Migrant and ethnic minority status as risk indicators for schizophrenia: new findings

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Purpose of review
Arguably, the strongest evidence of an environmental contribution to the cause of psychosis is the increased risk for certain groups of migrants and ethnic minorities. This article summarizes findings published since 2016.

Recent findings
Two studies suggested that migration or minority status are proxies for exposure to an inferior social status. A study from Bologna, Italy, showed that the psychosis risk for internal migrants from Southern Italy was as much increased as that for international migrants. A report from New Zealand reported a higher risk for Maoris than for the remainder of the population.

Furthermore, a Danish investigation showed that own-group ethnic density of the neighbourhood at age 15 strongly modified the psychosis risk at adult age. This rules out differential mobility during the prodromal phase as an explanation for the ethnic density effect. Preliminary evidence suggests that the psychotogenic effect of migration may be mediated by elevated dopamine in the striatum.

Summary
An increasing body of evidence suggests that the higher psychosis risk for certain migrant or ethnic minority groups is due to an inferior social status. Neuroimaging of the dopamine system appears to be a promising avenue for research into pathogenesis.

Keywords
dopamine, ethnicity, migration, schizophrenia, social exclusion

INTRODUCTION
Previous work has demonstrated an increased risk of nonaffective psychotic disorder (NAPD) for migrants and their children, with pooled risk ratios of 2.3 [95% confidence interval (95% CI) 2.0–2.7] for first and 2.1 (95% CI 1.8–2.5) for second-generation immigrants [1]. There is also evidence of an increased risk for certain ethnic minorities. Bresnahan et al. [2], for example, reported an increased risk for African-Americans. The aim of this review is to provide an update of relevant epidemiological, biological and experimental findings published in 2016 and 2017. It concerns migrants and their children, as well as members of ethnic minority groups without a migration history who share with migrants the experience of minority-related stress.

IS THE INCREASED PSYCHOSIS RISK IN IMMIGRANTS A TRUE FINDING?
Sampling and diagnostic bias have been suggested to (partially) account for findings supporting the association between migrant status and risk for NAPD.

Sampling bias
Hogerzeil et al. [3*,4] compared two methodologies for including new psychosis cases in incidence studies, the first-contact and the longitudinal register-method. This was possible in the city of the Hague where a first-contact incidence study was conducted, while at the same time a psychiatric register was operational. Because the first-contact approach had a tendency to miss older Dutch patients who

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The increased incidence of NAPD in certain migrant and ethnic minority groups appears to be a true finding that cannot be explained in terms of diagnostic or sampling bias. This increased risk also applies to internal migrants and ethnic minorities without migration history, emphasizing the role of outsider position in psychosis aetiology. Living in a high own-group ethnic density area during puberty protects against the onset of psychosis in later life. Preliminary evidence shows that the association between migrant status and risk of NAPD may be mediated by elevated dopamine in the striatal regions.

were treated for another disorder before the onset of psychosis, the longitudinal psychiatric register method resulted in a significantly higher incidence in this group [4]. On the basis of register data, the incidence of schizophrenia among immigrant groups was still significantly increased [relative risk (RR) = 1.7; 95% CI 1.3–2.2], but less increased than when based on the first-contact method (RR = 1.9; 95% CI 1.2–3.3) [3*].

Although these findings are of interest, it is worthwhile to note that many registry studies from Sweden, Denmark and the Netherlands counted new cases of psychotic disorder, regardless of previous contacts for other disorders, and reported consistently increased psychosis incidence rates for migrants from developing countries [5–7].

Sampling bias may also arise when incident cases are not treated in the regular mental health-care system and not included in incidence studies. A systematic review reported consistently higher prevalence rates of psychotic disorder among black migrant and ethnic minority detainees in different parts of the world, including Australia, Western Europe and the USA [8].

In conclusion, sampling bias is probably present in most studies and may augment or attenuate the true relative risk of psychotic disorder in migrant and ethnic minority groups. Although its influence is unlikely to change overall conclusions, efforts should be made to minimize sampling bias.

Diagnostic bias

Zandi et al. [9] interviewed native Dutch and Moroccan-Dutch patients twice: using a standard version and a culturally sensitive version of the Comprehensive Assessment of Symptoms and History (CASH and CASH-CS, respectively) [10,11]. Using the standard version, they found a tendency towards over-detection of delusions and under-detection of mania in Moroccan-Dutch patients.

Using another outcome than diagnostic categories, Termorshuizen et al. [12*] examined dispensing rates of antipsychotic medication by ethnicity in the four largest Dutch cities. Adjusted for age, sex, socioeconomic status (SES) and household composition, the RR for incident dispensing of antipsychotics among the Turkish and Moroccan-Dutch was 2.1 (95% CI 1.9–2.3) and 2.1 (95% CI 1.9–2.4) respectively. Remarkably, incident and prevalent dispensing of antipsychotics was not increased among Surinamese and Antillean-Dutch individuals, for whom an increased incidence of psychotic disorder has been reported [13,14]. This may be explained by undertreatment or a decreasing incidence over time, due to successful integration [12*]. It is important to mention, however, that dispensing of antipsychotic medication does not equal the prevalence or incidence of psychotic disorder, because this medication is also prescribed to individuals with other diagnoses.

Pignon et al. [15] conducted a survey in a large sample of the French population. They reported a significantly increased prevalence of both psychotic disorder, and subclinical psychotic symptoms in first, second and third-generation migrants, which supports the influence of migrant position along the psychosis continuum [16].

It has been suggested that an excess of brief, reactive psychoses causes a high incidence in Black minorities [17]. Consequently, the results of a 10-year follow-up study in the UK are of great interest. AESOP-10 concerns 532 individuals who initially presented with a first-episode psychosis (FEP) in three relatively deprived and ethnically diverse catchment areas in south-east London and Nottingham [18**]. Compared with White British patients, the trajectory of psychosis in Black Caribbean patients showed a more continuous course of illness and lower rates of recovery. Both Black Caribbean and Black African patients had worse social functioning and service use outcomes through their course of illness, including a higher likelihood of compulsory admission and police involvement. Intriguingly, the difference seemed to increase after more years of follow-up, which may explain why some previous short-term follow-up studies failed to detect this [18**]. For example, the GAP-5 study reports on the 5-year outcome of 245 FEP patients of the same ethnic groups in South London using electronic psychiatric clinical notes [19]. They found similar ethnic disparities in service use outcomes, that is, more compulsion and longer hospital
IS THE INCREASED RISK FOR NONAFFECTIVE PSYCHOTIC DISORDER AMONG IMMIGRANTS A SPECIFIC FINDING?

A meta-analysis of the incidence studies of mood disorders in first and second-generation immigrants obtained a slightly increased risk in the first, not the second generation (RR = 1.3, 95% CI 1.1–1.4). Furthermore, there was no evidence of a significantly increased risk of bipolar affective disorder [20]. A large population survey in France observed a similar pattern: an increased lifetime prevalence for unipolar depression in immigrants (RR = 1.4, 95% CI 1.3–1.5), not for bipolar disorder or dysthymia [21]. In sum, RRs for mood disorders are lower than those reported for NAPD.

Previous studies from the UK, however, have reported increased rates of bipolar affective disorder [22] or affective psychotic disorder [23,24] for Black minorities. One could hypothesize, therefore, that certain migrant groups are at an increased risk for mood disorders with psychiatric features and not, or to a much lesser extent, for mood disorders without such features.

Furthermore, a large study examining the risk of eating disorders in immigrants to Denmark and Sweden found decreased incidence rates for anorexia and bulimia nervosa [25]. Studies investigating migrant or ethnic minority status in relation to the incidence of autism-spectrum [26] or substance use [27] disorders have produced mixed findings and are inconclusive.

Altogether, the research findings indicate a certain degree of specificity for the relationship between migrant status and risk for NAPD.

OTHER EPIDEMIOLOGICAL ADVANCES

One interesting question for this research field is the putatively higher risk for refugees than for nonrefugees. As several variables related to a migrant’s region of origin may influence psychosis risk [30,31], it is important to distinguish between refugees and nonrefugees from the same area.

Hollander et al. [32**] conducted the first study comparing the incidence of NAPD in political refugees granted asylum in Sweden and economic migrants from the same regions. Refugees and nonrefugees from sub-Saharan Africa had a similarly increased risk. Refugees from the other three regions, that is, the Middle East and North Africa, Asia and Eastern Europe and Russia had a higher risk for NAPD than nonrefugee migrants from these respective areas (overall RR = 1.7, 95% CI 1.3–2.1). This may suggest that the exposure to social adversities before migration, including war and persecution, may have an additive, ‘refugee effect’ on psychosis risk [32**]. Although this is a plausible explanation, the categories of region of origin in this study were very broad (e.g. ‘Asia’) and the comparability of a political refugee from Bangladesh to an economical migrant from Japan remains questionable.

Researchers of the SEPEA study included all incident cases of psychosis in a rural setting in the East of England where 10% of the population is of non-British white, mostly European origin, following the EU expansion in 2004 [33*]. After controlling for possible confounders, such as SES, population density and deprivation, the risk pattern in Black African, Black Caribbean and Pakistani migrants in this rural environment resembled findings previously observed in urban environments [23,34]. Importantly, there was little evidence of an increased risk in white, non-British (mostly Eastern European) immigrants [33*].

A curious finding in the field concerns the excessive sex gap in psychosis risk among North African migrants in Europe [35]. Pooled estimates from five European incidence studies yielded male-to-female...
risk ratios of 5.1 (95% CI 3.1–8.4) for migrants from the Maghreb compared with 1.8 (95% CI 1.3–2.5) for native Europeans. Possible explanations for the disproportionately high rates in male immigrants from the Maghreb include achievement-expectation mismatch, social marginalization and/or excessive illicit drug use [35].

Two thought-provoking reports from Italy [36†] and New Zealand [37†] concerned internal migration and a special kind of minority status. A study from Bologna, Italy, reported a two-fold increased psychosis risk for internal migrants in comparison with native Italians from Emilia Romagna, the region surrounding Bologna [36†]. Most of these internal migrants moved from South Italy, where educational levels are lower and rates of unemployment and poverty higher [38]. The risk increase for internal migrants was as high as that for the foreign-born. A study from New Zealand reported a two-fold higher incidence of schizophrenia among the Maori than among the non-Maori. Of note, the Maori constitute the original population of New Zealand and the non-Maori are migrants or descendants of migrants [37†]. These findings are of eminent interest, because they suggest that migration or ethnic minority status are proxies for exposure to an inferior social status or discrimination.

One of the most striking findings in this research area is the protective effect of ethnic density, that is, the greater the proportion of the own ethnic group in the neighbourhood, the lower the risk for psychotic disorder. It has now been replicated in a nationwide study from Denmark [39**]. An important strength of the Danish study is the measurement of ethnic density at age 15 instead of at the time of diagnosis. This excludes the possibility that individuals with a genetic liability moved to particular neighbourhoods during the prodromal phase of the illness. Another strength of this study is that it has high external validity, because the entire population of Denmark was included [39**]. In conclusion, ethnic density, perhaps as a proxy for social cohesion, may mitigate the pathogenic effects of minority stress.

Das-Munshi et al. [40] conducted a longitudinal cohort study including more than 18 000 individuals with schizophrenia, schizoaffective or bipolar affective disorder, and determined mortality rates by ethnicity. Adjusted hazard ratios indicated that Black Caribbean, Black African and South Asian ethnic minority patients had an overall lower mortality rate of at least 27% than their white British counterparts. Potentially protective factors, such as high ethnic density, social support and protective social norms deserve further investigation.

ADVANCES ON UNDERLYING MECHANISMS

Neurobiological evidence on underlying brain mechanisms points to increased dopamine synthesis capacity, dopamine release and baseline synaptic dopamine concentrations in individuals with psychotic disorder [41]. If migrant status is a risk factor for psychosis, one could hypothesize that it is associated with dopamine function.

Egerton et al. [42**] report on two complementary Canadian and UK-based PET imaging studies among three different clinical groups of individuals, one at clinical high risk (CHR) for psychosis, one with schizophrenia and one group consisting of healthy controls. The Canadian researchers examined dopamine release during exposure to the Montreal Imaging Stress Task (MIST). The MIST is a validated laboratory task during which participants receive negative feedback following an arithmetic task. As hypothesized, they found an elevated striatal dopamine release in response to MIST-induced stress in immigrants compared with nonmigrant Canadians across clinical groups. The purpose of the UK-study was to measure striatal dopamine synthesis capacity. The researchers used data on healthy controls and CHR patients and compared migrants with nonmigrants. The results showed that the striatal dopamine synthesis capacity was elevated in migrants, independent of clinical status. The authors conclude that dopamine function may be influenced by social stress [42**].

Akdeniz et al. [43] investigated structural alterations of the perigenual anterior cingulate cortex (pACC) in healthy participants (n = 124), native Germans and second-generation migrants, because previous studies had revealed functional changes in this brain area in second-generation migrants [44]. The results showed a significant reduction in pACC grey matter volume in migrant males in relation to German males, although there was no such reduction in female migrants [43].

Lastly, an examination of polygenic risk scores reported that these discriminated between cases and controls of European ancestry, but much less so between those of African ancestry (9.4 versus 1.1% of the variance explained) [45]. A differential genetic architecture or environmental exposure are possible explanations.

Although epidemiological findings on migrants provide indirect evidence for social stress in the aetiology of psychosis, it remains unclear, however, exactly which elements of the social environment lead to psychotic symptoms. Using experimental paradigms, such as Virtual Reality experiments, which try to mimic real-life situations, one can test
stress sensitivity in a controlled social environment. Veling et al. [46] validated this paradigm by demonstrating that psychosis liability was associated with paranoid thoughts and subjective distress in response to environmental stressors, specifically population density and hostility. Yet, an ethnic density effect, as operationalized by increased paranoia and subjective distress in a Virtual Reality environment with low own-group ethnic density, was not observed [46]. Another Virtual Reality study found a positive correlation between reported ethnic discrimination and paranoid persecutory ideation, but this was not observed in the Virtual Reality environment [47].

An alternative paradigm that has been developed for testing social stress sensitivity among members of ethnic minority and migrant groups is the Digital Social Peer Evaluation Experiment (digi-SPEE) [48], during which the individual is exposed to identity-based rejection. Contrary to expectation, Gevonden et al. [49] observed a blunted response to rejection in Moroccan-Dutch men. Unconscious denial of defeat and a tendency to keep up appearances have been hypothesized to account for these findings [50]. Why this defence mechanism of denial would apply to individuals with a different ethnic background and not to other defeated groups, such as individuals with a history of abuse or a hearing impairment, is, as yet, unclear.

CONCLUSION

Although some researchers emphasize the potential influence of diagnostic and sampling bias in migrant studies, the evidence generally supports the idea that certain migrant and ethnic minority groups are at an increased risk for NAPD. In fact, outcome studies from the UK show that psychosis in immigrants is not characterized by a benign course of illness. For the search of the true exposure that drives the higher incidence, it is important to note that the risk increase extends to other marginalized populations than international migrants. This seems to suggest that migration or ethnic minority status is rather a proxy for an inferior social position. Lastly, elevated dopamine in the striatal regions among immigrants could operate as an underlying neurobiological mechanism associated with psychosis susceptibility.

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Schizophrenia and related disorders


33. A study suggesting that compared with the native Swedish-born population, the incidence of NAPD is higher in refugees than in nonrefugee migrants from similar regions of origin.


35. A large incidence study showing that the risk pattern of NAPD among immigrants in rural Britain resembles findings from urban environments.


