Psychoses sans frontieres: towards an interdisciplinary understanding of psychosis risk amongst migrants and their descendants

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Abstract

Understanding the excess risk of psychotic disorders in migrant and ethnic minority groups has long been an important research focus in psychiatric epidemiology and public mental health. Heterogeneity between migrant groups based on region of origin, minority status and other socioeconomic factors may provide clues as to the underlying aetiological mechanisms explaining this risk, as well as informing our general understanding of psychotic disorders. Nonetheless, disentangling the mechanisms underlying this association has been the focus of more speculation and theory to date than empirical research. Now more than ever, we need to move beyond studies which demonstrate excess rates in migrant and ethnic minority groups to novel population-based studies which identify the determinants and mechanisms through which this risk is shaped. In this article we review the main hypotheses proposed to explain these disparities and current level of support for them. We then highlight recent evidence from epidemiology and neuroscience which provides important new clues in our understanding of the aetiology of psychotic disorders. We concluded with suggestions for future interdisciplinary research to prevent this public mental health inequality within a generation.

Overview of psychosis risk in migrant and ethnic minority groups

Understanding the excess risk of psychotic disorders in migrant and ethnic minority groups has long been an important research focus in psychiatric epidemiology and public mental health. First observed by Ødegaard (1932) in the 1930s, further epidemiological research in the past four decades has consistently demonstrated that migrants and their children have, on average, over twice the risk of developing psychosis compared with native-born individuals (Cantor-Graae & Selten 2005; Bourque *et al.* 2011). Further research suggests that the association between psychosis and migration may extend to third generation groups (Coid *et al.* 2008; Amad *et al.* 2013). Exact risk appears to vary based on region of origin and visible minority status (Bourque *et al.* 2011), with black African and Caribbean groups in Europe at up to 5 times higher risk than their white European counterparts. To date, much of this research has been conducted in Northern Europe, including a large number of studies from the UK, Sweden, Denmark, and the Netherlands (Cantor-Graae *et al.* 2003; Fearon *et al.* 2006; Hogerzeil *et al.* 2016; Hollander *et al.* 2016). More recently these findings have been extended to other European settings, including France (Tortelli *et al.* 2014) and Italy (Tarricone *et al.* 2012; Lasalvia *et al.* 2014), extending the international evidence base. While less research has been conducted outside of Europe, studies from North America show similar trends (Bresnahan *et al.* 2007; DeVylder *et al.* 2013; Anderson *et al.* 2015). Two studies in Israel have found discrepant findings. The first found increased psychosis risk in both migrants and their children (Weiser *et al.* 2008), although the second found no such evidence children of migrants compared with Israeli-born individuals (Corcoran *et al.* 2009).

Despite this exception, the overwhelming body of evidence reveals a strong, consistent association between migrant status and psychosis risk, marking this out as a critical and pressing public mental health priority. Heterogeneity between migrant groups based on region of origin, minority status and other socioeconomic factors may provide clues as to the underlying aetiological mechanisms explaining this risk, as well as informing our general understanding of psychotic disorders. Nonetheless, disentangling the mechanisms underlying this association has been the focus of more speculation and theory to date than empirical research. In this article, we argue that now more than ever, we need to move beyond studies which consistently and robustly demonstrate a disproportionate burden of psychotic disorders is shouldered by a few migrant and ethnic minority groups to novel population-based studies which seek to identify the determinants and mechanisms through which this risk is shaped. In the next section, we briefly review the main hypotheses which have been proposed to explain these severe mental health disparities and the current level of support for them. In the following two sections, we highlight recent evidence from epidemiology and neuroscience generating important new clues in the search for aetiological factors which account for the excess psychosis risk in some migrant groups. We concluded with suggestions for future research.

Main hypotheses

Several hypotheses have been proposed to explain excess risks in several migrant and ethnic minority groups (see Box 1). Here, we provide a brief overview of those hypotheses, and the current strength of evidence to support them.

<Box 1 about here>

Prior to migration, several factors have been proposed to explain elevated risk amongst migrant groups (Bhugra 2000; Fung *et al.* 2009; Hollander *et al.* 2016). For example, higher background rates

of psychotic disorder in migrants' countries of origin have been proposed as one possible explanation of excess rates in migrant groups. However, research conducted in Jamaica (Hickling & Rodgers-Johnson 1995), Trinidad (Bhugra *et al.* 1996), and Barbados (Mahy *et al.*, 1999) has refuted this explanation for the excess rates observed in black Caribbean migrants (Kirkbride *et al.* 2012; Tortelli *et al.* 2015). Such research means that the excess risk of psychosis amongst these migrants cannot be accounted for solely by genetic factors. Although important, comparable studies outside of these Caribbean islands is missing. We do not know whether the excess rates of psychotic disorder observed in ethnic minority groups of black African, Pakistani and Bangladeshi origin is due to higher rates in their countries of origin, and further epidemiological studies in other low and middle income countries are urgently required (see, for example, Morgan *et al.*, 2016).

Selective migration of individuals at risk of psychosis was one of the earliest hypotheses proposed to explain elevated rates of psychotic disorder in migrants (Ødegaard 1932). Current evidence strongly refutes this possibility (Lundberg *et al.* 2007; van der Ven *et al.* 2015), notwithstanding the possibility that exposure to pre-migratory traumas partially increases psychosis risk in migrants (Hollander *et al.* 2016). Experiences of trauma or social adversity may be important push factors for some migrants who choose – or are forced – to emigrate. In non-migrants, exposure to trauma (Schäfer & Fisher 2011), loss (Morgan *et al.* 2007) or cumulative disadvantage (Morgan *et al.* 2008) may increase psychotic disorder and symptoms, particularly amongst those vulnerable to psychosis (Spauwen *et al.* 2006). Relatedly, a recent study in Sweden found refugees were 66% more likely to be diagnosed with schizophrenia than non-refugee migrants from the same region of origin (Hollander *et al.* 2016), consistent with a role for additional traumas in the aetiological pathway. Direct evidence for such an effect, is, however, missing and should be a priority for future epidemiological research in this field. Recently, frequently moving house in childhood and adolescence, which may both result from and generate social instability, has been associated with increased risk of future psychotic disorders (Price *et al.* n.d.).

In addition to exposures prior to migration, migration itself may be a risk factor for psychosis. Migration can be a stressful or traumatic experience, particularly when people encounter difficulties during transit, in obtaining temporary residence in a "transit" country, or if detained upon arrival in the host country (Al-Baldawi 2002). Like other stressors, if these occur during vulnerable developmental periods, this may increase psychosis risk; several studies have shown that migration during childhood and adolescence increases risk (Veling *et al.* 2011; Pedersen & Cantor-Graae 2012; Kirkbride *et al.* 2017). Differential migration experiences, including the presence of family members, access to resources, and the social and economic position of the migrants may affect the level of stress experienced during the migration process (Al-Baldawi 2002), but further research is needed to better understand these different experiences. While factors prior to and during migration may explain some of the elevated risk amongst migrants, they are not able to account for the observed excess risk in children of migrants (Bourque *et al.* 2011), suggesting that post-migratory factors also affect psychosis risk.

These factors may include acculturative stresses, social adversity, experiences of discrimination, living in areas of low ethnic density or social defeat. Acculturative stress, including low mastery of dominant language, has been associated with increased psychological distress in migrants (Fassaert *et al.* 2011), though this has yet to be examined for psychosis. Acculturating to a new society may be more challenging for migrants from culturally distant areas, which may explain part of the heterogeneity in risk based on region of origin. Social adversity, including low socioeconomic status, unemployment, poor housing, poverty, social exclusion, and discrimination has been linked to increased risk of developing psychosis (Wicks *et al.* 2005), and specifically accounts for some (but not

all) of the excess psychosis risk in migrant populations (Hjern, Wicks and Dalman, 2004; Kirkbride *et al.*, 2008). Experiences of interpersonal discrimination and systemic racism in the post-migration environment have also been associated with elevated risk of psychotic symptoms (Oh *et al.* 2014) and disorders (Veling *et al.* 2007) in ethnic minority groups. Furthermore, perceived discrimination has been observed to predict conversion to psychosis in people at high risk of psychotic disorders (Stowkowy *et al.* 2016). Not all studies have observed that perceived discrimination is a risk factor for schizophrenia (Veling *et al.* 2008a), and further research on this issue is required. Social defeat, or the prolonged exclusion from the majority group, may play a role in the development of psychosis (Selten & Cantor-Graae 2005; Selten *et al.* 2013). Social defeat may also be linked to experiences of interpersonal discrimination and systemic racism which may include negative stereotyping of people from ethnic minority groups, can restrict the opportunities people of ethnic minority groups have available, including educational attainment, access to safe and secure housing, or employment status. While social defeat is an attractive hypothesis, it is yet to be operationalised in empirical research. Nonetheless, there is strong evidence that social adversities increase the risk of psychosis generally, and that migrant groups may be more likely to experience multiple forms of such adversity.

Cultural biases in psychiatric care resulting in the misdiagnosis of psychotic disorders amongst migrant groups has also been suggested as an explanation for excess psychosis risk. However, while racialized stereotypes has been shown to affect clinical judgment, it is not clear that this results in over-diagnosis of schizophrenia within migrant and ethnic minority groups (Lewis *et al.* 1990). Use of a "culturally-sensitive" diagnostic tool over standard diagnostic assessments reduced the relative risk of schizophrenia observed in Moroccan migrants in the Netherlands (Zandi *et al.* 2010). Nevertheless, use of such a tool has been disputed (Selten *et al.* 2010). Overall levels of non-schizophrenia psychotic disorders remained over four times greater in Moroccan immigrants using either diagnostic tool, making it unlikely that these raised rates could be attributable to misdiagnosis. Nonetheless, it has been suggested that systemic racism within the mental healthcare system could lead to misunderstanding of symptoms, misdiagnosis, and non-optimal treatment for those with mental health problems (McKenzie and Bhui, 2014). Since the consequences of misdiagnosis, or incorrect attribution of excess rates of psychotic disorder in migrant and ethnic minority groups to misdiagnosis, will have harmful effects on the public mental health of these groups, we require carefully-conducted, unbiased epidemiological studies to categorically resolve this issue.

Finally, increased exposure to biological factors before, during, and after migration, including infection, obstetric complications, or Vitamin D insufficiency, may also provide clues to the observed elevation in psychosis risk. Limited research has investigated if prenatal infection (Selten *et al.* 1998, 2000; Brown 2006) or obstetric complications (Hutchinson *et al.* 1997; O'Neill *et al.* 2016) explain excess psychosis risk in migrants and their children. While there is some evidence that prenatal infection may increase rates of psychosis in offspring (Brown 2006), other studies did not find evidence that prenatal infection explained elevated risk in the children of migrants (Selten *et al.* 1998, 2000). Similarly, obstetric complications have been posited as a biologically plausible explanation for the elevated risk of psychosis (Morgan *et al.* 2010), however, studies to date have been inconclusive (O'Neill *et al.* 2016). An alternate hypothesis for elevated rates of psychosis in migrants is Vitamin D insufficiency, whereby reductions in sun exposure, particularly for migrants with dark skin, could result in higher rates of psychosis (McGrath 2011; Huibers *et al.* 2014). Vitamin D insufficiency in pregnant migrants could also affect psychosis risk in their offspring (McGrath 1999; Dealberto 2007).

The current evidence-base most is most consistent with a role for social determinants in accounting for the excess risk of psychotic disorders in migrants and their descendants. Nevertheless, hypotheses which posit that biological factors or even cultural and methodological biases may account for these raised rates have received insufficient empirical attention to date, and novel studies will be required to further test such possibilities. In the next section, we present emerging evidence from psychiatric epidemiology which may potentially shed new light on these questions.

An emerging evidence-base

Although not a new idea (Faris & Dunham 1939), a consistent line of studies have found evidence that the proportion of ethnic minority groups at the neighbourhood level is inversely proportional to psychosis risk faced by such groups (Mintz & Schwartz 1964; Boydell *et al.* 2001; Kirkbride *et al.* 2007, 2008b; Veling *et al.* 2008b; Schofield *et al.* 2011, 2017, 2018; Richardson *et al.* 2018). If causal, the mechanism through which ethnic density affects psychosis would be most consistent with a "social adversities" hypothesis. Indeed, it is less obvious how increased psychosis risk following exposure to other environmental exposures, including vitamin D deficiency, obstetric complications or cannabis use would be conditional on the ethnic density of one's immediate neighbourhood. Instead, it seems more parsimonious to suppose that people exposed to high levels of own-group ethnic density may benefit from greater bonding social capital conferred through similar or shared sociocultural, ethnic or immigrant backgrounds, and as a result mitigates social stress which may have otherwise increased psychosis risk. While intuitive, this theory is predicated on two assumptions which have yet to be fully proven. First, that bonding social capital is associated with reduced psychosis risk, for which there is some, though not definitive support (Kirkbride *et al.*, 2008), and second that failing to mitigate exposure to social stress leads to altered neurobiological processes implicated in psychosis (see below). More fundamental and epidemiological research is needed to answer these important questions, and to rule out methodological artefact as possible explanation. Most obviously, ascertainment bias may be patterned by ethnic density, if people with psychotic disorder from communities with higher levels of own-group ethnic density are less likely to be enumerated within the context of healthcare systems or via epidemiological research. Recent research has used longitudinal data to show that neighbourhood ethnic density at age 15 is inversely associated with subsequent migrant risk of non-affective psychosis (Schofield *et al.* 2017). Demonstration of such temporality is potentially consistent with causality, although replication of this finding in other settings is clearly necessary. Further research is also needed to determine whether ethnic density matters for all groups, including the majority population, whether threshold effects exist, and whether ethnic density effects exist for first and later generation migrants. Interestingly, recent research suggests that ethnic density may have a strong protective effect in children of migrants compared with their parents (Schofield *et al.* 2018).

Neighbourhood ethnic density may not operate in the same way for all groups with respect to psychosis risk. In one study in East London (Kirkbride *et al.* 2014), neighbourhood-level own-group ethnic density was associated with a reduced incidence of non-affective psychosis in people of black African origin, but for people from black Caribbean backgrounds better integration into the general population was a more important driver of reduced rates. These patterns emphasise the need to more carefully consider the social contexts in which people live their lives, and whether different acculturation strategies (i.e. Berry *et al.*, 1987) adopted by different individuals and groups affect future psychosis risk. In the example above, the findings may lead one to consider whether for people of black African origin living in East London, maintaining a strong ethnic identity was an important component of a socially cohesive group, which led to better social support, less stress and

lower rates of psychosis. By contrast, for those of Caribbean descent in the same community, integration with the remainder of the population may have been a more desirable social outcome, reducing stressors associated with social exclusion and leading to lower psychosis rates. While such studies provide clues as to possible hypotheses, testing these ideas often rubs up against the limits of psychiatric epidemiology, particularly in studies using register-based or routine datasets. Sample sizes for rare outcomes in some minority populations are often too small to even investigate ethnic density effects, let alone the underlying meaning, social narratives and acculturative strategies which might be in play amongst a diverse population. We suggest that genuine interdisciplinary research will be needed to tackle these issues, where qualitative studies are an inherent feature of the design of large, mixed methods studies to understand the risk and protective factors experienced by migrant and ethnic minority groups. Epidemiological studies should continue to play a central role in designing representative samples from which to explore these issues and test novel questions. One such example is demonstrated through the application of a novel method to examine familial social capital at the time of immigration amongst those immigrating to Sweden (Dykxhoorn *et al.* 2018). Exploiting family-linkages in the Swedish register data, this prospective cohort study of over 800,000 immigrants to Sweden was able to examine whether migrating with or to join first degree relatives in Sweden conferred any protection against risk of non-affective psychosis. The study found that for women, migrating alone increased future psychosis risk by around 40%. Interestingly, however, migrating with or to join immediate family increased risk for men by up to 30%. These results, while requiring confirmation, imply that even at the most basic level, the psychosocial processes experienced during migration may differ for men and women. This is support by another study which have shown that women, but not men, from Pakistani and Bangladeshi backgrounds (Kirkbride *et al.* 2008a) – and particularly first generation migrants (Coid *et al.* 2008) – are at substantially elevated rates of psychotic disorder, increasing the possibility that social isolation experienced during or after migration has an impact on risk.

Beyond psychiatric epidemiology

Emerging neuroscience supports the possibility that exposure to migration and minority status are associated with structural and functional differences relevant to psychosis. For example, in non-psychotic volunteers, Akdeniz et al (2014) demonstrated that second generation Turkish groups in Germany showed greater reactivity in the amygdala and perigenual Anterior Cingulate Cortex (pACC) in response to social stress following disapproving observed feedback following a stress test (arithmetic). This area of the brain is involved in emotion and stress processing, and has been shown to be disrupted in people with schizophrenia (Radua *et al.* 2012). Moreover, in the same study (Akdeniz *et al.*, 2014), people who perceived their ethnic group as experiencing more discrimination (which has been associated with psychosis risk (Veling *et al.* 2007)) showed greater activation in the pACC and ventral striatum, a region strongly associated with the onset of psychotic symptoms following dopaminergic dysregulation (Howes & Murray 2014). Indeed, elevated stress-induced striatal dopamine release and synthesis capacity has been demonstrated in migrants compared with non-migrants via positron emission topography [PET], a difference which became progressively more pronounced in clinical high risk and FEP groups (Egerton *et al.* 2017). Other recent evidence suggests that people of both white and black ethnicity show greater activation in the amygdala and pACC in response to outgroup faces. Interestingly, for people of black ethnicity, this reactivity was greater amongst those living in less ethnically dense neighbourhoods. It has been suggested that this emerging evidence, which needs to be strengthened by further work in epidemiological samples, including those with FEP, supports the possibility that neural social stress processing is disrupted in

groups exposed to social marginalisation, including migrants, ethnic minorities and others who may be subjugated by other groups (Akdeniz *et al.* 2014a).

Future directions

Converging evidence supports a causal association between migrant and ethnic minority status and subsequent risk of psychotic disorder. Epidemiological studies have been pivotal in demonstrating this gross public mental health inequality, but we now need to develop novel, epidemiologically-informed interdisciplinary longitudinal studies to identify the risk and protective factors which underpin this risk. These studies should include qualitative components and input from a variety of stakeholders, including public and patient involvement, to identify the potential experiences most likely to account for these inequalities. Current evidence supports a role for exposure to social adversity, isolation or traumas occurring before, during or after immigration, or as an ethnic minority group. Nevertheless, fundamental epidemiological research is also needed to more fully test whether other factors – including biological factors such as inflammation, infection or vitamin D deficiency – account for any of the excess risks observed in migrants and their descendants. We also need better study designs which carefully and objectively test the extent to which misdiagnosis may account for any variation in psychosis risk. Generating such new knowledge, which will inform our aetiological understanding of psychotic disorders, should be regarded as an international priority in the context of unprecedented global migration. Our risk of being diagnosed with psychotic disorder should not be conditional on whether or not we chose – or in some cases are forced – to cross national borders. With accelerated investment in research in this field, we should be able to identify and prevent the factors which give rise to this global public mental health inequality within a generation.

Acknowledgements

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Box 1: Main hypotheses proposed to account for higher rates of psychotic disorder in migrants & their descendants

Hypothesis	Description	Dominant narrative	Quality of evidence (e.g.s)
Social adversities	Pre-, during or post-migratory stressors increase risk, particularly in childhood & adolescence	Accepted	Strong (Price *et al.* n.d.; Morgan *et al.* 2007, 2008; Hollander *et al.* 2016)
Sociodemographic differences	Confounding by age, sex or socioeconomic status	Refuted	Strong (Kirkbride *et al.*, 2008; Kirkbride *et al.*, 2017)
Selection effects	People with liability to psychosis more likely to migrate	Refuted	Strong (Ødegaard 1932; Selten *et al.* 2002; van der Ven *et al.* 2015)
Misdiagnosis	Raised rates in BME groups due to racial bias in clinical diagnoses or culturally insensitive diagnostic tools	Refuted	Indirect (Lewis *et al.* 1990; Hickling *et al.* 1999; Fearon *et al.* 2006; Heuvelman *et al.* 2018)
Infections, obstetric complications, substance use	Greater exposure to these risk factors confound the association between psychosis risk and BME status	Refuted	Limited (Hutchinson *et al.* 1997) / indirect (Sandwijk *et al.* 1995; Coulthard *et al.* 2002; Veen *et al.* 2002; Sharp & Budd 2003)
Higher rates in county of origin	Higher background rate in other countries mean this is not a migration / BME effect *per se*	Refuted	Limited to Caribbean (Hickling and Rodgers-Johnson, 1995; Bhugra *et al.*, 1996; Mahy *et al.*, 1999)
Novel hypotheses	Mechanisms through exposure to social or other early-life adversities (i.e. substance use, obstetric complications, infections) impact psychosis mediated via cognitive impairments	Untested	Untested

Legend: Main hypotheses to explain elevated psychosis risk in migrants and their descendants. Current evidence most consistently supports a social adversities hypothesis, while sociodemographic and selection effects have been refuted on the basis of reasonable evidence. Other hypotheses have been refuted, but the evidence base to do so is indirect or limited (yellow and red boxes, right hand column), suggesting this may be premature. Novel hypotheses require investigation.