), methods of T2DM assessment (blood testing, self-report, charts) are summarized in Table 1. The separate meta-regressions are presented in Table 2.

There were no significant differences between the various treatment settings, and data collection before versus after the year 2000. There was also no difference in T2DM prevalence between population based and non-population based studies. In contrast, a higher T2DM prevalence was observed in studies relying upon clinical data gleaned from file and chart reviews versus self-report studies. A trend for higher T2DM was found in retrospective studies versus cross-sectional (p = 0.054) and versus prospective (p = 0.053) studies.

Diagnostic subgroups

The pooled T2DM prevalences for the different diagnostic subgroups are presented in Table 1. Relative risk meta-analyses established that there was no significant difference in T2DM in studies directly comparing schizophrenia alone (14.1%, 95% CI: 9.8%-20.2%; Q = 5, p = 0.51; N = 4,963) versus schizophrenia spectrum disorders (including schizoaffective disorder, schizophreniform disorder and related psychoses) (18.3%, 95% CI: 14.9%-22.2%; Q = 2.1, p = 0.34; N = 694) (three studies; odds ratio, OR = 0.80; 95% CI: 0.52-1.25, z = -0.97, p = 0.33; Q = 2.66, p = 0.26, I² = 24.9).

The same was true for the comparison of schizophrenia (13.7%, 95% CI: 8.2%-22.1%; Q = 131, p < 0.01; N = 6,005) versus bipolar disorder (13.7%, 95% CI: 9.2%-20.0%; Q = 46, p < 0.01; N = 3,138) (six studies; OR = 1.22, 95% CI: 0.84-1.77, z = 1.08, p = 0.28; Q = 17.1, p = 0.004, I² = 70.8); and of schizophrenia (13.7%, 95% CI: 11.6%-16.1%; Q = 0.3, p = 0.58; N = 893) versus MDD (11.1%, 95% CI: 9.2%-13.3%; N = 911) (two studies; OR = 1.27, 95% CI: 0.96-1.68, z = 1.66, p = 0.10; Q = 6.0, p = 0.80, I² = 0). There were insufficient studies directly comparing T2DM prevalence in patients with bipolar disorder versus MDD.

Comparing T2DM in first- versus multi-episode patients within the different diagnostic subgroups (see Table 1) demonstrated that first-episode schizophrenia patients (4.0%, 95% CI: 2.5%-6.2%) had a significantly lower T2DM prevalence than multi-episode schizophrenia patients (13.1%, 95% CI: 11.7%-14.8%, z = -3.89, p < 0.001). There were no data in first-episode bipolar disorder or MDD patients, precluding a comparison with multi-episode patients.

Demographic variables

A relative risk meta-analysis across 29 studies (including 32 comparisons) directly comparing T2DM frequencies in men (N = 35,400) versus women (N = 33,283) with SMI found a higher T2DM prevalence in women (RR = 1.43; 95% CI: 1.20-1.69, p < 0.001).

Pooled T2DM prevalences per geographical region are displayed in Table 1. The T2DM prevalence was significantly higher in North America (12.5%, 95% CI: 10.9%-14.3%; 58 studies) than in Europe (7.7%, 95% CI: 6.3%-9.3%; 32 studies) (p < 0.001). No other significant geographical differences were observed.

Separate meta-regression analyses (see Table 2) revealed that higher T2DM frequencies were moderated by older age, longer illness duration, and first-episode versus multi-episode status, but not by gender, ethnicity, and smoking status.

When all significant demographic predictors were entered in a multivariable meta-regression model, multi-episode versus first-episode status (β = 1.889, 95% CI: 0.1445-3.6335, z = 2.12, p = 0.03) remained the only significant moderator of the variance of T2DM. The final multivariable model accounted for just over
Table 1 Subgroup analyses of moderators of type 2 diabetes mellitus (T2DM) in people with severe mental illness

<table>
<thead>
<tr>
<th>Study design</th>
<th>Number of studies</th>
<th>Pooled T2DM prevalence (%)</th>
<th>95% CI</th>
<th>Between-group difference p-value</th>
<th>F</th>
<th>Q</th>
<th>p-value</th>
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<td>7.9-10.8</td>
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<td></td>
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<tr>
<td>Population based</td>
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<td>8.5-11.6</td>
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<td>37</td>
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<td>7.1-10.5</td>
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<td>9.3-14.1</td>
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<td>79.3</td>
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<td>Before 2000</td>
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<td>6.9-12.8</td>
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<tr>
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<td>4.8-8.4</td>
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<td>5.9-10.3</td>
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<td>58</td>
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<td>10.9-14.3</td>
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<td>99.0</td>
<td>6026.7</td>
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<td>6.3-9.3</td>
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<td>2486.6</td>
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<td>8.5-13.1</td>
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<td>5.7-14.5</td>
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<td>3.1-15.0</td>
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<td>Antipsychotic medication use</td>
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<tr>
<td>Antipsychotic-naive</td>
<td>10</td>
<td>2.9</td>
<td>1.7-4.8</td>
<td>&lt;0.001</td>
<td>78.0</td>
<td>41.0</td>
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<td>Clozapine</td>
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<td>11.0-21.3</td>
<td></td>
<td>38.4</td>
<td>15.0</td>
<td>0.11</td>
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</tbody>
</table>
Significant between-group differences are highlighted in bold prints.

Half of the between-study heterogeneity in T2DM frequency ($I^2=0.52$, $p<0.001$).

**Medication use**

Separate meta-regression analyses (see Table 2) showed that treatment duration, percentage of antidepressant use and percentage of lithium use, but not percentage of other mood stabilizers use, were significant mediators of T2DM prevalence.

Thirty-four studies provided data on T2DM prevalences compared with general population controls (N=133,470; 95% CI: 12.2%, 95% CI: 9.7-15.2%; Q=6166, p<0.001) had significantly increased risk of T2DM (RR=1.85, 95% CI: 1.45-2.37) that found in matched general population comparison samples.

**DISCUSSION**

To our knowledge, this is the first meta-analysis of T2DM including and comparing data from the three main SMIs, namely schizophrenia and related psychotic disorders, bipolar disorder and MDD. Approximately one in 10 individuals with SMI (11.3%; 95% CI: 10.0%-12.6%) had T2DM, and the relative risk for T2DM in multi-episode persons with SMI was almost double (RR=1.85, 95% CI: 1.45-2.37) that found in matched general population comparison samples.

T2DM prevalences were consistently elevated for each of the three diagnostic subgroups compared to the general population, and comparative meta-analyses found no significant differences across schizophrenia, schizophrenia spectrum disorders, bipolar disorder and MDD. Thus, other diagnostic-independent factors likely influence T2DM frequency, including hyperglycaemia following psychotropic medication use and long-term exposure to unhealthy lifestyle behaviors, as well as potential genetic factors linking psychiatric and medical risk.

We showed for the first time in a large scale meta-analysis that T2DM risk indeed increased with increasing treatment duration, supported further by a multivariate meta-regression model in which multi-episode status remained a unique significant predictor, explaining half of the variance. We also observed a significantly increased prevalence of T2DM in North America versus Europe, in keeping with the overall population prevalences, which suggests a combined impact of genetic, lifestyle and/or environmental risk factors.

Knowledge of factors associated with a high T2DM risk can help identify individuals at greatest need for intensive monitoring and intervention. In contrast with general population studies, we found that women with SMI had a higher risk for...
developing T2DM than men. This finding warrants further investigation, but may be related to a greater propensity to obesity and central obesity in women with SMI compared to men, since central obesity is a significant risk factor for hyperglycaemia. On the other hand, only a minority of analyzed studies did provide information about the mean age in women and men, and it is possible that women with schizophrenia were older, which could have confounded the results.

Our results also show that T2DM prevalence was higher in individuals with multi-episode schizophrenia compared with persons in their first episode. The current meta-analysis adds to the evidence that a first-episode diagnosis is a unique predictor of lower T2DM prevalence independent of mean age, a finding that was also apparent in a recent analysis of metabolic syndrome prevalences across patients with the same three main SMIs. Our results point toward the need to adopt a prevention/early intervention approach in order to reduce cardiometabolic risk in people with SMI. Further research is needed to explore the mechanisms underlying this increased T2DM risk with the transition of the illness from an initial episode to a multi-episode disorder.

Our data confirm prior evidence that psychotropic medication use, including that of antidepressants, lithium and antipsychotic medications, is associated with higher T2DM prevalence. Except for aripiprazole and amisulpride, all antipsychotics were associated with a significantly increased T2DM risk compared to antipsychotic-naive patients. Variations in the risk for glucose abnormalities are evident in the literature, with the highest risk being associated with clozapine, olanzapine and quetiapine in carefully designed studies.

### Table 2 Meta-regressions of moderators of type 2 diabetes mellitus (T2DM) in people with severe mental illness

<table>
<thead>
<tr>
<th>Moderator</th>
<th>Number of comparisons</th>
<th>β</th>
<th>95% CI</th>
<th>p-value</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design (vs. retrospective)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>113</td>
<td>−0.35</td>
<td>−0.72</td>
<td>0.007</td>
<td>0.054</td>
</tr>
<tr>
<td>Prospective</td>
<td>64</td>
<td>−0.51</td>
<td>−1.04</td>
<td>0.008</td>
<td>0.053</td>
</tr>
<tr>
<td>Population based (yes/no)</td>
<td>134</td>
<td>−0.002</td>
<td>−0.34</td>
<td>0.33</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>Setting (vs. mixed)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.02</td>
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<tr>
<td>Inpatients</td>
<td>74</td>
<td>0.32</td>
<td>−0.12</td>
<td>0.77</td>
<td>0.15</td>
</tr>
<tr>
<td>Outpatients</td>
<td>73</td>
<td>0.30</td>
<td>−0.15</td>
<td>0.76</td>
<td>0.19</td>
</tr>
<tr>
<td>Community patients</td>
<td>58</td>
<td>0.19</td>
<td>−0.32</td>
<td>0.70</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>T2DM assessment (vs. self-report)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.09</td>
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<tr>
<td>Blood testing</td>
<td>60</td>
<td>−0.02</td>
<td>−0.53</td>
<td>0.49</td>
<td>0.92</td>
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<td>Charts</td>
<td>87</td>
<td>0.63</td>
<td>0.18</td>
<td>1.07</td>
<td>0.006</td>
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<tr>
<td><strong>Publication data (before 2000 or not)</strong></td>
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<td></td>
<td></td>
<td></td>
<td>0.00</td>
</tr>
<tr>
<td>First episode (yes/no)</td>
<td>134</td>
<td>−0.08</td>
<td>−0.56</td>
<td>0.40</td>
<td>0.75</td>
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<tr>
<td>Mean age (years)</td>
<td>81</td>
<td>1.31</td>
<td>0.80</td>
<td>1.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>123</td>
<td>0.25</td>
<td>−0.37</td>
<td>0.88</td>
<td>0.42</td>
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<tr>
<td>Ethnicity (% Caucasian)</td>
<td>37</td>
<td>−0.65</td>
<td>−1.48</td>
<td>0.17</td>
<td>0.12</td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>29</td>
<td>0.03</td>
<td>0.007</td>
<td>0.06</td>
<td>0.01</td>
</tr>
<tr>
<td>Smoking (% smokers)</td>
<td>31</td>
<td>−0.24</td>
<td>−1.83</td>
<td>1.35</td>
<td>0.77</td>
</tr>
<tr>
<td>Treatment duration (years)</td>
<td>9</td>
<td>0.07</td>
<td>0.03</td>
<td>0.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antidepressants use (%)</td>
<td>16</td>
<td>2.82</td>
<td>1.08</td>
<td>4.55</td>
<td>0.001</td>
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<tr>
<td>Lithium use (%)</td>
<td>11</td>
<td>3.07</td>
<td>1.46</td>
<td>4.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other mood stabilizers use (%)</td>
<td>13</td>
<td>−0.47</td>
<td>−2.09</td>
<td>1.14</td>
<td>0.57</td>
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<tr>
<td>Geographical region (vs. North America)</td>
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<td></td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>Europe</td>
<td>90</td>
<td>−0.55</td>
<td>−0.96</td>
<td>−0.13</td>
<td>0.009</td>
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<tr>
<td>Asia</td>
<td>86</td>
<td>−0.23</td>
<td>−0.67</td>
<td>0.22</td>
<td>0.31</td>
</tr>
<tr>
<td>Australia</td>
<td>63</td>
<td>−0.30</td>
<td>−1.15</td>
<td>0.55</td>
<td>0.49</td>
</tr>
<tr>
<td>South America</td>
<td>63</td>
<td>−0.48</td>
<td>−1.44</td>
<td>0.48</td>
<td>0.32</td>
</tr>
<tr>
<td>Africa</td>
<td>60</td>
<td>−0.59</td>
<td>−1.93</td>
<td>0.75</td>
<td>0.39</td>
</tr>
<tr>
<td>Middle East</td>
<td>60</td>
<td>−0.19</td>
<td>−1.49</td>
<td>1.12</td>
<td>0.78</td>
</tr>
</tbody>
</table>

Significant p-values are highlighted in bold prints.
In the current meta-analysis, quetiapine (and a trend for clozapine) was associated with an even higher T2DM risk than olanzapine use. However, this finding should be interpreted with caution, as order effects cannot be excluded, in that patients who acquired marked T2DM risk or developed even frank T2DM on a higher-risk agent, such as olanzapine, could have been switched to another antipsychotic, including quetiapine, potentially leading to risk misattribution.

Finally, as expected, patient self-report yielded numerically the lowest T2DM prevalences; the T2DM prevalence was significantly lower compared with chart review data. This finding is likely due to the fact that, in chart review studies, patients were followed back a longer time, extending the detection period. In line with this interpretation, there was a trend for retrospective studies to be associated with higher T2DM prevalences than prospective ones.

Clinical implications

Our meta-analysis highlighted geographical differences in T2DM, mirroring the different prevalences in the general population, indicating the possible influence of lifestyle and other environmental factors with or without genetic risk differences. Thus, considering the observed increased T2DM risks, screening for and trying to minimize risk factors (including adverse lifestyle factors and specific antipsychotic medication choice) should be a key priority in the multidisciplinary treatment of people with SMI.

Our data clearly demonstrate that people with SMI should be considered as a “homogeneous and important high-risk group” that needs proactive screening for T2DM. It is particularly important to establish baseline T2DM risk at initial presentation, so that any subsequent change during treatment can be monitored. The medical history and examination should, at a minimum, include: a) history of previous CVD, T2DM or other related diseases; b) family history of premature CVD, T2DM or other related diseases; c) smoking, dietary and physical activity habits; d) weight and height in order to calculate body mass index, and waist circumference; e) fasting blood glucose and/or hemoglobin A1c (HBA1c); f) blood pressure (measured twice and average taken); and g) past medication history.

As there are differences in T2DM prevalences across assessment methods, it is recommended that fasting blood glucose measurements (ideally even oral glucose tolerance testing as the gold standard) should be obtained prior to the first prescription of antipsychotic medication. The frequency of glucose metabolism testing will depend on the patient’s medical history and the prevalence of baseline risk factors. For patients on antipsychotic medication with normal baseline tests, it is recommended that measurements should be repeated at 12 weeks after initiation of treatment and at least annually thereafter, with more frequent assessments in high-risk patients, such as those with significant weight gain, post-partum diabetes or a first-degree family history of diabetes. In patients with T2DM (and those with pre-diabetes), fasting blood glucose and HBA1c should be measured more frequently (approximately every 3-6 months). An annual examination should include measurement of CVD risk factors, glomerular filtration rate and albumin to creatinine ratio, an eye examination, ideally including fundus photography, and foot examination to diagnose early signs of complications.

Despite the imperative to screen for T2DM, screening for T2DM and CVD risk factors is still suboptimal, with only slight improvement over the last decade. The low glucose screening rates (44.3%; 95% CI: 36.3%-52.4%) may reflect both patient and professional barriers. Professional barriers to screening within mental health settings may in their turn reflect lack of clarity about whose clinical responsibility the screening is, lack of understanding about what should be measured and when, uncertainty about how to interpret results, and lack of access to necessary equipment, as well as incomplete communication between primary and secondary care. Without systematic screening following detailed recommendations and using acceptable and accurate diagnostic tests, the true prevalence of T2DM in patients with SMI will remain unknown and underestimated.

Even after an established diagnosis of T2DM is made, many of those with mental ill health are not offered timely treatment. Thus, it should be clarified that routine screening is only the first step. Psychiatric centers should cooperate with diabetes centers to establish shared care pathways and ensure an integrated approach for people with mental illness and T2DM. Such an approach would reflect recent calls for the breaking down of the traditional “silo” approach to physical and mental health care, in line with the internationally endorsed Healthy Active Lives Declaration (www.iphs.org).

Those with diagnosed T2DM should also be seen regularly by a multidisciplinary team, including physicians, diabetes nurses, physical therapists or exercise physiologists and dieticians, to advise not just on diabetes but also on other risk factors and medical comorbidities.

When T2DM is detected, people with SMI are likely to require additional pharmacological management, but this is unlikely to be significantly different from the general population. However, clinicians should be aware that any deterioration in mental health may result in compromised management of T2DM, and comprehensive management may require an adjustment to the diabetes care plan.

Limitations

Whilst this is the most comprehensive and thorough meta-analysis of T2DM in people with SMI conducted to date, we acknowledge some limitations that largely reflect problems in the primary data.

First, only a limited number of studies assessed T2DM using an oral glucose tolerance test as the gold standard. There are inherent problems with using chart reviews in relation to se-
lection bias and the reliability and validity of the T2DM diagnosis. Second, because our study findings were mainly based on cross-sectional rather than longitudinal data, directionality of the association between medication use and observed T2DM risk cannot be deduced with certainty; that is, it is possible that those with inherently higher metabolic risk factors may be more likely to receive antipsychotics. Also, given that many of the studies reported cross-sectional data, it is possible that people with SMI deemed to be at particular risk for glucose abnormalities were preferentially prescribed antipsychotics perceived to be of lower risk, such as aripiprazole and amisulpride.

Third, variables such as clinical subtypes of MDD and bipolar disorder were not reported and controlled for. Fourth, a threat to the validity of any meta-analysis is publication bias and heterogeneity, which we encountered in most of our analyses. Nevertheless, we adjusted for publication bias using the trim and fill analysis, and were able to explain over half of the between-study heterogeneity in our multivariable meta-regression analysis. Fifth, there were inadequate data on lifestyle behaviors, precluding meta-analytic assessment of these factors as moderating or mediating variables.

Future research

Since antipsychotic medications are increasingly used as first line treatments for bipolar disorder 43 and MDD 44, additional research on the underlying mechanisms for the development of hyperglycaemia after pharmacotherapy initiation is needed. Moreover, future studies should examine whether different clinical subtypes of depression (i.e., melancholic, psychotic, atypical or undifferentiated) and bipolar disorder (e.g., type 1 or 2), specific mood states (manic, depressive, mixed or euthymic), or different antidepressants or mood stabilizers significantly moderate T2DM risk. For example, previous studies 45 found that some antidepressants may, in some circumstances, reduce hyperglycaemia, normalize glucose homeostasis and also increase insulin sensitivity, whereas others, including tricyclic antidepressants, may exacerbate glycaemic dysfunction or have little effect on glucose homeostasis 46,47.

Furthermore, the pathophysiology underlying the association between SMI and T2DM is complex and not well understood, requiring further investigation. Emerging evidence 48 suggests that SMI and T2DM share some pathophysiological features, including hypothalamic-pituitary-adrenal and mitochondrial dysfunction, neuro-inflammation, common genetic links and epigenetic interactions.

Future research should also comprehensively assess T2DM risk factors, and evaluate the optimal monitoring regimen and interventions. Finally, long-term follow-up is required to accurately document the emergence of more distal outcomes, such as ischemic heart disease, medical costs, and premature mortality 49.

REFERENCES

Smoking cessation should be an integral part of serious mental illness treatment

The treatment of persons with serious mental illness is finally beginning to incorporate smoking cessation1. Why has this taken so long? In part, the delay reflects widely held beliefs that smoking is beneficial for these patients, plus concerns that stopping smoking might exacerbate the underlying mental illness. In part, the change stems from emerging evidence about the pervasive effects of using combustible tobacco in general, and the huge differential toll smoking exerts on persons with behavioral health conditions.

Despite a gradual worldwide decline in smoking prevalence, tobacco remains the number one killer in the world (approximately 5 million deaths per year) and in developed nations such as the U.S. (540,000 annual deaths). Additionally, many people suffer from tobacco-attributable illnesses such as chronic lung and heart disease. In the U.S. alone, this amounts to an estimated 14 million people2. In addition to the well-known links with lung cancer, heart disease and chronic obstructive pulmonary disease, smoking is also associated with increased risk for premature delivery, Alzheimer’s disease, many oral-pharyngeal and gastrointestinal cancers, cataracts and osteoporosis. No other risk factor comes close as a cause of death and disease.

Because persons with mental illnesses not only are more likely to smoke but also smoke more frequently, they bear a disproportionate burden. For example, persons with behavioral health problems account for 25% of the adult population, but consume 40% of cigarettes sold in the U.S.3. These persons die much earlier than the general population, with estimates ranging from 8 to 20 years of life lost4. Most of the causes of early deaths come from smoking-attributable conditions, such as chronic lung and heart disease, diabetes and lung cancer.

Although the global prevalence of adult smoking declined between 1980 and 2012 from 41% to 31% for men, and from 11% to 6% for women, because of population growth the actual number of world smokers increased during that time, from 718 million to an estimated 966 million. In general, smoking prevalence for those with mental illness is two to three times higher than the overall population. Rates are highest in persons with schizophrenia and bipolar disorder. Recent declines in smoking in the U.S. did not include those with mental illness, who were then deprived of the major health benefits accruing from reduced smoking rates5.

The following myths about smoking and mental illness have been refuted by recent studies6:

Myth: Tobacco use is necessary self-medication. Response: Many symptoms relieved by smoking are in fact symptoms of nicotine withdrawal. Furthermore, some of the studies alleging benefit are suspect, since they were sponsored by the tobacco industry.

Myth: Persons with mental illness are not interested in quitting. Response: Studies have shown that smokers with mental illness are just as interested in quitting (about 70%) as the general population7.

Myth: Persons with mental illness are not able to quit. Response: Quit rates are low for all smokers, ranging from 3-5% for unassisted quit attempts to 16-30% for drug trials with strong counselling and follow-up. Probably the “real world” cessation rate for smokers receiving both counselling and cessation medications is more like 10-15%8. Despite this discouragingly low rate, after repeated quit attempts many smokers do quit; in the U.S. there are now more former smokers than current ones. Quit rates for smokers with mental health conditions mirror the results of the general population, although with slightly less success9.

Myth: Quitting worsens recovery from mental illnesses and also worsens prospects for sobriety in persons with substance use disorders. Response: As discussed below, stopping smoking can have a salutary effect on these conditions.

Myth: Smoking cessation is a low priority problem. Response: The urgency surrounding acute manifestations of psychiatric illnesses does often crowd out longer range considerations. But because smoking is the biggest killer of those with mental illness, attention to smoking cessation should be a paramount long range goal.

For many decades these myths have been ingrained within the culture of mental health treatment, resulting in ignoring tobacco use. Smoking was tolerated – and even rewarded – in treatment settings, and mental health clinicians themselves had higher rates of smoking than clinicians in other medical specialties1. Stopping smoking is the healthiest choice a patient can make, and health benefits accrue no matter what age cessation occurs. For someone quitting at ages 25-34 years, an additional 10 years of life are gained. Corresponding figures for later age groups are 9 years gained at ages 35-44 years, 8 years gained at 45-54 years, and 4 years gained at 55-64 years10. Even very old quitters live longer compared to those who continue smoking. Within one year of stopping smoking, the risk of coronary heart disease is only half of continuing smokers, and within 15 years it reaches that of people who never smoked. Within five years, the risk of a stroke decreases to that of a never-smoker; within ten years, lung cancer risk declines to half that of continuing smokers.

Beyond healthier lives and longer life spans, there are specific benefits for those with severe mental illness. Because some ingredients in tobacco smoke (but not nicotine) accelerate the catalysis of most antipsychotic drugs and many antidepressants, therapeutic levels of drugs established in smoke-free hospitals become sub-therapeutic when smoking resumes. In addition,
since in many nations smoking is becoming stigmatized, persistent smoking presents a barrier to integrating persons with mental illness into society. Another concern is costs: as tobacco taxes increase, the cost of acquiring cigarettes consumes a larger portion of the usually constrained budgets of those persons. Furthermore, a recent meta-analysis showed that smoking cessation leads to less depression, anxiety and stress, as well as increased positive mood and quality of life. These benefits apply equally to those with and without mental illnesses, and the effect sizes are equal to or larger than those of antidepressant treatment for mood and anxiety disorders. As evidence mounts about the harms from smoking and benefits from quitting, the culture of mental health treatment is evolving from one of well-meaning but ill-advised neglect to one embracing smoking cessation. Examples of that shift are the movement of state psychiatric hospitals in the U.S. from 20% smoke-free in 2005 to 83% by 2011; the increasing use of telephone quitlines by smokers with mental health conditions; and the actual or pending adoption of smoking cessation as a core policy by professional and advocacy organizations such as the American Psychiatric Nurses Association, the American Psychiatric Association, the American Psychological Association, and the National Alliance for Mental Illness. In addition, the Substance Abuse and Mental Health Services Administration, the largest U.S. federal agency focused on behavioral health clients, has integrated smoking cessation into its core goals.

Clinical approaches to smoking cessation mirror those used in the general population, following the principle that more is better. These include clinician advice, motivational interviewing, and – equally important and better if combined – counseling (including toll-free telephone quitlines) and one of the seven medications approved for smoking cessation (five forms of nicotine replacement therapy, bupropion and varenicline). In addition, there have been several programs focusing specifically on persons with serious mental illness, often including peer to peer counseling, involvement of clinic staff, outreach to community settings, plus longer duration of counseling and pharmacotherapy than recommended for the general population. Because smoking is such a huge health risk for persons with serious mental illness, the question is not whether smoking cessation should become an integral part of treatment, but how quickly that integration will proceed. Changing long-standing practice habits is daunting, and the powerful tobacco industry will continue to market its products aggressively. Several relevant issues are also unresolved, such as the risk/benefit ratio of the electronic cigarette and the risk profile of core smoking cessation medications such as varenicline. While it may be comforting to realize that declines in smoking will continue to occur among all populations, the truth is that every missed opportunity to accelerate that decline translates into needless death and disability.

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3. Substance Abuse and Mental Health Services Administration. Adults with mental illness or substance use disorder account for 40 percent of all cigarettes smoked. Rockville: Substance Abuse and Mental Health Services Administration, 2013.

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Physical activity and mental health: evidence is growing

Physical activity should be viewed as a continuum ranging from virtually no movement at all (e.g., sedentary behaviour or sitting time) through light physical activity (e.g., light ambulation) to moderate-to-vigorous physical activity, MVPA (e.g., exercise, playing sports, cycling to work). While it is often MVPA and “exercise” that are considered to be associated with better mental health, we should not rule out the positive changes that can occur from lower down the continuum. It is also important to note that people have widely varying preferences for the types of activity they wish to engage in. Some of the mental health benefits may be associated with doing something people “want to” and enjoy. We should not be too prescriptive, therefore, concerning the types of activity we recommend for mental health.

In the expanding literature on physical activity and mental health, researchers have addressed the effects of both single bouts and programs of physical activity. In addition, a wide variety of psychological outcomes have been studied, including effects on mood, self-esteem, cognitive functioning and decline, depression, and quality of life.

“Exercise makes you feel good” is a common assumption and refers to often-reported psychological effects of single bouts of physical activity, such as walking or structured exercise. While mood enhancement has been well documented,
this can be dependent on the intensity of exercise undertaken. While more moderate levels often lead to the reporting of pleasure and positive mood, more intense forms of exercise may lead to displeasure, although such feelings will subside with time after exercise. Such findings have implications for promoting physical activity. If we want more people to lead physically active lives, it may be better to avoid very high levels of exercise intensity.

It is often believed that physical activity, such as sport, can boost self-esteem. However, the nature of participation will affect whether self-esteem is elevated or even decreased. It is likely that changes in global self-esteem through physical activity will be from changes in aspects of the physical self, including improvements in skills and competence, body image, and physical fitness. Indeed, the association between physical activity and global self-esteem is small (meta-analytic effect size $d=0.23$), but at the level of physical self-worth or even body image these associations would expect to increase.

The argument that physical activity can positively affect cognitive functioning is a powerful one. This has been used to advocate for more physical activity in schools, as well as in older adults to ameliorate or prevent cognitive decline. A meta-analysis of randomized controlled trials (RCTs) examining exercise training studies in adults aged 55-80 years found that exercise was associated with enhanced cognitive functioning, especially for tasks involving more complex executive functioning. A meta-analysis of prospective studies found that baseline measures of physical activity predicted the risk of overall dementia and Alzheimer’s disease: the most active groups showed a 28% risk reduction for dementia and 45% risk reduction for Alzheimer’s disease compared to the least active.

Dishman et al assessed whether it is possible to state that there is a causal link between physical activity and cognitive decline. They used the five factors of strength of association, temporal sequencing, consistency, dose-response, and plausibility. It was concluded that there is increasing evidence suggestive of a causal link between physical activity and reduced risk of cognitive decline. However, there is a great deal of research still needed to increase our confidence that this conclusion is robust.

The most widely studied area of physical activity and mental health is that concerning depression. This has been researched as a transient sub-clinical mood effect or in populations with, or at risk of, clinical depression. For example, Dishman et al reported 20-33% lower odds of depression for active groups in prospective cohort studies. While the evidence has nearly always been suggestive of beneficial effects of physical activity on depression, media coverage, or the promotion of findings by journals, has sometimes been less positive. For example, the BMJ headline in 2001 suggested that exercise was not effective for the treatment of depression. This was based on a meta-analysis of 14 studies. Yet, the meta-analysis showed a large effect size ($-1.1$) for exercise compared to no-treatment. The authors stated that the effectiveness of exercise in reducing symptoms of depression “cannot be determined because of lack of good quality research on clinical populations with adequate follow up”. However, the results were similar to other therapies for depression.

The results of the TREAD trial also led to media-reported doubt about exercise for depression. This was a two-arm RCT with both arms receiving usual general practitioner care for depression and the intervention arm also having additional sessions with a physical activity counsellor. Both groups had decreased depression scores over time, but there was no advantage to the physical activity intervention arm. The authors noted that “clinicians and policy makers should alert people with depression that advice to increase physical activity will not increase their chances of recovery from depression”. This conclusion, however, may be misguided, because there was no waitlist or a no-treatment control group to compare to.

Physical activity has been used in interventions designed to reduce alcohol and other drug dependence and enhance smoking cessation. While the evidence is complex, it does support a role for physical activity in populations who often have low fitness or comorbidities such as depression. In addition, there is extensive evidence linking physical activity with improved sleep outcomes.

Strong compulsions to exercise, sometimes referred to as exercise “addiction” or “dependence” have been noted in psychiatry. Exercise dependence is characterized by a frequency of at least one exercise session per day, a stereotypical daily or weekly pattern of exercise, recognition of exercise being compulsive, and of withdrawal symptoms if there is an interruption to the normal routine, and reinstatement of the normal pattern within one or two days of a stoppage. The population prevalence of exercise dependence, however, is likely to be very low.

To sum up, physical activity is a major health behaviour strongly recommended for the prevention and treatment of several non-communicable diseases. The behaviour itself is multi-faceted and may comprise less sitting, more light-intensity activity, as well as traditional MVPA. The evidence concerning mental health effects is extensive, but still growing. Associations are clear, but more needs to be known about clinical effectiveness for some population groups and conditions, as well as on the underlying causal mechanisms responsible for what ancient societies have always been aware of, i.e., that “movement is good for you” and sloth is associated with poor mental and physical health.

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Is neuroimaging clinically useful in subjects at high risk for psychosis?

Although the massive amount of cross-sectional neuroimaging findings has improved our understanding of the pathophysiological processes underlying emerging psychosis, the clinical implications of these findings have remained scarce. To adequately examine the clinical utility of neuroimaging for the prediction of psychosis onset, a longitudinal analysis of brain changes over time with standardized measures is required. However, such study designs demand high efforts from both participants and investigators.

The few studies tracing gray matter volume over time found reductions in frontal, temporal, parietal and cerebellar cortex in high-risk subjects who developed psychosis\(^1\). Comparing the longitudinal course of converters with non-converters, some studies found reduced gray matter volumes in frontal, temporal and insular brain regions in the former\(^2\), while other studies reported no differences\(^3\). Considering white matter alterations, a longitudinal study found a progressive reduction in fractional anisotropy in the left frontal cortex of high-risk subjects who developed psychosis that was not evident in subjects who did not make the transition\(^4\). There is also a positron emission tomography (PET) study exploring presynaptic striatal dopaminergic function within subjects as they progressed from a prodromal phase to the first episode of psychosis, which found a progressive increase in striatal dopamine synthesis capacity as patients developed psychosis\(^5\).

Some limitations, however, prevent translation of these findings into clinical applications at the moment. The first issue is that most studies are clearly underpowered. The largest published study so far, from the North American Prodrome Longitudinal Study (NAPLS) project, has recently found a steeper rate of gray matter loss in frontal brain regions of 35 high-risk individuals who converted to psychosis compared to 239 subjects without transition\(^6\), but the low transition rate (14.6%) challenges whether these subjects were really at risk.

Another point of contention is the clinical heterogeneity of high-risk samples. This is due to the different high-risk criteria used across centres. Thus, an important next step is to develop standardized clinical instruments for the definition of the high-risk state and a consensus on what we are trying to predict. A further major point is the focus on univariate analyses at the group level. This strategy compares each voxel separately across groups and is thus not taking into account alterations of distributed brain patterns, which is critical given that psychosis is most probably characterized by abnormal (network) connectivity.

Fortunately, the field has been taking huge endeavours to address the above-mentioned limitations. Currently ongoing multicentre studies – such as PRONIA (Personalised Prognostic Tools for Early Psychosis Management), PSYSCAN (Translating Neuroimaging Findings From Research Into Clinical Practice) and NAPLS – will be able to overcome the hurdle of underpowered studies by collecting large high-risk data samples. These data sets should then be analyzed in the light of previously established evidence, leading to hypothesis-driven strategies rather than trying to find the needle in the haystack.

A first and probably the most straightforward strategy is to systematically follow-up replicated evidence from previous cross-sectional studies in chronic psychosis. A nice example of this strategy has been provided in a sample of 243 high-risk subjects obtained from the NAPLS project. This resting state functional magnetic resonance imaging (fMRI) study focused on thalamo-cortical connectivity, because this pathway has been previously implicated in established psychosis\(^7\). In particular, it explored whether thalamo-cortical connectivity differed between high-risk subjects and healthy controls and whether dysconnectivity was more severe in high-risk subjects with a later transition. The findings revealed hypo-connectivity between the thalamus and prefrontal and cerebellar areas, as well as hyper-connectivity between the thalamus and sensory-motor regions. Both patterns were more prominent in high-risk subjects who converted to psychosis and significantly correlated with prodromal symptom severity. This finding has now to be tested in longitudinal studies to probe whether thalamic connectivity does have prognostic implications for risk of conversion to full-blown psychosis. Furthermore, having in mind that the Human Connectome Project\(^8\) suggests that psychiatric disorders share overlapping patterns of dysconnectivity, it is important to compare longitudinal thalamo-cortical connectivity in high-risk converters with that of other psychiatric illnesses, to validate its specificity.

Another approach is to translate findings from animal research. A concrete example is provided by the methylazoxymethanol acetate (MAM) rodent model, which suggests that augmented hippocampal function (secondary to a loss of interneuron function) underlies elevated striatal dopamine levels associated with psychosis\(^9\). Although caution is required when translating findings from animals to humans, a recent review showed that neuroimaging findings in high-risk subjects are broadly consistent with the MAM model\(^10\). Guided by this model, recent cross-sectional investigations in high-risk samples are trying to relate functional with chemical measures within the hippocampal-midbrain-striatal network, which hopefully will provide a scaffold for longitudinal investigations.

However, to address alterations at the brain network level, as for example within the hippocampal-midbrain-striatal circuitry, more sophisticated connectivity approaches are required. Biophysically informed computational modeling allows unifying different aspects of information from the molecular to the system level, thereby helping to formulate more comprehensive pathophysiological hypotheses. One suitable computational
Identifying multimodal signatures associated with symptom clusters: the example of the IMAGEMEND project

Mental disorders are amongst the leading causes of disability worldwide. This is in part attributable to ongoing challenges in defining biological markers that can usefully aid in the diagnosis and treatment of individuals with these disorders. In order to move forward we need to address conceptual and experimental challenges that include: a) imprecise determination of the pathophysiological processes involved; b) insufficiently powered patient cohorts; c) uninformative pharmacological probes, given the poor differentiation in mode of action of existing agents; d) the logistic complexity of the multi-site investigations needed to establish generalizability and reproducibility; e) the limited predictive and explanatory power of individual biological markers; f) concerns about the statistical, logistic and financial viability of complex algorithms in routine care.

The Imaging Genetics for Mental Disorders (IMAGEMEND) project provides a platform for addressing these challenges. It brings together 14 institutions from nine countries (Australia, Germany, Iceland, Italy, Norway, Switzerland, The Netherlands, U.K. and U.S.). Workflow is organized in targeted workpackages. The focus is on three disorders – schizophrenia, bipolar disorder and attention-deficit hyperactivity disorder (ADHD) – that show significant genetic, environmental and clinical overlap. Here we outline the conceptual premises and organizational design of the project. Details on the samples, measures and bioinformatics approaches used can be found at http://www.imagemend.eu/.

The first essential element of the project is its transdiagnostic focus. Multiple lines of evidence support the notion that pathophysiological processes relevant to mental disorders may be more directly linked to symptom clusters transcending diagnostic boundaries than to specific syndromes1. The goal of the study is to identify multimodal signatures associated with symptom clusters using a data-driven approach that harnesses the power of the collaborative bioresource of the
Consortium. However, current clinical diagnoses are both familiar to clinicians and patients and also form the basis of current treatment planning and drug licensing. With this in mind, the study will also test whether DSM and ICD diagnoses of schizophrenia, bipolar disorder and ADHD may be associated with multimodal signatures that can be clinically useful.

A second essential element of the project is the multimodal systems-level approach. Three research modalities, namely neuroimaging, genetics and environmental exposures, have made significant contributions to our current understanding of mental disorders. Neuroimaging has documented that schizophrenia, bipolar disorder and ADHD are brain disorders that involve structural and functional neural networks\(^1\)-\(^4\). Alterations in these networks have been shown to have diagnostic relevance in differentiating patients from controls\(^5\) and in predicting outcome\(^6\) and treatment response\(^7\). Environmental exposures, such as urbanicity\(^8\), and genetic variation\(^9\) known to increase the risk of polygenic scores\(^10\) based on available genetic studies of risk. The availability of genotypic data enables the estimation of diagnosis or course of treatment response. Additionaly, therapeutic tools will include a clinical real-time functional magnetic resonance imaging software with a novel interface that allows illness-related selection of feedback paradigms and automatic definition of brain regions and networks for individualized neurofeedback training.

To sum up, IMAGEMEND is a large collaborative effort to identify clinically relevant multimodal signatures, based on a systems-level understanding of pathophysiological processes, and to translate this knowledge into tools for the advancement of clinical care for mental disorders.

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The 30-year mental health legacy of the Chernobyl disaster

Thirty years ago, on April 26, 1986, the Chernobyl nuclear power plant exploded, emitting tons of radionuclides into the atmosphere and exposing millions of people in Ukraine and neighboring countries to the fallout. Ultimately, 350,000 people living near the plant were permanently relocated, and 600,000 military and civilian personnel from throughout the Soviet Union were recruited as clean-up workers (locally referred to as liquidators). By the 20th anniversary (2006), ~6,000 children under age 18 in 1986 were diagnosed with papillary thyroid cancer, an otherwise rare disease. At the 25th anniversary (2011), the liquidators were found to have increased rates of leukemia, other hematological malignancies, thyroid cancer, and cataracts. Yet, from a public health perspective, the biggest impact of the Chernobyl disaster throughout the years has been on mental health, specifically major depression, anxiety disorders, post-traumatic stress disorder (PTSD), stress-related symptoms, and medically unexplained physical symptoms. The most vulnerable segments of the population have been women from the Chernobyl region who were pregnant or had young children in 1986, and liquidators, particularly those who worked at the site in April to October, 1986.

The mental health effects were fueled in part by an exaggerated sense of the danger to health from presumed exposure to radiation, that was propelled by the local medical community and government officials. Liquidators, evacuees and people living in contaminated regions were officially labeled as “sufferers” or “Chernobyl victims”, terms that were adopted by the mass media. Being recognized as a Chernobyl “victim” entitled people to financial, medical and educational compensation, which, combined with continuous monitoring by local and international organizations, may have had an iatrogenic effect on psychological well-being.

In our 25-year review of the impact of Chernobyl on mental health, we concluded that the psychological consequences, especially for mothers and liquidators, continued to be a concern, and that mental health care in affected regions was not adequate to meet their needs. Given the extensive literature on comorbidity of mental and physical health, we also called on surveillance and long-term medical studies to integrate mental health measures into their assessment protocols. To our knowledge, the latter recommendations have not yet been fully embraced.

Between the 25th and 30th anniversaries, with a single exception, no new epidemiologic studies of the long-term mental health aftermath of Chernobyl were conducted. Rather, recent publications are based on data obtained prior to 2011. The exception is a health registry study in Tallinn, Estonia, that found an increase in clinical diagnoses of nervous system disorders and intentional self-harm in liquidators compared to controls. Other recently published research on liquidators includes a survey from Tallinn that confirmed findings from Ukraine about elevated rates of common mental disorders and suicidal ideation, and papers on neurocognitive abnormalities in Ukrainian liquidators. However, in sharp contrast to Chernobyl cancer studies, the results reported in the latter studies from Ukraine have not been verified by an international panel of experts.

Consistent with findings from early studies conducted in Gomel (Belarus) and Bryansk (Russia), two recent papers analyzed data from general population surveys conducted prior to 2011 and found poorer life satisfaction and socio-economic well-being among residents of areas with mildly elevated levels of radiation (albeit within normal limits of natural background radiation) compared to other areas. The authors also estimated that these socio-economic adversities had a substantial negative impact on Ukraine’s global gross domestic product. The authors inferred that these differences were a consequence of negative risk perceptions about radiation, though these perceptions were not measured directly. To our knowledge, no other reliably sampled, general population surveys of affected regions have been published.

In our 25 year review, we pointed out that findings regarding the cognitive functioning of children exposed in utero or as infants were inconsistent and suggested that any plans for continued monitoring of their health should include neurocognitive and psychological measures as well as indicators of social and occupational functioning. This cohort is now in their early 30s. No new light has been shed on this highly contentious issue. We maintain that the most reliable, direct and transparent evidence points to no significant impact of (low-level) radiation exposure on this cohort. However, we continue to advocate for a long-term study of the biopsychosocial and neuropsychiatric wellbeing of this cohort compared to demographically similar controls. This is particularly critical because early childhood exposure to major stress, which many of these children experienced as a result of their mothers’ and physicians’ concerns about their health and life expectancy, is a well-established risk factor for adult onset psychopathology. It is also imperative that such a long-term study be conducted collaboratively by international experts and local scientists, as was the case in our own research, and that dissemination of study findings be done by local authorities entrusted with the welfare of the population.

It is unfortunate that not a single Chernobyl related mental health intervention trial has been published. On the other hand, it is important to emphasize that the majority of people we and others have studied in relation to Chernobyl did not have a psychiatric diagnosis or elevated psychiatric symptomatology. Indeed, what has been missing from past research is an emphasis on understanding resilience. The importance of identifying and treating psychologically vulnerable individuals after disasters is incontrovertible. However, it is equally important not to overstate the effect, as this may further contribute to a culture of victimhood.

There is growing concern in Ukraine about the neuropsychiatric effects of the war on the Eastern border on combat personnel. It is important to determine if rates of PTSD in this personnel
Problem Management Plus (PM+): pilot trial of a WHO transdiagnostic psychological intervention in conflict-affected Pakistan

The mental health consequences of conflict and natural disaster are substantial and wide-ranging\(^1\)-\(^3\). There is an urgent need for interventions by non-specialist workers that can address a range of mental health problems\(^3\). The World Health Organization (WHO)'s Problem Management Plus (PM+) is a brief transdiagnostic psychological intervention employing evidence-based strategies of problem solving, behavioural activation, strengthening social support, and stress management\(^4\).

We adapted the individual treatment format of this intervention for conflict-affected Peshawar in Pakistan. It consisted of five face-to-face sessions, with a key feature of being affordable in most settings, because it can be offered not only by specialists but also by supervised non-specialists with no prior training or experience in mental health care delivery. We used an apprenticeship (on-the-job learning) model for training and supervising the non-specialists\(^5\), which involved an initial 6-day training programme by a master trainer to local mental health specialists, who in turn provided an 8-day training programme to six non-specialists. Training of both supervisors and non-specialists was followed by four weeks of practice under supervision of the local trainers. The local trainers themselves were supervised 3-weekly through audio calls by the master trainer, building skills in the intervention as well as in training and supervision. All non-specialists were evaluated for their competency by independent assessors using a competency rating tool evaluating basic helping skills and use of PM+ strategies through observation of specially designed role plays. Competency was rated using a 5-point scale. In total, four out of six achieved scores indicating competency in all basic helping skills and five out of six achieved all competency scores on PM+ strategies. Following additional training and supervision, all non-specialists demonstrated adequate proficiency in requisite skills.

We conducted a single-blind pilot randomized controlled trial (RCT) to explore the feasibility and acceptability of the intervention in Peshawar. PM+ was compared to enhanced treatment as usual, consisting of management by primary care physician who received one day of basic training in treatment of common mental disorders. The study was conducted from March to May 2014 in two primary care centres in Gulbahar Union Council, a low-income peri-urban locality in Peshawar district. Participants were primary care attenders aged 18 or above, referred for screening by the primary care physician. Screening was conducted by trained members of the research team following informed consent to recruit persons with both marked distress and impairment. Invited participants scored: a) 2 or above on the General Health Questionnaire (GHQ-12)\(^6\), a 12 item questionnaire of general psychological distress with a 4-point scale ranging from 0 to 3 scored bi-modally when used as a screener (possible range 0-12), and b) 17 or above on the WHO Disability Assessment Schedule (WHODAS 2.0)\(^7\), a screener for functional impairment with 12 items measured on a scale ranging from 1 to 5 (possible range 12-60). We excluded individuals with imminent suicide risk, severe cognitive impairment (e.g., severe intellectual disability or dementia) or with expressed acute needs/protection risks (e.g., recent abandonment by husband and his family). We also excluded individuals who reported having experienced a major traumatic event during the past month and individuals with severe mental disorder (psychotic disorders, substance dependence). Individuals meeting the exclusion criteria were referred to specialist centres depending upon their needs.

Ethical approvals were obtained from the Ethics Review Board at the Lady Reading Hospital, Peshawar, and WHO's Ethical Review Committee. Approval was also obtained from the district primary care administration. Participants were interviewed after voluntary written consent. Out of 1,286 people seen by a physician during the study period, 94 were referred for screening, 85 met study criteria, 81 were accessible, and 60 consented to participate in the trial. Randomization to the PM+ intervention or enhanced treatment as usual was performed by an independent researcher not involved in the project.
Treating post-traumatic stress disorder by resource activation in Cambodia

There is a need for effective, low-threshold psychotherapeutic treatments in post-conflict settings. However, systematic outcome research on site is still extremely rare. To address this problem we integrated rigorous research procedures into a humanitarian program, the so called Mekong Project, and conducted a randomized controlled trial for the treatment of post-traumatic stress disorder (PTSD) in Cambodia. In short, the Mekong Project aims at establishing independent psychotherapeutic services in several Southeast Asian countries via the systematic training of local health professionals and offering free of charge psychological help to traumatized civilians.

Cambodia is one of the least developed countries in Asia, facing many challenges (e.g., poor standards of health and education, rural exodus, and political instability). Mental health morbidity in Cambodia is high. It has been found that 53.4% of the Cambodian population suffer from a mental disorder, with anxiety and PTSD being the most frequent (40.0% and 28.4% respectively). Thus, although some stability has been observed in Cambodia, the need for urgent mental health care remains. The results of this pilot study should encourage further adaptation and large-scale fully-powered RCTs of this new, transdiagnostic psychological intervention.

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(EMDR) (short: ROTATE). ROTATE aims at strengthening resilience and coping capacities by activating positive personal resources, and largely draws on psychodynamic principles of the therapeutic relationship. It includes a variety of imagina-
tive resource-activating methods as well as resource develop-
ment and installation, an EMDR technique aiming at system-
itically developing and anchoring resources using alternating
bilateral stimulation. ROTATE has several advantages: a) it can be safely applied even to complex trauma conditions, with no major side effects being observed so far; b) instead of solely focusing on PTSD symptoms, it also considers the mental comorbidities typically found in these clients, notably depression and anxiety; c) it is especially suitable for clients from non-Western countries, as traditional healing resources like mindfulness strategies can be integrated in an overall frame-
work of resource activation; d) its basic elements can easily be
taught, even to paraprofessionals.

Our trial was carried out in cooperation with the Royal Uni-
versity of Phnom Penh and was located in Phnom Penh City
and the nearby Kandal Province. Help-seeking outpatients
screening positively for PTSD (PTSD Check List ≥ 44) were eli-
gible for inclusion. We allowed for comorbid mental health
conditions except for psychosis, organic brain disorder, cogni-
tive impairment, dementia, acute suicidality, and acute need
for treatment.

Overall, 800 patients were screened for eligibility, of whom
86 (mean age 27 years, 61% female) fulfilled the selection crite-
ria and were randomly assigned to either 5 weekly sessions of
ROTATE (N=53) or a 5-week waiting list control group (N=33).
Symptoms were measured before and after the intervention
(or waiting period). Assessments were performed via personal
interview by an investigator blind to treatment allocation. All
patients in the control group were offered treatment after the
end of the waiting period. The primary outcome was PTSD
symptom change on the Indochinese version of the Harvard Trauma Questionnaire (HTQ). The PTSD scale of the HTQ
includes 16 items reflecting the DSM-IV criteria for PTSD. Sec-
ondary outcomes included depression, anxiety and social
functioning. All applied instruments have been validated for
the Cambodian population. The therapy was provided by six
Cambodian psychologists who had completed a 3-year course
in trauma therapy as part of the Mekong Project.

Based on previous findings of psychological therapies for
PTSD, we expected ROTATE to be superior to waiting list with
a between group effect size of at least d=0.65 on the primary
outcome. To detect this difference with a power of 0.80 at
x=0.05, 2-sided test, 2 × 40 patients were required. Unfortu-
nately, the concept of randomization, especially being ran-
domized to a waiting list, was very difficult for some clients. As
a consequence, randomization failed in 38 patients, leading to
an unbalanced allocation ratio (1.6:1), with an overrepresen-
tation of patients randomized to treatment. The trial stopped
when the necessary sample size to achieve a power of 0.80 was
reached. Data were analyzed by general linear regression mod-
els, controlling for baseline symptom severity. The drop-out
rate during the intervention was very low (N=2, one in each
group), thus only complete data were analyzed (N=84).

Most frequent types of trauma were traffic accidents (24%),
domestic violence (23%) and sexual abuse (16%). Patients
receiving ROTATE showed significant reductions in PTSD
symptoms compared to the waiting list (baseline adjusted
means post-treatment: 1.39, 95% CI: 1.23-1.54 for ROTATE,
and 2.86, 95% CI: 2.66-3.06 for waiting list, p<0.00001). The
between-group effect size was large (d=2.59). The within-
group effect size was also large for ROTATE (d=4.43), while it
was moderate in the control group (d=0.52). No harms were
reported.

We conclude that a treatment focusing on stabilization ra-
ther than confrontation, by establishing a secure patient-
therapist relationship, applying stabilization techniques, and
putting an emphasis on a patient’s own resources, significantly
reduced symptoms of PTSD in comparison to a waiting list.

The strengths of our study are the following: a) it was con-
ducted on site by local psychologists, which meant that com-
munication between therapists and patients was natural and
no interpreters were needed; b) therapists and patients had
similar cultural backgrounds, so that culture specific interpre-
tations of symptoms could be taken into account, a factor that
has been identified as vital in the therapeutic work with Cam-
bodian patients; c) local psychologists were trained in ROTATE,
which is expected to facilitate patient access to a psychological
treatment in a country struggling with insufficient mental
health care.

Conducting a randomized controlled trial in a developing
country is challenging. Nevertheless, we were able to show
that the implementation of such a trial was possible and that
this specific form of trauma therapy was well accepted by
therapists and patients. Our results are preliminary but prom-
fising. Further research is required to corroborate the findings.


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3. Reddemann L. Psychodynamic imaginative trauma therapy, PITT – Manu-
High burden of subthreshold DSM-5 post-traumatic stress disorder in U.S. military veterans

A substantial proportion of individuals worldwide develop post-traumatic stress disorder (PTSD) following exposure to traumatic events. Although the epidemiology of PTSD has been widely studied, fewer studies have examined subthreshold PTSD, defined as experiencing clinically significant symptoms of PTSD but not meeting full diagnostic criteria for the disorder. With the field of psychiatry increasingly moving towards a dimensional perspective of mental disorders, it is important to understand the burden of subthreshold manifestations of these disorders.

The lifetime prevalence of subthreshold PTSD has ranged from 3.6 to 25.6%. While not a formal diagnosis, subthreshold PTSD is associated with elevated rates of comorbid psychiatric disorders, suicidality, and physical health problems compared to trauma-exposed individuals without subthreshold or threshold PTSD. To date, however, only two studies have examined the epidemiology of subthreshold PTSD as defined using the DSM-5. The first analyzed data from the World Health Organization World Mental Health Surveys and found that the prevalence of subthreshold PTSD ranged from 0.7 to 4.6%, depending on the definition used. Further, individuals with subthreshold PTSD were 2.5-5 times more likely to have a comorbid mood or anxiety disorder compared to trauma-exposed controls. This study was limited by the operationalization of PTSD, which was derived from a DSM-IV module and did not include the new DSM-5 symptoms. The second study of a national sample of Vietnam veterans found that the prevalence of current subthreshold PTSD ranged from 1.9 to 5.7%, and that the comorbidity between DSM-5 subthreshold PTSD and comorbid disorders ranged from 0.7 to 30.9%. While these studies provide important insight into the prevalence and correlates of subthreshold DSM-5 PTSD, additional population-based data are needed to better understand the burden of this condition.

We analyzed data from the National Health and Resilience in Veterans Study (NHRVS), a contemporary, nationally representative cohort of U.S. military veterans, to examine the prevalence and clinical correlates of DSM-5 subthreshold PTSD. The NHRVS, conducted in 2013, surveyed 1,484 veterans aged 20+. The sample was ascertained from KnowledgePanel, a nationally representative survey research panel representing approximately 98% of U.S. households. Post-stratification weights were applied to permit generalizability of results to the U.S. veteran population. Study constructs were assessed with the following tools: Trauma History Screen, PTSD Checklist for DSM-5 (PCL-5), Mini International Neuropsychiatric Interview and Patient Health Questionnaire-4 for lifetime and current psychopathology, respectively, Fagerstöm Test for Nicotine Dependence, and Short Form-8 (SF-8) Health Survey for mental and physical functioning.

Lifetime PCL-5 responses were used to create a three-group variable: a) no/low PTSD symptoms (defined as endorsement of ≤1 PTSD criteria B-E at a severity of “moderate” or higher); b) subthreshold DSM-5 PTSD (defined as endorsement of 2 or 3 B-E criteria, or all 4 B-E criteria but not 1 month symptom duration and/or functional impairment); and c) probable lifetime DSM-5 PTSD (defined as meeting criteria A-G for PTSD). A comparable three-level variable was created for past-month PTSD symptoms, with a score ≥38 on the PCL-5 distinguishing between subthreshold and probable PTSD in the absence of past-month symptom duration and functional impairment assessment in the NHRVS. Weighted prevalence of lifetime and past-month subthreshold DSM-5 PTSD was computed in the full sample (N=1,478; 6 subjects had missing data). Other analyses were conducted in only trauma-exposed veterans (N=1,268). Logistic regression and multivariable analyses of covariance were conducted to examine associations of probable and subthreshold PTSD with comorbid psychiatric disorders and SF-8 scores. Analyses were adjusted for socio-demographic variables, combat veteran status, number of lifetime traumas, and any lifetime mental disorder.

The lifetime and past-month prevalence of subthreshold PTSD was 22.1% and 13.5%, respectively, and, higher than the prevalence of lifetime (8.0%) and past-month (4.5%) probable PTSD. The prevalence of lifetime subthreshold PTSD was higher in women than in men (30.3% vs. 21.2%, X²=10.3, p=0.006) and, although the prevalence of lifetime probable PTSD decreased across age groups (20.8% in 18-34 year olds to 1.9% in 75+ year olds), the prevalence of subthreshold PTSD remained relatively stable across all but the 75+ age group (21.1% to 26.6%).

Lifetime subthreshold PTSD was associated with a greater likelihood of all lifetime (i.e., major depressive, social anxiety, alcohol and drug use disorders) and current (i.e., major depressive and generalized anxiety disorders, suicidal ideation) psychiatric outcomes, except nicotine dependence, relative to veterans reporting no/low symptoms (adjusted odds ratio, AOR range from 1.7 for lifetime alcohol use disorder to 4.9 for current generalized anxiety disorder). Veterans with probable PTSD had a greater likelihood of all outcomes relative to veterans with no/low symptoms, and these associations were numerically larger in magnitude relative to the subthreshold PTSD group (AOR range...
Big Data in mental health: a challenging fragmented future

Big Data has been a buzzword in almost every possible field during the last few years. The rapid integration of massive amounts of information from diverse sources fed the hope for a new era also in health sciences. Following its impact on other fields (i.e., marketing and commerce), many authors hypothesized that, by dynamically merging diverse datasets and a mining process, groundbreaking conclusions would be obtained in almost every medical specialty. This would, allegedly, represent a paradigm shift on how research is performed and, as a consequence, a dramatic change in clinical practice.

Neurosciences were not out of this wave of – somewhat grandiose – expectations over the Big Data potential, given the increasing need to bridge the gap between brain structure/function and behavior. This complexity requires a comprehensive, holistic perspective in order to fully understand the course of an illness. However, one of the most important limitations in brain research is that it has so far yielded partial, diverse and not generalizable results, which can hardly be directly transferred into clinical practice. Moreover, psychiatry research has not been able to link the current taxonomy and brain functioning, so that psychiatry is apparently doomed to remain one of the few medical branches in which nosology does not relate to etiology. Therefore, the Big Data promise seemed like a hand in a glove to get the full picture of psychiatric disorders and fill the gap between biomedical and behavioral data. Yet, as years went by, Big Data stood still as it was first born: a promise failing to bring significant integrative answers to neurosciences.

While Big Data relies on numerous and different sources of information, the wide availability of mobile technologies is, out of doubt, amongst the most significant factors that boosted its potential. Mobile devices with hundreds of sensors and powerful processors are carried ubiquitously all day long by more and more people, for multiple and seamless purposes. This is gradually surpassing personal computers usage as a source of information for Big Data. In addition, there is an increasing preference of consumers to integrate mobile technologies and the data they can offer into their own personal health care. Physical activity, sleep patterns and location tracking data sets are easily obtained from either increasingly cheaper smartphones or newer, discrete and affordable wearables. Big technological corporations did not miss this opportunity, offering a number of devices and cloud services which could store and integrate all the health data generated (e.g., Apple’s Health, Google Fit). Likewise, some of these companies grew progressively interested in health research through their promising platforms (Apple Research kit and Google Study kit, respectively).

These technologies can bring many advantages over traditional research methods in mental health. For instance, ecological momentary assessments allow a continuous and real-time assessment of mental health states, offering the possibility of studying the effects of external factors on mental health. Moreover, the use of social media data could provide insights into the social and environmental factors that influence mental health. However, there are also several challenges and ethical issues that need to be addressed, such as data privacy and security, the interpretation of data, and the potential for oversimplification of complex mental health phenomena. Therefore, the potential of Big Data in mental health is enormous, but its realization will require careful consideration of these challenges and ethical issues.
time data collection in the subject’s own environment. Additionally, users’ interactions with their mobile devices and their respective sensors could provide passive, objective information about their behavior patterns. In theory, this kind of information has the potential to help designing newer prophylactic strategies as well as allowing personalized treatments. Moreover, integrating behavioral and biomedical data (i.e., genetics, biomarkers, neuroimaging, etc.) and analyzing these datasets could ultimately allow the development of new predictive models, and the identification of previously unsuspected etiopathogenic factors and possibly new treatment targets.

However, in practice, big challenges lie ahead in the pathway of translating the above promises into reality alongside the expected barriers of age and education level. One problem affecting not only behavioral sciences, but all mobile technologies which could provide an essential component of Big Data, is that of fragmentation. The market fragmentation of current mobile operating systems (Android, iOS, Windows Phone, Blackberry, etc.) and smartphones ownership represents a still unaddressed and growing issue in the field. According to the International Telecommunications Union, in 2015, around 95% of the worldwide population had a subscription for a mobile-cellular telephone, but less than 50% of these devices were connected to the Internet. Among smartphones users, Android and iOS together have 96.4% of market share according to the International Data Corporation, with 78% of this amount pertaining to Android. The fragmentation in the market of wearable devices is much more problematic, with more than 20 companies offering these products, which are continuously feeding information to independent databases.

Hence, the promising future of the components of Big Data provided by mobile devices might be severely hampered by the companies’ aim of selling their own products with data collected through non-open platforms. In other words, any smartphone or wearable provides relevant information to databases owned by these companies, not available for being exported or integrated with clinical information.

In order to obtain significant results from the promised potential of Big Data, it may seem that fragmentation is a small technical problem in comparison to other relevant issues, such as ethical and sociological aspects. However, keeping in mind that the ultimate goal of the Big Data promise is to integrate data from multiple sources and that mobile technologies play a key role in this process, fragmentation should not be underestimated. This problem can be overcome on the long run, providing there is a true effort of both public and private sectors to altruistically collaborate towards an open health science, which could ultimately improve health research and as a result have a significant impact on public health.

### Specific anxiety disorders and subsequent risk for bipolar disorder: a nationwide study

Anxiety disorders are highly prevalent in people with bipolar disorder and substantially worsen the course of the illness as well as treatment response. Anxiety disorders typically precede the onset of bipolar disorder and might therefore represent markers of risk for subsequent bipolar disorder. However, anxiety disorders are heterogeneous, and large-scale studies delineating their relationship to bipolar disorder are scarce.

We conducted a large population-based study in order to determine which specific anxiety disorders increase the risk of developing bipolar disorder. We also assessed whether patients with anxiety disorders are more likely to transition from unipolar to bipolar disorder, and which specific anxiety disorders in parents increase their offspring’s risk for bipolar disorder.

Using the Danish Civil Registration System, we selected a cohort of 3,379,205 people born in Denmark between January 1, 1955 and November 31, 2006. We identified all patients diagnosed with bipolar disorder (ICD-8: 296.19 and 296.39; ICD-10: F30.00-F31.90) based on the Danish Psychiatric Central Registry and the Danish National Hospital Registry. Next we singled out individual and parental diagnoses of anxiety disorders leading to in- and outpatient contacts (ICD-10: F40.00-F40.20, F41.00-F41.10, F42.00-F42.99, F43.10; covering agoraphobia, generalized anxiety disorder (GAD), obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, specific phobia, and social phobia) and psychiatric case history in general (ICD-8 codes: 290-315; ICD-10 codes: F00-F99).
Data were examined by survival analysis following cohort members from their 5th birthday or January 1, 1995 until the onset of bipolar disorder, date of death, date of emigration from Denmark, or December 31, 2012, whichever occurred first. In incidence analyses, we determined the risk for bipolar disorder in patients with anxiety disorders compared to the general population, using a log linear Poisson regression model as implemented in SAS, version 9.3 (SAS Institute, Cary, NC, USA) and adjusted for calendar year, age, gender, place of residence at time of birth, and the interaction of age with gender. We subsequently tested whether anxiety disorders were also associated with a higher risk for bipolar disorder among persons with a psychiatric case history. Finally, we evaluated whether any specific anxiety disorder contributed to the risk for bipolar disorder over and above anxiety disorders in general.

In the analyses focusing on the risk of transition from unipolar depression to bipolar disorder, cohort members were followed from their first contact due to depression (ICD-8 code: 296.09, 296.29, 296.89, 296.99, 298.09, 298.19, 300.49 and 301.19; ICD-10 code: F32.00-F32.9, F33.00-F33.99, F34.10-F34.90 and F38.00-F39.99) or January 1, 1995 until first admission for bipolar disorder, date of death, date of emigration from Denmark, or December 31, 2012, whichever occurred first. We compared the transition rates for specific anxiety disorders to anxiety disorders in general. The effect of parental anxiety disorders was determined using a hierarchical model simultaneously adjusting for calendar year, age, gender, place of residence at time of birth, and the interaction of age with gender. The incidence rate ratio (IRR) was calculated using log-likelihood estimation. The p values and 95% confidence intervals (CIs) were based on likelihood ratio tests.

Among the 3,167,632 persons followed from 1995 to 2012, 9,283 were diagnosed with bipolar disorder during the 49,148,258 person-years at risk. Of those patients, 8.0% had been previously diagnosed with an anxiety disorder, corresponding to a crude IRR of 13.03 (95% CI: 12.10-13.78) and an adjusted IRR of 9.11 (95% CI: 8.44-9.82) for patients with anxiety disorders compared to the general population. All specific anxiety disorders increased the risk for bipolar disorder, with GAD (IRR = 1.41, 95% CI: 1.31-1.53) and panic disorder (IRR = 2.64, 95% CI: 2.29-3.04) and parental anxiety disorder (IRR = 1.20, 95% CI: 0.99-1.45) additionally increased the offspring’s transition risk.

The results of this prospective study show a nine times higher risk of bipolar disorder among patients with anxiety disorders compared to the general population. The effect of specific anxiety disorders seemed differential, as GAD and panic disorder were found to increase the risk for bipolar disorder more than anxiety disorders in general. Patients with comorbid anxiety disorders were also more likely to transition from unipolar to bipolar disorder. Anxiety disorders were linked with a higher risk of bipolar disorder across generations: parental anxiety disorders were found to significantly increase the offspring’s risk to be diagnosed with bipolar disorder and to transition from unipolar to bipolar disorder. Although a direct causal interpretation is not possible, these associations might have important implications for clinical practice. Screening for anxiety disorders could allow the identification of high-risk individuals who might benefit from careful mood monitoring and possibly targeted interventions (e.g., people with anxiety disorders whose parents have a bipolar disorder).

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Tracing Emil Kraepelin in the Nobel Prize archive

The medical historian E. Ackerknecht argued that the trends of 20th century medicine are illustrated by the names of those who received the Nobel Prize for physiology or medicine. If we follow this assumption, where does psychiatry stand? To date, three Nobel prizes have been awarded to psychiatrists or in recognition of psychiatric therapies: J. Wagner-Jauregg received the prize in 1927 for his discovery of the therapeautical value of malaria inoculation in the treatment of dementia paralytica, A.E. Moniz in 1949 for his discovery of the therapeutical value of lobotomy in certain psychoses, and E. Kandel in 2000 for his research on the physiological basis of memory storage in neurons.

As we went through nomination letters in the Nobel Prize archive in Sweden, we noticed that some scholars were disturbed by the fact that so few scientists within the field of psychiatry had been honoured. In 1958, the German psychiatrist K. Kolle, for example, stated in a nomination for K. Jaspers: “Last year I expressed my irritation that besides Wagner-Jauregg no single clinical psychiatrist has been considered prize-worthy”. To give historical examples of overlooked candidates, Kolle mentioned E. Kraepelin.

Indeed, Kraepelin was nominated for the Nobel Prize eight times, over a period of 17 years. The nominators were R. Gaupp from Tübingen in 1909, E. Meyer from Königsberg in 1911, E. Bleuler from Zurich in 1917, again R. Gaupp in 1918, O. Bumke from Leipzig and again E. Bleuler in 1923, G. Mingazzini from Rome in 1925, and W. Weygandt from Hamburg in 1926.

R. Gaupp stated that Kraepelin had not only revolutionized scientific psychiatry in theory and practice, but also that his engagement regarding the temperance movement and his ideas on how to protect the German race had to be taken into consideration. E. Bleuler argued that Kraepelin had managed to form a basis for scientific psychiatry by “cutting stairs into the mountain”, so that all clinicians could benefit from his work.

W. Weygandt stated that psychiatry as a whole had been a chaotic disaster before Kraepelin, and that he had introduced experimental psychological methods to foster the understanding of mental diseases in a previously unimagined way. However, Weygandt’s nomination had an unexpected twist which was also hidden in other nominations: he was not able to point at one single discovery by Kraepelin that would deserve the Nobel Prize. Instead, Weygandt put Wagner-Jauregg up front for his work on malaria inoculation.

It is noteworthy that both Wagner-Jauregg and Moniz would no longer be regarded as prize-worthy from today’s perspective. However, the significance of their contributions turned out obvious for the Nobel Prize committee. One “breakthrough” technique rather than gradual successful work or a lifetime achievement seemed to be at the root of the Nobel Prize recognition. Indeed, M. Sakel also received much attention for his insulin shock therapy, widely used in patients with schizophrenia in the 1930s, and his nominators compared him with Wagner-Jauregg, arguing that he had been at least equally influential, and that insulin shock therapy had a much wider application than malariasever therapy. Other strong candidates were U. Cerletti and L. Bini, who introduced electroconvulsive therapy in the late 1930s.

In summary, Kraepelin’s Nobel Prize sponsors were full of praise for his systematic clinical observations and classifications, experimental studies of mental processes, and for linking psychiatry with public health and racial hygiene. However, the nominations remained half-hearted, in the absence of clear practical results or solid evidence. The nominators used unspecific phrases such as “Kraepelin has completely changed the standards of psychiatry” which in the end did not make him a prime candidate. Even worse, some of the nominators after the praise of Kraepelin promoted other candidates. This explains the final negative outcome.

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Files on E. Kraepelin in the Nobel Prize archive were kindly provided by the Nobel Committee for Physiology or Medicine, Medicinska Nobelinstitutet, Solna, Sweden.


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Correction

It has been brought to our attention that in the References of the paper “Treatment engagement of individuals experiencing mental illness: review and update”, by Dixon et al, published in the February 2016 issue of World Psychiatry, the author in ref. 8 was reported incorrectly. The correct reference is: Stewart KD. Factors contributing to engagement during the initial stages of treatment for psychosis. Qual Health Res 2012;23:336-47.
Improving the mental health of women and girls: psychiatrists as partners for change

The WPA was established to promote the advancement of psychiatry and mental health for all citizens of the world. As a global association, it is in a unique position to support the initiatives of its Member Societies and work in partnership with regional societies and other international organizations.

Its ability to promote sustainable change and improvement depends on two main factors. One is its capacity to collaborate successfully with other organizations. The other is its potential to engage psychiatrists from around the world in new challenges. The expertise of psychiatrists is essential to promote good health and offer comprehensive health care. Our patients and their families need us to work alongside them and other partners in clinical practice, teaching, research and advocacy. The WPA and its Member Societies need to be centrally involved in national and international debates, policies and initiatives in mental health.

Every three years the WPA reassesses priorities within its strategy. Recent action plans have focused on defining the needs for advancement in psychiatry and mental health, on education and psychiatry, and on social justice and mental health. Building on all these initiatives, the priority for action in 2017-2020 will be the mental health of women and girls, particularly those living in adversity caused by poverty, war, natural disasters, and exposure to interpersonal violence and human rights abuse. Mental health is integral to women’s overall health, and connected closely with their central roles in the development of civil societies and the health and functioning of their families. It is a neglected priority in health, child development and economic development, especially but not exclusively in low- and middle-income countries.

The mental health of women and girls is intimately and intricately interwoven with their social status, economic status and hence their participation as valued members of society. From conception, the life experiences of women and girls differ from those of men and boys. The biggest differences reflect disparities in opportunities, responsibilities and roles through life. These have consequences for all aspects of health, including mental health. Overlooking the mental health needs of women has significant, deleterious effects on the functioning of women and their families and the wellbeing of the next generation, and on social cohesion. M. French Gates wrote recently in the journal Science that “the development field needs to be more serious about gender inequities and women’s empowerment … helping women and girls realize their own power to advance the wellbeing of their families, their communities, and their societies”.

Participation and the empowerment underlying it, as advocated also by UN Women, are components of good mental health and wellbeing. The strategies for promoting mental health in women and girls and tackling mental health problems include a strong focus on changing social attitudes and investment, which require involvement of multiple stakeholders.

The WPA program will support mental health promotion among women and girls as well as the prevention and treatment of mental illnesses. It will take necessarily a cross-sectoral approach. It will collaborate in local and international initiatives to address human rights, education, social and economic participation, safety and freedom from discrimination, as an essential first step to improving mental health. The WPA will work with partners to provide unbiased information about the magnitude and nature of the problems in different settings and globally and the interventions that can be used by health and social services and other sectors to promote mental health. In the health sector, it will support gender-sensitive clinical and public health services, and gender-informed research to gather local evidence and monitor and evaluate interventions.

The WPA will work with local and international partners in specific disadvantaged regions to identify needs, develop projects and evaluate the outcomes and their sustainability. The settings for action include community groups, schools, primary health care, and maternal and child health services. The WPA will encourage psychiatrists and other mental health professionals to use their expertise in diverse settings to promote participatory approaches to health and mental health and facilitate the mental health work of non-specialists across a range of community settings.

Important needs are: the psychological consequences of violence, including violence in the home, genital mutilation, rape and the trafficking of women and girls for prostitution; improving mental health in the perinatal period; the isolation of women as caregivers; deaths from suicide among young women in low- and middle-income countries; and the needs of women and girls in displaced populations and in emergencies.

The mental health challenges facing women and men are different. The needs of women and girls are considered separately for this reason. The fact that the WPA is developing a program on women’s mental health does not neglect the mental health needs of men and boys. On the contrary, we wish to understand and exploit the interconnected needs of women and girls, men and boys and develop interventions that work across genders as well as those that are gender specific.

This program will be complemented by another one that focuses on improving the conditions for people living with long-standing mental illnesses and disabilities, and their caregivers, in mental hospitals and other settings. Both will be built on a set of principles for the
prevention and treatment of mental ill health and the promotion of mental health, matched with the purposes of WPA. They will be supported by activities in a range of topics important to the future of psychiatry and improved mental health for women, men and children around the world.

These plans gain momentum from the international attention focused on the need to include both the health of women (and children) and mental health among the new sustainable development goals. The WPA can contribute to the establishment and achievement of these goals in low- and middle-income countries, and equivalent initiatives among disadvantaged groups in high-income settings. My colleagues and I are eager to receive comments and suggestions about how, together, we can develop these programs.

Helen Herrman
President Elect, World Psychiatric Association


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WPA Scientific Sections: update on the activities

Scientific Sections are coming up as an essential component of WPA and play a pivotal role in promoting and disseminating scientific knowledge around the globe. The current number of Sections has increased to 72, with Sections on Positive Psychiatry, Stress Research, and Early Career Psychiatrists as the new ones approved during 2015. Inclusion of Early Career Psychiatrists is proving an important step towards involvement of young psychiatrists in the WPA functioning as well as for developing their leadership skills and enhancing their organizational abilities.

As Sections keep on having their elections every three years, it is encouraging to note that new and younger members are getting elected for officer positions. This indeed reflects their keen desire and enthusiasm for their future contributions towards WPA’s work. The Sections’ Operational Committee is currently reviewing the by-laws related to Sections’ functioning and is going to submit its recommendations to the Planning Committee. There have also been some discussions on Sections’ future work, including clustering of Sections on the basis of common interests and activities. This will hopefully help to promote further collaboration and links among Sections.

During the years 2014-2015, there has been a noticeable increase in the number of WPA co-sponsored meetings, joint intersectional activities and other related intersectional accomplishments. Scientific Sections have also continued developing training courses and producing position statements. Noteworthy among the latter is the Position Statement on Spirituality and Religion in Psychiatry, published in the February 2016 issue of World Psychiatry.

The WPA Action Plan for 2014-2017 has been another focal point for many Sections’ activities during this triennium. 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 mental health promotion and prevention psychiatry by producing educational materials for the WPA website.

Intersectional collaboration has continued to be a focused activity for a number of Sections during the current triennium. Organization of Intersectional Forums and Intersectional Educational Programmes has been an ongoing practice at WPA Regional and International Conferences held in Romania, Taiwan and Philippines, and similar activities are planned for the forthcoming meetings in Turkey and South Africa during this year.

Section officers and members are also contributing extensively to the WPA official journal World Psychiatry. Their interest and participation in the development of the chapter on mental disorders of the ICD-11 is another ongoing contribution to the psychiatric field.

Programmes promoting the interest of medical students in the field of psychiatry as a future career have also been a focus for the current work of Sections. Sections on Education and Early Career Psychiatrists, in particular, have been involved in formulating a plan with the following remit: a) to prepare a WPA statement on “Promoting psychiatry as an inspiring medical speciality and introducing psychiatry as a prospective future career for medical students”; b) to set up programmes for promotion of psychiatry in undergraduate medical education, exploring innovative ways of engaging medical students in psychiatry and collating examples of good practice; c) to prepare general educational materials for medical students introducing psychiatry as an essential medical discipline; d) to prepare an outline of the topics that need to be incorporated in the undergraduate curriculum. It is expected that this work will be completed and highlighted in the scientific deliberations of 2016 WPA International Conferences, with a proposed round table discussion in Cape Town on developments in this area.

It is anticipated that the current enthusiasm of Sections’ leadership and
their dedicated work will continue adding further contributions to the progress of scientific knowledge and the development of innovative approaches in psychiatric practice.

Afzal Javed
WPA Secretary for Sections


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The World Psychiatric Association (WPA)

The WPA is an association of national psychiatric societies aimed to increase knowledge and skills necessary for work in the field of mental health and the care for the mentally ill. Its member societies are presently 135, spanning 118 different countries and representing more than 200,000 psychiatrists. The WPA organizes the World Congress of Psychiatry every three years. It also organizes international and regional congresses and meetings, and thematic conferences. It has 69 scientific sections, aimed to disseminate information and promote collaborative work in specific domains of psychiatry. It has produced several educational programmes and series of books. It has developed ethical guidelines for psychiatric practice, including the Madrid Declaration (1996).

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

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World Psychiatry

World Psychiatry is the official journal of the World Psychiatric Association. It is published in three issues per year and is sent free of charge to psychiatrists whose names and addresses are provided by WPA member societies and sections. Research Reports containing unpublished data are welcome for submission to the journal. They should be subdivided into four sections (Introduction, Methods, Results, Discussion).

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