

# Migration and psychosis: a meta-analysis of incidence studies

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## Original Article

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### Abstract

**Background.** The aims of this meta-analysis are (i) to estimate the pooled relative risk (RR) of developing non-affective psychotic disorder (NAPD) and affective psychotic disorder (APD) among migrants and their children; (ii) to adjust these results for socioeconomic status (SES); (iii) to examine the sources of heterogeneity that underlie the risk of NAPD.

**Methods.** We included population-based incidence studies that reported an age-adjusted RR with 95% confidence interval (CI) published 1 January 1977–12 October 2017 and used a random-effects model.

**Results.** We retrieved studies performed in Europe ( $n = 43$ ), Israel ( $n = 3$ ), Canada ( $n = 2$ ) and Australia ( $n = 1$ ). The meta-analysis yielded a RR, adjusted for age and sex, of 2.13 (95% CI 1.99–2.27) for NAPD and 2.94 (95% CI 2.28–3.79) for APD. The RRs diminished, but persisted after adjustment for SES. With reference to NAPD: a personal or parental history of migration to Europe from countries outside Europe was associated with a higher RR (RR = 2.94, 95% CI 2.63–3.29) than migration within Europe (RR = 1.88, 95% CI 1.62–2.18). The corresponding RR was lower in Israel (RR = 1.22; 0.99–1.50) and Canada (RR = 1.21; 0.85–1.74). The RR was highest among individuals with a black skin colour (RR = 4.19, 95% CI 3.42–5.14). The evidence of a difference in risk between first and second generation was insufficient.

**Conclusions.** Positive selection may explain the low risk in Canada, while the change from exclusion to inclusion may do the same in Israel. Given the high risks among migrants from developing countries in Europe, social exclusion may have a pathogenic role.

## Introduction

Migrants face the difficult task of settling into the society of a new country. It is not surprising, therefore, that a recent meta-analysis found migrants to be at increased risk of developing mood disorders (pooled relative risk, RR, 1.25, 95% CI 1.11–1.41) (Mindlis and Boffetta, 2017). Meta-analytic evidence, however, suggests that migrants and their children are at an even higher risk for schizophrenia or other non-affective psychotic disorders (NAPDs), with RRs exceeding 2.0 (Cantor-Graae and Selten, 2005; Bourque *et al.*, 2011).

As the last meta-analysis included studies up to 2008, there is a need for an up-to-date, comprehensive meta-analysis that estimates not only the risk of NAPD, but also that of affective psychotic disorder (APD), and that adjusts for socioeconomic status (SES) in the country of destination. Two competing theories have been proposed to explain the low SES of individuals who develop a psychotic disorder (PD): social causation (stress) and social selection (downward mobility of the genetically predisposed). Since there is little evidence of an association between parental SES and risk of psychosis, the mechanism of social selection may be more important than that of social causation (Dohrenwend *et al.*, 1992; Kwok, 2014). Indeed, research has shown that a large part of this downward mobility occurs before the development of psychosis, in that many patients with psychosis fail to reach their expected educational level (Kendler *et al.*, 2016). However, since a role for social causation cannot be entirely excluded, it is important to adjust any effect of migration for SES.

A previous meta-analysis reported that the risk of NAPD did not differ significantly between first- and second-generation migrants (Bourque *et al.*, 2011), which suggests that ethnic minority status rather than migration is an important factor in the development of psychosis. In order to investigate this and other potential factors, we performed a meta-analysis of incidence studies (i) to estimate the pooled RR (*v.* the reference population) of developing APD, NAPD, or any of these disorders, among international migrants and their children; (ii) to adjust these results for SES; and (iii) to examine sources of heterogeneity with reference to the RR of NAPD, such as generational status (first or second), region of destination, region of origin, developmental level of country of origin, skin colour, refugee status and sex.

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## Method

### Study selection

In order to be considered for the meta-analysis, studies were required (i) to report a risk ratio (RR, incidence rate ratio, hazard ratio or odds ratio) with 95% confidence interval (CI) for the incidence or prevalence of APD and/or NAPD among migrants in a circumscribed geographical area (or to provide numerators and denominators for the calculation of such measures); (ii) to adjust the risk ratio for differences in age between migrants and the reference population (or to provide data that make this adjustment possible); and (iii) to have been published in a peer-reviewed journal. For the purpose of the present study, we used incidence studies only.

For details of the study selection, see online Supplementary Methods and Supplementary Fig. S1.

### Quality check

Two authors (FT and EV) evaluated the quality of the articles independently, using the criteria given in online Supplementary Table S1 (range: 0–15). The inter-rater reliability of this procedure was good (intraclass correlation coefficient = 0.85). The averages of these scores were divided into tertiles and considered as indicating low ( $\leq 9$ ), medium ( $> 9$  to  $\leq 11$ ) or high ( $> 11$ ) quality.

### Data extraction

Two authors (FT and JPS) extracted the effect sizes independently. They recorded information about diagnosis (NAPD, APD or PD without distinction between affective or non-affective), country of destination, country or region of origin, developmental level of country of origin, skin colour, refugee status, sex, birthplace (first or second generation), adjustment for age, sex and/or SES. In case of any discrepancy, consensus was reached by discussion.

### Meta-analysis

First, we calculated the pooled RR for the development of any PD (NAPD, APD or PD), NAPD and APD among migrants and their children worldwide, adjusted for age and sex (analysis 1.1 for any PD, 1.2 for NAPD, 1.3 for APD).

The analyses were performed using the ‘metan’ procedure of STATA (Palmer and Sterne, 2016). Given the significant heterogeneity across studies, the use of a random-effects model was indicated. This model assumes that there is heterogeneity between studies that is not due to within-study variance (i.e. the standard error of the effect estimate) and leads to downplaying of outliers and often a broader 95% CI.

We repeated the analyses using the STATA command ‘robmeta’, which takes into account clustering of effect estimates that originate from the same study, and compared the results to those obtained using ‘metan’.

The effect of study quality on inter-study heterogeneity was investigated using the ‘metareg’ procedure of STATA (analysis 2). Funnel plots were used to investigate possible publication bias (analysis 3).

Since only two studies adjusted the results for SES at birth (Hjern *et al.*, 2004 for youth study group; Corcoran *et al.*, 2009), we adjusted the results for current SES, i.e. at first contact for treatment of psychosis. For this purpose, we selected studies that reported two effect sizes: one adjusted for age and sex, and another

one adjusted for age, sex and current SES. We then compared the two summary RRs (analysis 4.1 for any PD, 4.2 for NAPD).

The analyses below concern the incidence of NAPD only. We calculated the differences between subgroups in univariable models using ‘metareg’ (Palmer and Sterne, 2016). This was done in two ways: (a) using all available effect estimates; (b) using effect estimates for subgroups derived from the same study, to assess confounding by study (as with SES).

In analysis 5.1, we examined the difference in risk between first-generation and second-generation (born in country of destination to a foreign-born father and/or foreign-born mother) migrants. Average effect estimates were calculated for migrants and their children according to region of destination (analysis 5.2) and region of origin (analysis 5.3). Owing to the small number of studies presenting effect sizes for migrants from different regions, a comparison of effect sizes in the same study (as for SES) was not feasible here. In analysis 5.4, we compared the effect of migration to Europe from countries outside Europe to that of (international) migration within Europe.

We classified the developmental level of the country or region of origin according to the definitions used by the United Nations Conference on Trade and Development (United Nations, 2002) and compared the risk of PDs in migrants and their children from developed countries to that of their peers from developing countries (analysis 5.5).

The effect of skin colour was examined by comparing migrants and their children from areas where the majority of the population is white, black or other. Since most individuals from North Africa and the Middle East are considered white, but are visibly different from white Europeans, we created the following categories: (1) white, i.e. from Europe, North America or Australia; (2) white other (i.e. from North Africa or the Middle East, including Turkey); (3) black (i.e. from the Caribbean or sub-Saharan Africa); (4) other (e.g. India, China, Greenland) or mixed (e.g. South America, Africa); and (5) unknown (analysis 5.6). For the comparison of groups with different skin colours, we selected studies with at least three of these groups.

Analysis 5.7 investigated the effect of refugee status, and analysis 5.8 that of sex (migrants and their children). Lastly, the results of analyses 5.5 (developmental level of country of origin) and 5.6 (skin colour) were adjusted for SES in analyses 6.1 and 6.2.

## Results

### Result of computerized search

Forty-nine articles were retrieved, which concerned 43 independent observational studies or data sources. Table 1 lists the studies, performed in Europe ( $n = 37$ ), Israel ( $n = 3$ ), Canada ( $n = 2$ ) or Australia ( $n = 1$ ). Forty-seven articles concerned the risk of NAPD and four the risk of APD. At least 20 633 first- and second-generation migrants developed a PD (affective or non-affective) during 35 890 528 person-years at risk. At least 96 850 members of the reference population did so during 623 587 721 person-years. From six studies, the relevant numbers of cases and/or denominators could not be derived (Rwegellera, 1977; Mortensen *et al.*, 1997; Fearon *et al.*, 2006; Werbeloff *et al.*, 2012; Bansal *et al.*, 2014; Manhica *et al.*, 2016).

### Meta-analysis

Low-quality studies yielded somewhat lower, but not significantly different, effect measures for any PD or NAPD than medium- or

**Table 1.** Population-based incidence studies included in meta-analysis of risk for psychosis associated with personal or parental history of migration, 1977–2017, by pertinent region of study, number of cases (migrants and non-migrants), diagnosis, study quality and type of analysis

Study	Country/region	Number of Cases <sup>a</sup>	Diagnosis	Quality	Included in analysis
Rwegellera (1977)	UK, London	35/47	NAPD <sup>b</sup>	Low	1.1 1.2 5.1 5.2 5.3 5.4 5.5 5.6 5.7
Hitch and Clegg (1980)	UK, Bradford	63/123	NAPD	Low	1.1 1.2 5.1 5.2 5.3 5.4 5.5 5.6 5.7 5.8
Krupinski (1980)	Australia, Victoria	423/1097	NAPD	Low	1.1 1.2 5.1 5.2 5.3 5.4 5.5 5.6 5.7 5.8
Dean <i>et al.</i> (1981)	UK, London	403/1191	NAPD	Low	1.1 1.2 5.1 5.2 5.3 5.4 5.5 5.6 5.7 5.8
McGovern and Cope (1987)	UK, Birmingham	51/98	NAPD	Low	1.1 1.2 5.2 5.3 5.4 5.5 5.6 5.7 5.8
Cochrane and Bal (1987)	UK	315/3669	NAPD	Low	1.1 1.2 5.1 5.2 5.3 5.4 5.5 5.6 5.7 5.8
Harrison <i>et al.</i> (1988)	UK, Nottingham	27/59	NAPD	Medium	1.1 1.2 5.1 5.2 5.3 5.4 5.5 5.6 5.7
Castle <i>et al.</i> (1991)	UK, London	36/53	NAPD	Medium	1.1 1.2 5.2 5.3 5.4 5.5 5.6 5.7
Thomas <i>et al.</i> (1993)	UK, Manchester	18/41	NAPD	Low	1.1 1.2 5.1 5.2 5.3 5.4 5.5 5.6 5.7 5.8
Selten and Sijben (1994)	The Netherlands	166/975	NAPD	Low	1.1 1.2 5.1 5.2 5.3 5.4 5.5 5.6 5.7 5.8
van Os <i>et al.</i> (1996)	UK, London	61/44	NAPD	Medium	1.1 1.2 5.2 5.3 5.4 5.5 5.6 5.7
Selten <i>et al.</i> (1997)	The Netherlands	933/10 726	NAPD	Medium	1.1 1.2 5.1 5.2 5.3 5.4 5.5 5.6 5.7 5.8
Harrison <i>et al.</i> (1997)	UK, Nottingham	32/136	NAPD	High	1.1 1.2 5.2 5.3 5.4 5.5 5.6 5.7 5.8
Bhugra <i>et al.</i> (1997)	UK, London	62/76	NAPD	High	1.1 1.2 5.2 5.3 5.4 5.5 5.6 5.7 5.8
Mortensen <i>et al.</i> (1997)	Denmark	725/?	NAPD	Low	1.1 1.2 5.1 5.2 5.7 5.8
Goater <i>et al.</i> (1999)	UK, London	44/29	NAPD	High	1.1 1.2 5.2 5.3 5.4 5.5 5.6 5.7
Selten <i>et al.</i> (2001)	NL, The Hague	116/65	PD <sup>c</sup>	High	1.1 4.1 4.2 6.5 6.6
Zolkowska <i>et al.</i> (2001)	Sweden, Malmö	22/34	NAPD	High	1.1 1.2 5.1 5.2 5.7
Reeves <i>et al.</i> (2001)	UK, London	36/25	NAPD	Medium	1.1 1.2 5.1 5.2 5.3 5.4 5.5 5.6 5.7 5.8
Cantor-Graae <i>et al.</i> (2003)	Denmark	1023/9221	NAPD	Medium	1.1 1.2 5.1 5.2 5.3 5.4 5.5 5.6 5.7
Mitter <i>et al.</i> (2004)	UK, London	13/27	NAPD	High	1.1 1.2 5.1 5.2 5.3 5.4 5.5 5.6 5.7 5.8
Hjern <i>et al.</i> (2004)	Sweden	249/1339	NAPD	Low	1.1 1.2 5.1 5.2 5.3 5.4 5.5 5.6 5.7
Cantor-Graae <i>et al.</i> (2005)	Sweden, Malmö	15/56	NAPD	High	1.1 1.2 5.1 5.2 5.7
Fearon <i>et al.</i> (2006)	UK, London	568 (all)	PD/NAPD/ APD <sup>d</sup>	High	1.1 1.2 1.3 5.2 5.3 5.4 5.5 5.6 5.7 5.8
Leao <i>et al.</i> (2006)	Sweden	754/1305	NAPD	Medium	1.1 1.2 4.1 4.2 5.1 5.2 5.3 5.4 5.5 5.6 5.7 5.8 6.5 6.6
Veling <i>et al.</i> (2006)	NL, The Hague	300/79	NAPD	High	1.2 5.1 5.2 5.3 5.4 5.5 5.6 5.7 5.8
Smith <i>et al.</i> (2006)	Canada, Br. Col.	548/259	NAPD	Medium	1.1 1.2 5.1 5.2 5.3 5.4 5.5 5.6 5.7
Weiser <i>et al.</i> (2008)	Israel	1640/46	NAPD	Medium	1.1 1.2 4.1 4.2 5.1 5.2 5.3 5.4 5.5 5.6 5.7 6.5 6.6
Cantor-Graae and Pedersen (2007a)	Denmark	905/9742	NAPD	Medium	1.1 1.2 5.2 5.2 5.3 5.4 5.5 5.6 5.7
Cantor-Graae and Pedersen (2007b)	Denmark	112/4472	NAPD	Medium	1.1 1.2 5.1 5.2 5.3 5.4 5.5 5.6 5.7 5.8
Coid <i>et al.</i> (2008) <sup>e</sup>	UK, London	280/82	NAPD	High	5.1
Kirkbride <i>et al.</i> (2008) <sup>e</sup>	UK, London	372/112	PD/NAPD/APD	High	1.1 1.2 1.3 4.1 4.2 4.3 5.2 5.3 5.4 5.5 5.6 5.7 5.8 6.5 6.6
Corcoran <i>et al.</i> (2009)	Israel	445/192	NAPD	Low	1.1 1.2 5.1 5.2 5.7
Zandi <i>et al.</i> (2010)	NL, Utrecht	15/32	PD/NAPD	High	1.1 1.2 5.2 5.3 5.4 5.5 5.6 5.7 5.8
Cheng <i>et al.</i> (2011)	UK, Cambridge	66/206	PD	High	1.1
Werbeloff <i>et al.</i> (2012)	Israel	2335/?	NAPD	Low	1.1 1.2 5.1 5.2 5.3 5.4 5.5 5.6 5.7 5.8
Tarricone <i>et al.</i> (2012)	Italy, Bologna	35/128	PD/NAPD	High	1.1 1.2 5.1 5.2 5.7
Sendra-Gutierrez <i>et al.</i> (2012)	Spain, Segovia	9/59	NAPD	Medium	1.1 1.2 5.1 5.2 5.7
Tortelli <i>et al.</i> , (2014)	France, Paris	122/ 136	PD	Low	1.1
Cantor-Graae and Pedersen (2013)	Denmark	3665/16 203	NAPD	High	1.1 1.2 5.1 5.2 5.7
Lasalvia <i>et al.</i> (2014)	Italy, Veneto	127/431	PD/NAPD/APD	High	1.1 1.2 1.3 5.2 5.7

(Continued)

Table 1. (Continued.)

Study	Country/region	Number of Cases <sup>a</sup>	Diagnosis	Quality	Included in analysis
Bansal <i>et al.</i> (2014)	Scotland	815/6861	NAPD	Low	1.1 1.2 4.1 4.2 5.2 5.3 5.4 5.5 5.6 5.7 5.8 6.5 6.6
Anderson <i>et al.</i> (2015)	Canada, Ontario	2305/20 959	NAPD	Medium	1.1 1.2 5.1 5.2 5.3 5.4 5.5 5.6 <b>5.7</b>
Hollander <i>et al.</i> (2016)	Sweden	472/3232	NAPD	Medium	1.1 1.2 4.1 4.2 5.1 5.2 5.3 5.4 5.5 5.6 <b>5.7</b> 5.8 6.5 6.6
Manhica <i>et al.</i> (2016)	Sweden	??	NAPD	Medium	1.1 1.2 4.1 4.2 5.1 5.2 5.3 5.4 5.5 5.6 <b>5.7</b> 6.5 6.6
Mule <i>et al.</i> (2017)	Italy, Palermo	21/183	PD/NAPD	High	1.1 1.2 5.1 5.2 5.7
Kirkbride <i>et al.</i> (2017a) Kirkbride <i>et al.</i> (2017b) <sup>¶</sup>	UK, East Anglia	173/514	PD/NAPD/APD	High	1.1 1.2 1.3 4.1 4.2 4.3 5.1 5.2 5.3 5.4 5.5 5.6 5.7 6.5 6.6
Barghadouch <i>et al.</i> (2016)	Denmark	95/297	NAPD	High	4.1 4.2 6.5 6.6
Markkula <i>et al.</i> (2017)	Finland	1494/2388	NAPD	High	4.1 4.2 6.5 6.6

<sup>a</sup>Among migrants/among natives.

<sup>b</sup>Non-affective psychotic disorder.

<sup>c</sup>Psychotic disorder, affective or non-affective.

<sup>d</sup>Affective psychotic disorder.

**5.7**, estimates for refugees, 5.7 estimates for migrants and/or their children, irrespective of refugee status.

§Two papers about the same study.

¶Two papers about the same study.

high-quality studies (Table 2; Fig. 1). The risk of developing APD was somewhat higher than the risk of developing NAPD. As expected, there was significant heterogeneity across studies.

The RRs estimated using the STATA command 'robumeta' were a little higher and had somewhat broader 95% CIs, but remained statistically significant (results available on request).

The funnel plot of studies of the risk of any PD showed evidence of publication bias (online Supplementary Fig. S1; Egger's test  $p = 0.01$ ). We therefore performed a sensitivity analysis by excluding studies with standard errors  $>0.2$  and by omitting a study that reported an excessive RR,  $>10.0$  (Harrison *et al.*, 1988). The pooled RR of any PD decreased from RR 2.10 (95% CI 1.97–2.24) to RR 1.92 (95% CI 1.81–2.05) and Egger's test was no longer significant ( $p = 0.098$ ). When we also excluded the low-quality studies, the RR of any PD was 1.97 (95% CI 1.84–2.10). Using robumeta, this figure was 2.23 (95% CI 1.80–2.76).

Application of these analyses to studies of the risk of NAPD yielded similar results: when we excluded the studies with standard errors  $>2.0$  and the Harrison *et al.* study, the RR was 1.93 (1.82–2.06). Using robumeta, the RR was 2.18 (1.86–2.55). When we also excluded the low-quality studies, the RR of NAPD was 1.98 (1.86–2.12), with robumeta: 2.19 (1.82–2.64).

Eight studies adjusted findings for SES. Although adjustment for SES resulted in a decrease in the RR of any PD (from RR 1.72, 95% CI 1.57–1.87, to RR 1.56, 95% CI 1.43–1.70), this measure remained significant. The same was true when the RR of APD and NAPD was adjusted for SES (Table 2).

When we considered all the available effect sizes with reference to NAPD, the RR of psychosis among first-generation migrants was significantly higher than that among second-generation migrants. However, when we restricted the analyses to those publications that reported effect sizes for both generations, the difference in RR became smaller and statistically not significant (Table 3).

The results presented below apply to migrants *and* their children, except one analysis on refugees.

The RR of developing NAPD was lowest in Israel and Canada and significantly higher in all European destinations (Table 4).

Region of origin had a substantial impact on this RR, which was highest among first- and second-generation migrants from Central and South America (mostly from the Caribbean), sub-Saharan countries and North Africa, and lowest among migrants from the Indian subcontinent or other parts of Asia (Table 4).

In Europe, the RR was higher for migrants and their children who came from countries outside Europe (RR 2.94, 95% CI 2.63–3.29) than among their peers from within Europe (RR 1.88, 95% CI 1.62–2.18). The funnel plot for the first analysis (from outside Europe to Europe) showed no evidence of publication bias (online Supplementary Fig. S1; Egger's test  $p = 0.24$ ).

The developmental level of the country of origin had a substantial impact: the RR of NAPD was higher among migrants from developing countries (Table 3). However, a black skin was the variable with the largest impact on the risk of NAPD (Table 3). Black migrants and their children were not only at a higher risk than members of the reference population in Europe, but also in Canada (pooled effect size for migrants from the Caribbean and Bermuda, West, East and Central Africa, RR 1.55, 95% CI 1.13–1.87) (Anderson *et al.*, 2015) and Israel (migrants from Ethiopia, hazard ratio 3.02, 95% CI 1.93–4.73) (Weiser *et al.*, 2008). The results showed no significant difference in RR between those with a white or other non-black skin colour.

The risk of NAPD was higher among refugees than among natives, but not significantly higher than that among migrants and their children in general. Four studies compared foreign-born refugees to foreign-born non-refugees, but the pooled RRs were not significantly different (Table 3).

The effect of sex was negligible (Table 3).

After adjustment for SES, the RR of NAPD among first- and second-generation migrants from developing countries and among those with a black skin was still increased (RR 1.84, 95% CI 1.55–2.19, and RR 2.70, 95% CI 1.99–3.68, respectively) (online Supplementary Table S2).

Owing to the small numbers of studies, it was not possible to repeat all the analyses using 'robumeta'. However, where this was possible, the conclusions remained the same.

**Table 2.** Meta-analysis of incidence studies examining the association between a personal or parental history of migration and psychosis, 1977–2017

Type of psychotic disorder	N <sup>a</sup>	RR <sup>b</sup>	95% CI	I <sup>2</sup> (%) <sup>c</sup>	Δ lnRR <sup>d</sup>	p	RR	95% CI	I <sup>2</sup> (%)
Any psychotic disorder	45 <sup>e</sup>	2.10	1.97–2.24	98.1					
Low quality	14	1.94	1.67–2.25	98.1	ref				
Medium quality	15	2.22	2.01–2.45	98.8	0.148	0.186			
High quality	16	2.08	1.88–2.29	94.6	0.076	0.519			
Adjusted for age, sex, SES (using all estimates available)	10 <sup>f</sup>						1.53	1.41–1.67	95.2
Adjusted for age and sex (paired observations)	8 <sup>g</sup>						1.72	1.57–1.87	98.0
Adjusted for age, sex, SES (paired observations)	8 <sup>g</sup>						1.56	1.43–1.70	92.5
Non-affective psychotic disorder	43 <sup>h</sup>	2.13	1.99–2.27	98.1					
Low quality	13	1.94	1.67–2.25	98.3	ref				
Medium quality	15	2.22	2.01–2.45	98.8	0.152	0.172			
High quality	15	2.15	1.95–2.37	94.7	0.124	0.297			
Adjusted for age, sex, SES (using all estimates available)	10 <sup>f</sup>						1.55	1.42–1.69	95.3
Adjusted for age and sex (paired observations)	8 <sup>g</sup>						1.74	1.59–1.90	98.0
Adjusted for age, sex, SES (paired observations)	8 <sup>g</sup>						1.57	1.44–1.71	92.9
Affective psychotic disorder	4	2.94	2.28–3.79	69.1					
Low quality	0								
Medium quality	0								
High quality	4	2.94	2.28–3.79	69.1					

Pooled relative risks, by psychosis type and quality of study. Idem, analysis restricted to incidence studies that adjusted the results for age and sex, as well as for age, sex and socioeconomic status (SES).

<sup>a</sup>Number of papers.

<sup>b</sup>Pooled relative risk, adjusted for age and sex.

<sup>c</sup>Measure of heterogeneity. All values were statistically significant.

<sup>d</sup>The difference between the logarithmically transformed RR of psychotic disorder among migrants v. natives in a certain category and the logarithmically transformed RR in the reference category.

<sup>e</sup>The number does not equal 49, because two papers (Barghadouch *et al.*, 2016; Markkula *et al.*, 2017) reported effect sizes adjusted for age, sex and SES (no effect size unadjusted for SES). From overlapping papers, Selten *et al.* (2001) was selected instead of Veling *et al.* (2006) and Kirkbride *et al.* (2008) instead of Coid *et al.* (2008).

<sup>f</sup>Eight studies that reported an effect size adjusted for age and sex, as well as an effect size adjusted for age, sex and SES (Selten, 2001; Leao *et al.*, 2006; Weiser *et al.*, 2008; Kirkbride *et al.*, 2008; Bansal *et al.*, 2014; Hollander *et al.*, 2016; Manhica *et al.*, 2016; Kirkbride *et al.*, 2017a, 2017b) plus two studies that reported an effect size adjusted for age, sex and SES (Barghadouch *et al.*, 2016; Markkula *et al.*, 2017).

<sup>g</sup>Derived from the above eight studies that reported an effect size adjusted for age and sex, and an effect size adjusted for age, sex and SES.

<sup>h</sup>The number does not equal 46, because two papers (Barghadouch *et al.*, 2016; Markkula *et al.*, 2017) reported effect sizes adjusted for age, sex and SES (no effect size unadjusted for SES). From overlapping papers, Veling *et al.* (2006) was selected instead of Selten *et al.* (2001).

## Discussion

Although findings indicate that migrants are at increased risk of developing APD and NAPD, the findings were heterogeneous, which precludes a conclusion about 'the' RR among migrants in general. While there was no evidence of a greatly increased risk among migrants in Israel or Canada, the risk among migrants in Europe, in particular those from developing countries outside Europe and/or those with a black skin, was greatly increased. Overall, the risk became somewhat attenuated after adjustment for SES at first contact. A comparison of risks for first- and second-generation migrants based on effect estimates derived from the same study yielded no significant difference. This indicates that membership of a disadvantaged ethnic minority group, rather than a personal history of migration, is an important determinant of risk. There was insufficient evidence to conclude that there is a difference in risk between refugees and non-refugees.

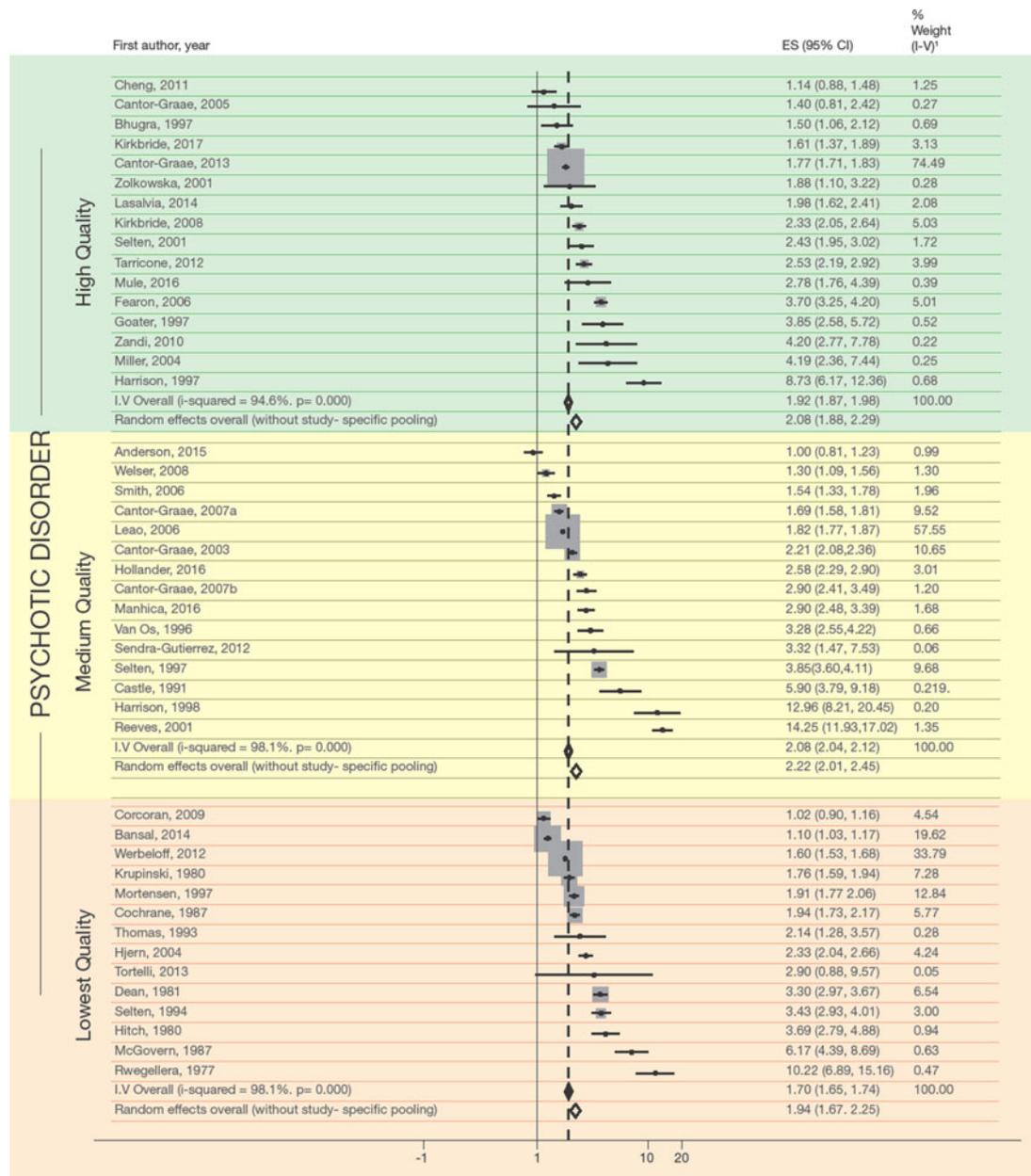
It is unlikely that the findings can be explained by bias. Some researchers (e.g. Zandi *et al.*, 2010) have argued that Western psychiatrists misunderstand patients from a different culture, but most studies of clinical presentation and long-term outcome

do not indicate that there is a major diagnostic bias (e.g. Morgan *et al.*, 2017).

Furthermore, this meta-analysis showed that the risk of PDs was high among migrants from Eastern Europe, who do not differ greatly in culture from Western Europeans. For a thorough discussion of these issues, see previous reviews (Cantor-Graae and Selten, 2005; Bourque *et al.*, 2011). Selection bias is an unlikely explanation, because field studies of major mental disorders have shown that the ratio of treated to untreated cases is negatively associated with SES (Link and Dohrenwend, 1980). There was evidence of publication bias, but its effect was modest.

Strengths of this meta-analysis are the large number of studies included, and, with reference to Europe, the diversity of the migrant groups examined. By using a 'pairwise' comparison of effect sizes derived from the same study (e.g. effect sizes adjusted and non-adjusted for SES), it was often possible to avoid confounding by study.

Our meta-analysis has several limitations. First, our results apply mainly to Europe. Of note, studies of first hospital admissions published before 1977 reported a modestly increased risk



**Fig. 1.** Meta-analysis of incidence studies examining the association between migration and psychosis, 1977–2017. Effect estimates for any psychotic disorder (i.e. psychotic disorder or non-affective psychotic disorder), by study quality. When a study reported separate effect sizes for PD and for NAPD, that for PD was selected, because it concerned the largest number of cases.

of schizophrenia among migrants to the USA. Malzberg (1964), for example, reported that the first admission rates among foreign-born white individuals in New York City, standardized for age and sex, exceeded those among the native-born white individuals by 16%. To our knowledge, no investigation has reported a greatly increased risk among migrants to the USA or Canada (Selten and Cantor-Graae, 2004).

Second, the quality of information on the risk for refugees was limited. Only one study compared the risk for refugees to non-refugees from the same part of the world (Hollander *et al.*, 2016). The result of this investigation, a significantly higher risk for refugees, remains inconclusive, however, because the parts of the world were as large as Asia. Since Asia comprises countries as diverse as Afghanistan and China, the comparability of refugees

and non-refugees remains uncertain. Leao *et al.* (2006) designated migrants from particular countries (e.g. African countries) refugees, while the authors did not know whether these subjects were the victims of political persecution. Consequently, the outcome of our meta-analysis, i.e. insufficient evidence of a difference in risk between refugees and non-refugees, should not be interpreted as evidence of no difference.

Third, the adjustment for current, rather than parental SES. This is problematic because low SES at onset of psychosis may also be the result of a disturbed neuro-development. Of note, there is a larger potential for downward mobility during the pre-psychotic period among natives than among migrants or their children, many of whom already belong to a lower social class. The situation is complex, because many migrants may have

**Table 3.** Meta-analysis of incidence studies examining the association between migration and psychosis, 1977–2017

Subgroups	Any estimate available						Estimates derived from the same study					
	<i>N</i> <sup>a</sup>	RR of NAPD <sup>b</sup>	95% CI	<i>I</i> <sup>2</sup> (%) <sup>c</sup>	$\Delta$ lnRR <sup>d</sup>	<i>p</i>	<i>N</i>	RR of NAPD	95% CI	<i>I</i> <sup>2</sup> (%)	$\Delta$ lnRR	<i>p</i>
Generational status												
First generation	29	2.55	2.31–2.82	97.9	ref		9	2.05	1.85–2.27	89.9	ref	
Second generation	13	1.78	1.66–1.90	94.2	–0.35	<0.001	9	1.80	1.68–1.93	81.6	–0.11	0.196
Developmental level of country of origin												
Developed country <sup>e</sup>	19	1.66	1.49–1.84	97.1	ref		15	1.43	1.25–1.65	90.7	ref	
Developing country <sup>e</sup>	30	2.54	2.26–2.86	97.6	0.43	<0.001	15	2.13	1.89–2.41	89.7	0.39	<0.001
Skin colour <sup>f</sup>												
White	19	1.65	1.46–1.85	97.1	ref		7	1.24	0.96–1.59	81.8	ref	
White other	8	1.94	1.54–2.44	87.6	0.15	0.334	3	1.86	1.23–1.81	83.9	0.40	0.095
Black	23	4.19	3.42–5.14	94.3	0.94	<0.001	7	2.78	2.12–3.63	86.3	0.80	<0.001
Other	11	1.73	1.41–2.14	95.1	0.05	0.685	5	1.52	1.12–2.05	90.5	0.20	0.288
Unknown/mixed	32	1.83	1.71–1.96	96.5	0.11	0.194	5	1.53	1.18–1.99	68.2	0.21	0.30
Refugee status												
Refugee	4	1.88	1.57–2.24	91.4	–0.15	0.342	4	1.87	1.56–2.24	91.5	0.066	0.524
Refugee or non-refugee	43	2.15	2.01–2.31	98.1	ref							
Non-refugee							4	1.75	1.59–1.93	89.5	ref	
Sex												
Male	22	2.25	1.99–2.54	98.3	ref		21	2.24	1.98–2.54	95.6	ref	
Female	21	2.26	2.01–2.53	97.2	0.011	0.915	21	2.26	2.01–2.53	92.5	0.012	0.912

Analysis of variables that may moderate the association between a personal or parental history of migration and incidence of non-affective psychotic disorder.

<sup>a</sup>Number of papers.

<sup>b</sup>Pooled relative risk of non-affective psychotic disorder, adjusted for age and sex. (except the analysis for sex differences: adjusted for age only).

<sup>c</sup>Measure of heterogeneity. All values were statistically significant.

<sup>d</sup>Difference between the logarithmically transformed RR of non-affective psychotic disorder among migrants *v.* natives in a certain category and the logarithmically transformed RR in the reference category.

<sup>e</sup>According to UNCTAD definition. United Nations: UNCTAD Handbook of Statistics. Geneva, United Nations Conference on Trade and Development, 2002.

<sup>f</sup>Predominant skin colour in region of origin. 'White other' refers to individuals from North-Africa or the Middle East. The results depicted in the right column are derived from a comparison of at least three effect sizes from the same study: one for a white group, a second one for a black group and a third one for another subgroup (white other, other or unknown/mixed).

**Table 4.** Meta-analysis of incidence studies examining the association between a personal or parental history of migration and psychosis, 1977–2017

Destination	Number of papers	RR of NAPD	95% CI	$I^2$ (%) <sup>a</sup>
Great-Britain	18	2.69	2.20–3.28	98.7
Scandinavia	11	1.89	1.79–2.00	93.0
The Netherlands	4	2.98	2.43–3.66	84.5
Southern Europe	4	2.79	1.94–4.01	83.6
Israel	3	1.22	0.99–1.50	95.5
Canada	2	1.21	0.85–1.74	91.2
Australia	1	2.10	1.22–3.82	n.a.
<b>Region of origin</b>				
Eastern Europe	7	1.93	1.38–2.70	93.3
Western Europe or 'Europe'	13	1.62	1.41–1.86	98.0
Indian subcontinent	7	1.65	1.31–2.07	79.6
Remainder of Asia or 'Asia'	15	1.52	1.22–1.89	89.2
North-Africa	4	2.88	1.85–4.49	68.7
Sub-Saharan Africa or 'Africa'	13	2.99	2.30–3.89	91.6
Central- or South-America	23	3.01	2.53–3.58	93.3
Other or unknown	28	1.89	1.76–2.04	97.1
<b>Combination of region of origin and destination</b>				
From outside Europe to Europe	10	2.94	2.63–3.29	95.7
Within Europe	28	1.88	1.62–2.18	98.3

Influence of destination and region of origin on risk of non-affective psychotic disorder (NAPD).

<sup>a</sup>Measure of heterogeneity. All values were statistically significant.

belonged to a higher social class before migration. Also, the definitions of SES varied considerably.

Fourth, the lower rates for migrants within Europe might be explained to some extent by the fact that it is relatively easy to seek support in the country of origin.

Finally, the arbitrary and imperfect classification of subjects on the basis of their skin colour. One could argue, for instance, that subjects from the Indian subcontinent are often darker than Africans and that the group 'other', consisting of people from South-America and the larger part of Asia is very heterogeneous. However, given the relatively small number of studies, we opted for this classification. With the designation of a group as white (e.g. Eastern Europeans), we do not suggest that this group is not exposed to prejudice or discrimination.

How should the findings be interpreted? It was previously thought that individuals with a genetic predisposition for psychosis are more likely to migrate than others (Odegaard, 1932), but not a single study has supported this negative selection hypothesis (Cantor-Graae and Selten, 2005). On the contrary, many studies from the USA and Canada have reported a better (somatic) health among migrants than among native-born individuals, while the results of similar studies from Europe vary greatly across migrant populations (Ikram *et al.*, 2016). In any event, due to the self-selection of healthy, resilient people who have the courage to move to a new environment, migrants from developing countries are probably healthier than those who stay behind. Current knowledge about the years before the first hospital admission, during which the patient often exhibits a lack of initiative (Hafner *et al.*, 1999), provides additional evidence against the negative selection hypothesis. Receiving countries can reinforce

a positive selection process through their immigrant admission policies. Since such policies are more rigorous in Canada and Australia than in Europe, the relatively low risk of PDs among many migrant groups in the first two countries may be due to positive selection (Vang *et al.*, 2017). Lastly, selective migration cannot explain the increased risk among Ethiopian Jews, because the whole population moved to Israel (Spector, 2005).

There is no evidence that the high incidence of psychosis among migrants from developing countries in Europe reflects a similarly high incidence in the country of origin. While there have been no high-quality incidence studies from Africa, studies from the Caribbean (Bhugra *et al.*, 1996), Surinam (Selten *et al.*, 2005), India and China (Baxter *et al.*, 2016) have reported 'normal' incidence or prevalence rates. This also implies that poverty by itself is an unlikely cause of psychosis.

However, as many migrants who move from a developing country to Europe find themselves in the lowest strata of European society, the effect of migration might be due, at least in part, to a (relative) social disadvantage (Morgan *et al.*, 2008) or social defeat. Indeed, a case-control study from the UK found strong associations between indicators of social disadvantage and psychosis. Indicators of disadvantage and isolation were more common in Black Caribbean subjects than in White British subjects (Morgan *et al.*, 2008).

The social defeat hypothesis of psychosis, which proposes that the negative experience of being excluded from the majority group increases the risk of psychosis by sensitizing the mesolimbic dopamine system, postulates a link with the brain (Selten and Cantor-Graae, 2005; Selten *et al.*, 2016). Sensitization of the mesolimbic dopamine system refers to an increased dopamine

function in response to stressors and becomes manifest in excessive presynaptic dopamine synthesis and release (Howes and Murray, 2014). Several lines of evidence support the social defeat hypothesis: (i) the risk of psychosis is increased in other groups exposed to social exclusion, such as individuals with a history of trauma or bullying in childhood, homosexuals, African-Americans, individuals with a low IQ or hearing impairment (for review, see Selten *et al.*, 2017); (ii) the protective effect of high ethnic density, i.e. residence in a neighbourhood where the own ethnic group is well-represented (Schofield *et al.*, 2017); (iii) experiments with rodents that demonstrate dopamine sensitization in defeated animals (Hammels *et al.*, 2015); (iv) a recent positron emission tomography study showing increased dopamine synthesis and increased stress-induced dopamine release in the striatum of individuals (healthy volunteers, clinical high-risk subjects and schizophrenia patients) with a personal or parental history of migration (Egerton *et al.*, 2017). Neuro-receptor imaging studies of non-psychotic individuals with a history of hearing impairment or childhood trauma have also reported dopamine sensitization (Gevonden *et al.*, 2014; Oswald *et al.*, 2014; Egerton *et al.*, 2016). Lastly, the pattern of findings in Israel (i.e. a modest increase in risk among first-generation non-black migrants and the absence of an increase in risk among second-generation migrants) may fit with this interpretation, because the migration of Jews to a Jewish state involves a change from social exclusion to inclusion.

An entirely different interpretation of the increased risk among individuals with a dark skin is that low prenatal levels of vitamin D are a risk factor for psychosis (McGrath, 1999). Indeed, a study from the Netherlands reported that pregnant women and infants from non-European ethnic backgrounds are at high risk of vitamin D deficiency (Vinkhuyzen *et al.*, 2016). However, the evidence of a causal role for low vitamin D in the aetiology of psychosis is inconclusive and the hypothesis does not explain the increased risk among first-generation migrants.

Given the fact that substance abuse in the general population is a lot more common among men than among women, the absence of a difference in RR between male and female migrants argues against a major role of drug abuse in the aetiology of the increased incidence.

There is anecdotal evidence and a tiny body of research to suggest that the ratio of risk among migrants and natives is inverted in countries where the original population occupies the weaker position. This may apply, for example, to Aborigines in Australia, Maori in New Zealand, Native Americans in the USA and Inuit in Canada (Sampath, 1974; Tapsell *et al.*, 2018). This is an important topic for further study.

In conclusion, the results of this meta-analysis confirm earlier European findings of an increased incidence of NAPD among migrants from developing countries, in particular those of African extraction (Cantor-Graae and Selten, 2005; Bourque *et al.*, 2011), and extend them by showing that individuals with an African background are also at an increased risk of PD in Canada and Israel, while migration to the latter countries is generally not associated with an increased risk.

From the large number of research implications, we would like to point out the importance of examining the interaction between ethnic background and host country: does the risk for an immigrant group vary according to the country of destination and which are the determinants of this? A prospective study could test the social defeat hypothesis by comparing striatal dopamine synthesis capacity between migrants and natives in early adult

age at two points in time: shortly after arrival in the country of destination and 3–5 years later. The hypothesis predicts a greater rise in striatal dopamine synthesis capacity among migrants than among natives (or a rise in this capacity among migrants and no such rise among natives).

We conclude that the increased psychosis risk among migrants and their children is a major public health problem. Since the lifetime morbid risk for psychosis (affective or non-affective) is about 1–2% for Europeans, our findings suggest that this risk may be 3–6% for migrants from outside Europe. The challenge is to advance our understanding of the underlying mechanisms and to find ways for prevention.

**Supplementary material.** The supplementary material for this article can be found at <https://doi.org/10.1017/S0033291719000035>.

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