Schizophrenia and Migration: A Meta-Analysis and Review

Elizabeth Cantor-Graae, Ph.D.

Jean-Paul Selten, Ph.D., M.D.

Objective: The authors synthesize findings of previous studies implicating migration as a risk factor for the development of schizophrenia and provide a quantitative index of the associated effect size.

Method: MEDLINE was searched for population-based incidence studies concerning migrants in English-language publications appearing between the years 1977 and 2003. Article bibliographies and an Australian database were cross-referenced. Studies were included if incidence reports provided numerators and denominators and if age correction was performed or could be performed by the authors. Relative risks for migrant groups were extracted or calculated for each study. Significant heterogeneity across studies indicated the need for a mixed-effects meta-analytic model.

Results: The mean weighted relative risk for developing schizophrenia among first-generation migrants (40 effect sizes) was 2.7 (95% confidence interval [CI]= 2.3–3.2). A separate analysis performed for second-generation migrants (seven effect sizes) yielded a relative risk of 4.5 (95% CI=1.5–13.1). An analysis performed for studies concerning both first- and second-generation migrants and studies that did not distinguish between generations (50 effect sizes) yielded a relative risk of 2.9 (95% CI=2.5–3.4). Subgroup comparisons yielded significantly greater effect sizes for migrants from developing versus developed countries (relative risk=3.3, 95% CI=2.8–3.9) and for migrants from areas where the majority of the population is black (relative risk=4.8, 95% CI=3.7–6.2) versus white and neither black nor white.

Conclusions: A personal or family history of migration is an important risk factor for schizophrenia. The differential risk pattern across subgroups suggests a role for psychosocial adversity in the etiology of schizophrenia.

(Am J Psychiatry 2005; 162:12–24)

Interest in migration as a putative risk factor for schizophrenia has accelerated in recent years, generated partly by alarmingly high incidence rates obtained for persons of African Caribbean background in the United Kingdom (1, 2). High incidence rates of schizophrenia have also been found for persons of Surinamese, Dutch Antillean, and Moroccan background in the Netherlands (e.g., reference 3). An increased risk for developing schizophrenia has recently been found for all migrants in Denmark, particularly those from Australia, Africa, and Greenland (4). Such findings have yet to be adequately explained.

The following meta-analysis provides a quantitative synthesis of population-based studies concerning the incidence of schizophrenia among migrants. The purposes of the meta-analysis are to gain an understanding of the overall effect size putatively indicated by the migrant risk factor and to gain insight into potential underlying mechanisms. In addition, the meta-analysis addresses the following questions: 1) How consistent are the findings of a higher incidence of schizophrenia among migrants? 2) Are certain groups at particularly elevated risk?

Background

Ödegaard (5), an early pioneer in the field, showed that the rate of first admissions for schizophrenia among Norwegian immigrants to the United States was twice as high as that for native-born Americans and Norwegians living in Norway. Ödegaard attributed this excess largely to selection, a conclusion that has been increasingly questioned (e.g., references 4, 6). Adjusting for population differences in age structure (e.g., references 7, 8) and urbanization (8), Malzberg found higher rates of first admissions for dementia praecox among foreign-born residents of New York State. Despite the work of these early innovators, researchers during succeeding decades were generally less attentive to demographic differences between the migrant and native-born populations. Cochrane's study of mental hospital admission rates in 1977 (9), however, set the benchmark for more rigorous standards of inquiry. Consequently, we selected a priori the year 1977 as the lower limit for inclusion of studies in our meta-analysis.

Migration/Ethnicity/Race: What Concept Is Being Studied?

The term "migrant" has been used variously in the literature, with some studies referring to mixed populations of first- and second-generation migrants as migrants (e.g., reference 10) and some studies referring to these same groups as ethnic minorities defined on the basis of color,

e.g., "blacks" (11), a shifting term that reflected the fact that large-scale migration to the United Kingdom from countries other than Ireland began only in the 1950s (12). Consequently, virtually all nonwhite persons and members of ethnic minorities included in British epidemiological studies conducted after 1977 were first- or second-generation migrants. For the current meta-analytic review, we used the term "migrant" to denote persons with foreign birthplace (first-generation migrant) or persons with one or both parents born abroad (second-generation migrant). In order to generate testable hypotheses concerning a higher incidence of schizophrenia in migrants, we created further stratifications on the basis of skin color and the level of economic development of the country of birth. Such groupings may well be proxies for factors of potential relevance for the development of schizophrenia, such as social status, uprootedness, or discrimination.

Method

Study Selection

Using the key words "migration," "ethnicity," "psychosis," and/or "schizophrenia," a computerized search of MEDLINE was systematically conducted for possibly relevant publications appearing between January 1977 and April 2003. A database of all schizophrenia incidence studies published during this period was also searched (provided by Dr. John McGrath, Brisbane, Australia). Bibliographies from identified articles were cross-referenced.

To be included in the meta-analysis, studies had to fulfill the following criteria: 1) the study reported schizophrenia incidence rates for one or more migrant groups residing in a circumscribed area or provided numerators and denominators for such calculations, 2) the study included correction for age differences between the immigrant group and the reference group or provided data that made this correction possible, and 3) the study was published in an English-language, peer-reviewed scientific journal.

In most studies, the designation of migrant status was based on the country of birth of the subjects in question or their parents. Denominators for studies conducted in the United Kingdom, however, were based largely on categories derived from national censuses, with some studies using "whites" (11, 13–15) or the "remainder of the general population" (e.g., references 10, 16) as the reference group. Thus, some members of the reference group might actually have recently migrated to the United Kingdom, and some "blacks" or members of ethnic minority populations might possibly have lived in the United Kingdom for more than two generations. This type of classification error would, however, primarily tend toward an attenuation of the relative risks currently obtained for migrants versus nonmigrants.

In selecting studies, we sometimes found that two or more articles reported epidemiological studies within the same region or time frame. When there was a complete overlap of samples, only one study was included in the analysis. The overlap of samples between the study by McGovern and Cope (Birmingham, England, 1980–1983) (17) and that by Cochrane and Bal (England, 1981) (18) was small, and both studies were included. Two Danish register studies (4, 19) overlapped partly in the years studied. The study by Cantor-Graae et al. (4) was selected because the information on ethnicity was more accurate and because that study included outpatients after 1995. The overlap between the studies by van Os et al. (14) and Boydell et al. (20), however, was large, and the former study was selected because it provided a better definition of ethnicity. One study conducted in Manchester, England, was excluded because no age correction could be performed (21).

Studies that combined the results for schizophrenia with those for other psychoses (e.g., schizophrenia and paranoia or schizophrenia and paranoid psychosis) were included. When the same study reported separate results for psychoses and for schizophrenia, the results for schizophrenia were selected.

Some studies presented figures for the first generation only. Other studies reported separate relative risks for first- and second-generation migrants or combined the results for both generations into one figure. Consequently, we prepared three different data sets. The first data set concerned the effect sizes for first-generation migrants only; the second data set concerned those for second-generation migrants only. To make use of a large data set that could be regarded as an aggregate of the general migrant effect and that could yield maximal power for a series of statistical analyses, we also composed a third data set. This data set included 1) studies that did not distinguish between first- and second-generation migrants, 2) studies that made this distinction but from which one could extract figures for the two generations combined, and 3) studies that reported effect sizes for the first or the second generation only. Only one effect size for each migrant group described in the selected study was included in this third data set.

Meta-Analysis

From each study, relative risks were obtained for one or more immigrant groups. Extraction of data and calculation of relative risks were performed by the two authors independently, and consensus was reached in case of discrepancies. The available data for numerators and denominators were used to calculate age- and gender-adjusted relative risks by Poisson regression analysis. When possible, separate relative risks were computed for first- and second-generation migrants and for male and female migrants.

There were large differences between studies in the presentation of details concerning numerators, denominators, and rates. In order to use the same method of variance estimation for all studies, we used the formula $V=1/N_n + 1/N_m$, where N_n is the number of native cases and N_m

TABLE 1. Population-Based Incidence Studies Included in Meta-Analysis of the Risk for Schizophrenia Associated With Migration

Study	Year of Publication	Country	Region of Birth or Ethnicity of Migrant Group	Level of Economic Development of Region of Birth[a]	First- or Second-Generation Migrants
Rwegellera (30)	1977	United Kingdom	Caribbean	3–4	First
			West Africa	5	First
Hitch and Clegg (28)	1980	United Kingdom	Eastern European	2	First
			India, Pakistan, and Caribbean	Mixed[d]	First
Krupinski and Cochrane (31)	1980	Australia	Great Britain	1	First
			Germany	1	First
			Italy	1	First
			Poland	2	First
Dean et al. (32)	1981	United Kingdom	Caribbean	3–4	First
			India	5	First
			Pakistan	5	First
			Africa (Asians from Uganda)	5	First
			Ireland	1	First
McGovern and Cope (17)	1987	United Kingdom	Caribbean	3–4	Both
Cochrane and Bal (18)	1987	United Kingdom	Caribbean	3–4	First
			Ireland	1	First
			India	5	First
			Pakistan, Bangladesh	5	First
Harrison et al. (16)	1988	United Kingdom	Caribbean	3–4	First
			Caribbean	3–4	Second
			Caribbean	3–4	Both
Castle et al. (13)	1991	United Kingdom	Caribbean	3–4	Both
Thomas et al. (33)	1993	United Kingdom	Caribbean	3–4	First
			Caribbean	3–4	Second
			Caribbean	3–4	Both
			Asian	5	First
			Asian	5	Second
			Asian	5	Both
Selten and Sijben (34)	1994	Netherlands	Turkey	4	First
			Morocco	4	First
Van Os et al. (14)	1996	United Kingdom	Caribbean	3–4	Both
			African	5	Both
Selten et al. (29)	1997	Netherlands	Surinam	4	First
			Dutch Antilles	3	First
Harrison et al. (10)	1997	United Kingdom	Caribbean	3–4	Both
Bhugra et al. (15)	1997	United Kingdom	Caribbean	3–4	Both
			Asian	5	Both
Goater et al. (11)	1999	United Kingdom	Black	Mixed[d]	Both
			Asian	5	Both
			Other	Mixed[d]	Both
Selten et al. (3)	2001	Netherlands	Surinam	4	First
			Dutch Antilles	3	First
			Turkey	4	First
			Morocco	4	First
			Other, Western	Mixed[d]	First
			Other, non-Western	Mixed[d]	First
			Surinam	4	Second
			Morocco	4	Second
			Other	Mixed[d]	Second
			Surinam	4	Both
			Dutch Antilles	3	Both
			Turkey	4	Both
			Morocco	4	Both
			Other	Mixed[d]	Both
Zolkowska et al. (27)	2001	Sweden	Outside Sweden	Mixed[d]	First
Cantor-Graae et al. (4)	2003	Denmark	Scandinavia (outside Denmark)	1	First
			Europe	1	First
			Middle East	3–4	First
			Asia	5	First
			Africa	5	First
			Australia	1	First
			North America	1	First
			South America	3–4	First
			Greenland	3	First
			Mixed[d]	Mixed[d]	Second

[a] Rated according to the United Nations Conference on Trade and Development (UNCTAD) categorization of economic development: 1=countries with developed market economies, 2=Eastern European countries, 3=developing countries with relatively high income (e.g., Trinidad), 4=developing countries with middle income (e.g., Jamaica), and 5=developing countries with low income (e.g., India).

[b] Skin color group categorization: 1=migrants from areas where the majority of the population is white (Europe, North America, North Africa, Turkey, Middle East, Australia), 2=migrants from areas where the majority of the population is black (the Caribbean, sub-Saharan Africa), 3=migrants from areas where the majority of the population cannot be classified as white or black (India, Pakistan, Asia, South America, Greenland).

Number of Patients in Migrant Group	Number of Patients in Reference Group	Study Type	Diagnosis or Criteria	Ethnicity, Skin Color Group[b]	Relative Risk	Analyses[c]
23	47	First contact	Schizophrenia, paranoia, schizoaffective disorder	2	5.7	1, 3, 4, 5
12	47			2	26.1	1, 3, 4, 5
22	123	First admissions	Schizophrenia, paranoia	1	4.6	1, 3, 4, 5
41	123			3	3.2	1, 3, 4
173	1,097	First admissions	Schizophrenia	1	1.1	1, 3, 4, 5
65	1,097			1	2.5	1, 3, 4, 5
126	1,097			1	1.8	1, 3, 4, 5
59	1,097			1	4.1	1, 3, 4, 5
108	1,191	First admissions	Schizophrenia	2	5.1	1, 3, 4, 5
58	1,191			3	3.1	1, 3, 4, 5
27	1,191			3	1.2	1, 3, 4, 5
80	1,191			3	4.2	1, 3, 4, 5
96	1,191			1	2.4	1, 3, 4, 5
51	98	First admissions	Schizophrenia, paranoia	2	6.2	3, 4, 5
109	3,773	First admissions	Schizophrenia, paranoia	2	3.2	1, 3, 4, 5
108	3,773			1	1.6	1, 3, 4, 5
58	3,773			3	1.3	1, 3, 4, 5
30	3,773			3	1.3	1, 3, 4, 5
10	59	First contact	ICD-9	2	8.9	1
17	59			2	16.5	2
27	59			2	13.0	3, 4, 5
36	53	First contact	Research Diagnostic Criteria	2	5.9	3, 4, 5
2	41	First admission	ICD-9	2	0.6	1
10	28			2	9.1	2
12	41			2	2.6	3, 4, 5
5	41			3	1.6	1
1	28			3	1.0	2
6	41			3	1.5	3, 4, 5
17	975	First admission	ICD-9	1 or 3	1.0	1, 3, 4, 5
39	975			1 or 3	3.3	1, 3, 4, 5
22	30	First admission	Research Diagnostic Criteria	2	3.1	3, 4, 5
23	30			2	4.2	3, 4, 5,
697	10,726	First admission	ICD-9	Mixed[d]	3.8	1, 3, 4
236	10,726			2	4.0	1, 3, 4, 5
11	46	First contact	ICD-10	2	7.7	3, 4, 5
38	38	First contact	CATEGO schizophrenia, paranoia, other[e]	2	1.7	3, 4, 5
24	38			3	1.4	3, 4, 5
25	21	First contact	ICD-9	2	4.7	3, 5
9	21			3	4.5	3, 4, 5
4	21			Mixed[d]	4.5	3
17	35	First contact	DSM-IV	Mixed[d]	3.2	1
3	35			2	2.9	1
3	35			1 or 3	0.8	1
13	35			1 or 3	4.5	1
3	35			Mixed[d]	1.1	1
13	35			2	5.7	1, 3, 4, 5
10	24			2	26.1	1, 3, 4, 5
4	24			1	4.6	1, 3, 4, 5
6	24			3	3.2	1, 3, 4
27	35			1	1.1	1, 3, 4, 5
3	35			1	2.5	1, 3, 4, 5
3	35			1	1.8	1, 3, 4, 5
17	35			1	4.1	1, 3, 4, 5
25	35			2	5.1	1, 3, 4, 5
22	34	First contact	DSM-IV	3	3.1	1, 3, 4, 5
106	8,684	First admission[f]	ICD-8, ICD-10	3	1.2	1, 3, 4, 5
178	8,684			3	4.2	1, 3, 4, 5
29	8,684			1	2.4	1, 3, 4, 5
74	8,684			2	6.2	3, 4, 5
41	8,684			2	3.2	1, 3, 4, 5
11	8,684			1	1.6	1, 3, 4, 5
36	8,684			3	1.3	1, 3, 4, 5
15	8,684			3	1.3	1, 3, 4, 5
81	8,684			2	8.9	1
426	8,684			2	16.5	2

[c] Analyses in which the data were included (see Method). Effect sizes included in analysis 4 were also included in analysis 4a, and effect sizes included in analysis 5 were also included in analysis 5a.

[d] Mixed ethnic population, mixed regions of birth, or mixed UNCTAD ratings. Mixed data were not included in analysis 4 or analysis 5.

[e] Diagnoses generated by CATEGO computer program.

[f] Outpatients were also included in the sample in the latter part of the study period.

is the number of migrant cases (derived from the formula for the variance of odds ratios) (22), as previously done by Aleman et al. (23). In order to prevent studies with very large samples from dominating the analyses, the number of subjects in studies with more than 500 patients was set at 500, as suggested by Shadish and Haddock (24). A homogeneity statistic, Q_W, was calculated to examine whether the various effect sizes that are averaged into a mean value can be assumed to estimate the same population effect size. Significant values of Q_W indicate heterogeneity across studies. The Q_B statistic was used to test whether differences in effect sizes between groups (e.g., risks for male versus female migrants) were statistically significant.

Since the effect size distributions remained heterogeneous even after modeling the between-study differences, analyses were carried out within the mixed-effects model. This model assumes that the effects of between-study variables are systematic but that there is a remaining unmeasured random effect in the effect size distribution in addition to subject-level sampling error. All analyses were performed with the Meta Win 2.0 statistical package (25).

We first analyzed the studies pertaining to first-generation migrants (data set 1, analysis 1) and second-generation migrants (data set 2, analysis 2). For the remainder of the analyses (analyses 3, 4, 4a, 5, 5a, and 6), data set 3 was used, starting with the computation of the mean relative risk for the studies in data set 3 (analysis 3).

In analyses 4 and 4a, the risks for migrants from developing countries were compared to those for migrants from developed countries. Countries were classified by using the United Nations Conference on Trade and Development (UNCTAD) classification of countries for the year 1995 (26). UNCTAD classifies countries into five categories: 1) countries with developed market economies, 2) Eastern European countries, 3) developing countries with relatively high income (e.g., Trinidad), 4) developing countries with middle income (e.g., Jamaica), and 5) developing countries with low income (e.g., India). In analysis 4, migrants from UNCTAD groups 1 and 2 were compared to migrants from developing countries as an aggregate category (UNCTAD groups 3–5). To compare extremes in developmental levels, we also examined a tripartite division: UNCTAD groups 1 and 2 versus groups 3 and 4 versus group 5 (analysis 4a). Migrants from regions (e.g., the Middle East) were classified according to the index of those countries from which most migrants originated. Effect sizes for groups with regionally mixed birthplaces, i.e., the groups studied by Zolkowska et al. (27), the groups designated "other" in the study by Selten et al. (3), blacks in the study by Goater et al. (11), and second-generation migrants in the study by Cantor-Graae et al. (4) were excluded from this analysis.

The effect of ethnicity as defined on the basis of skin color was examined in analysis 5 by comparing migrants from areas where the majority of the population is classified as white (Europe, North America, North Africa, Turkey, the Middle East, Australia; skin color group 1) to migrants from areas where the majority of the population is classified as black (the Caribbean, sub-Saharan Africa; skin color group 2) and to migrants from areas where the majority of the population cannot be classified as white or black (India, Pakistan, Asia, South America, Greenland; skin color group 3). In addition to excluding the three effect sizes for groups of mixed birthplace (3, 4, 27), we excluded three effect sizes for migrants who constituted a mix of groups 2 and 3; i.e., the Asian and Caribbean migrants in the study by Hitch and Clegg (28) and the Surinamese migrants in the study by Selten et al. (3, 29). Migrants from Turkey, Morocco, and the Middle East were assigned to skin color group 1, i.e., white (analysis 5), and also, in a separate analysis, to skin color group 3 (analysis 5a). Finally, possible gender effects were examined in analysis 6.

Results

Eighteen studies met our criteria for inclusion in the meta-analysis: eight first-contact incidence studies (3, 10, 11, 13, 15, 16, 27, 30) that included both inpatients and outpatients and 10 hospital-based first-admissions studies (4, 14, 17, 18, 28, 29, 31–34), four of which were national register studies (4, 18, 29, 34). One study was conducted in Australia (31), and the remainder in the United Kingdom, the Netherlands, Denmark, and Sweden. The characteristics of these studies, including the relative risks identified for migrant groups, are summarized in Table 1. Five studies used semistructured diagnostic interviews (3, 10, 11, 15, 16). Nonstandardized systems of diagnostic criteria were used in six studies (17, 18, 28, 30–32). Almost all of the effect sizes implied higher risks for migrants than for nonmigrants.

The results of the meta-analyses are shown in Table 2. Analysis 1, which concerned all studies of first-generation migrants (40 effect sizes), yielded a mean (weighted) relative risk of 2.7 (95% confidence interval [CI]=2.3–3.2). The heterogeneity across studies was found to be significant. Analysis 2, which concerned all studies of second-generation migrants, yielded a mean relative risk of 4.5 (95% CI= 1.5–13.1) and no evidence for heterogeneity, but the power to demonstrate heterogeneity across seven effect sizes was limited.

Analysis 3 was conducted with the largest data set, which also included the studies that did not distinguish between first- and second-generation migrants (data set 3, 50 effect sizes). Figure 1 shows the effect sizes and confidence intervals for the migrant groups included in analysis 3. The mean relative risk was found to be 2.9 (95% CI= 2.5–3.4), and the evidence for heterogeneity was again significant. The studies that used semistructured diagnostic interviews (12 effect sizes) and the studies that used other diagnostic methods (38 effect sizes) yielded similarly significant results (relative risk=3.4, 95% CI=2.3–4.9; relative

TABLE 2. Results of Meta-Analyses of Population-Based Studies Examining the Association Between Migration and Incidence of Schizophrenia

Data Set, Analysis, and Variable	k[a]	Relative Risk	95% CI	Q_W[b]	Q_B[c]	p[d]
Data for first-generation migrants (analysis 1: effect of first-generation migrant status)	40	2.7	2.3–3.2	55.4		<0.05
Data for second-generation migrants (analysis 2: effect of second-generation migrant status)	7	4.5	1.5–13.1	4.5		0.62
Data for first- and second-generation migrants						
Analysis 3: effect of first- and second-generation migrant status	50	2.9	2.5–3.4	68.3		<0.04
Analysis 4: effect of United Nations Conference on Trade and Development (UNCTAD) rating					5.0	<0.03
Developing countries	35	3.3	2.8–3.9			
Developed countries	11	2.3	1.7–3.1			
Analysis 4a: effect of UNCTAD rating					12.5	0.002
Developed market economies	9	2.0	1.5–2.8			
Eastern Europe and developing countries, high or medium income	24	3.6	3.0–4.4			
Developing countries, low income	11	2.8	2.0–3.8			
Analysis 5: skin color[e]				25.2		<0.0001
White	16	2.3	1.8–3.0			
Black	16	4.8	3.7–6.2			
Nonwhite/nonblack	11	2.2	1.6–3.0			
Analysis 5a: skin color[f]				25.6		<0.0001
White	11	2.3	1.7–3.1			
Black	16	4.8	3.7–6.2			
Nonwhite/nonblack	16	2.2	1.7–2.9			
Analysis 6: gender				0.1		0.72
Male	21	2.5	2.0–3.2			
Female	21	2.4	1.8–3.1			

[a] Number of effect sizes.
[b] Q_W=within-category homogeneity statistic, df=k–1.
[c] Q_B=between-category homogeneity statistic, df=1 (analyses 4 and 6) or df=2 (analyses 4a, 5, and 5a).
[d] p value for Q_W or Q_B.
[e] Skin color group categorization: white=migrants from areas where the majority of the population is white (Europe, North America, North Africa, Turkey, Middle East, Australia), black=migrants from areas where the majority of the population is black (the Caribbean, sub-Saharan Africa), nonwhite/nonblack=migrants from areas where the majority of the population cannot be classified as white or black (India, Pakistan, Asia, South America, Greenland).
[f] Skin color group categorization: white=migrants from areas where the majority of the population is white (Europe, North America, Australia), black=migrants from areas where the majority of the population is black (the Caribbean, sub-Saharan Africa), nonwhite/nonblack=migrants from areas where the majority of the population cannot be classified as white or black (India, Pakistan, Asia, South America, Greenland, Morocco, Turkey, Middle East).

risk=2.8, 95% CI=2.4–3.4, respectively). The studies that used nonoperational diagnostic criteria (18 effect sizes) and operational diagnostic criteria (32 effect sizes) yielded similar mean relative risks. The mean relative risk obtained by using the ICD criteria (21 effect sizes, relative risk=3.1, 95% CI=2.5–3.8) did not differ significantly from the relative risk obtained by using narrower criteria (11 effect sizes, relative risk=2.6, 95% CI=1.9–3.7) (p=0.09). Funnel plots of effect sizes in data sets 1–3 provided no evidence for publication bias.

A significant association of risk with level of economic development of the region of birth was found (analysis 4), with greater risks for migrants from developing countries than for migrants from developed countries. Analysis 4a showed that the risks for migrants from countries in UNCTAD groups 2, 3, and 4 were significantly greater than those for migrants from countries in UNCTAD groups 1 and 5.

A significant association of risk with skin color was found (analysis 5). The mean weighted relative risk for migrants from countries where the majority of the population was black was 4.8 (95% CI=3.7–6.2), approximately two times greater than that for migrants from countries where the majority was white or nonwhite/nonblack. When people from Turkey, Morocco, and the Middle East were regarded as neither white nor black, similar results were obtained (analysis 5a, Table 2). When analyses 4, 4a, 5, and 5a were carried out by using data set 1, the results were similar.

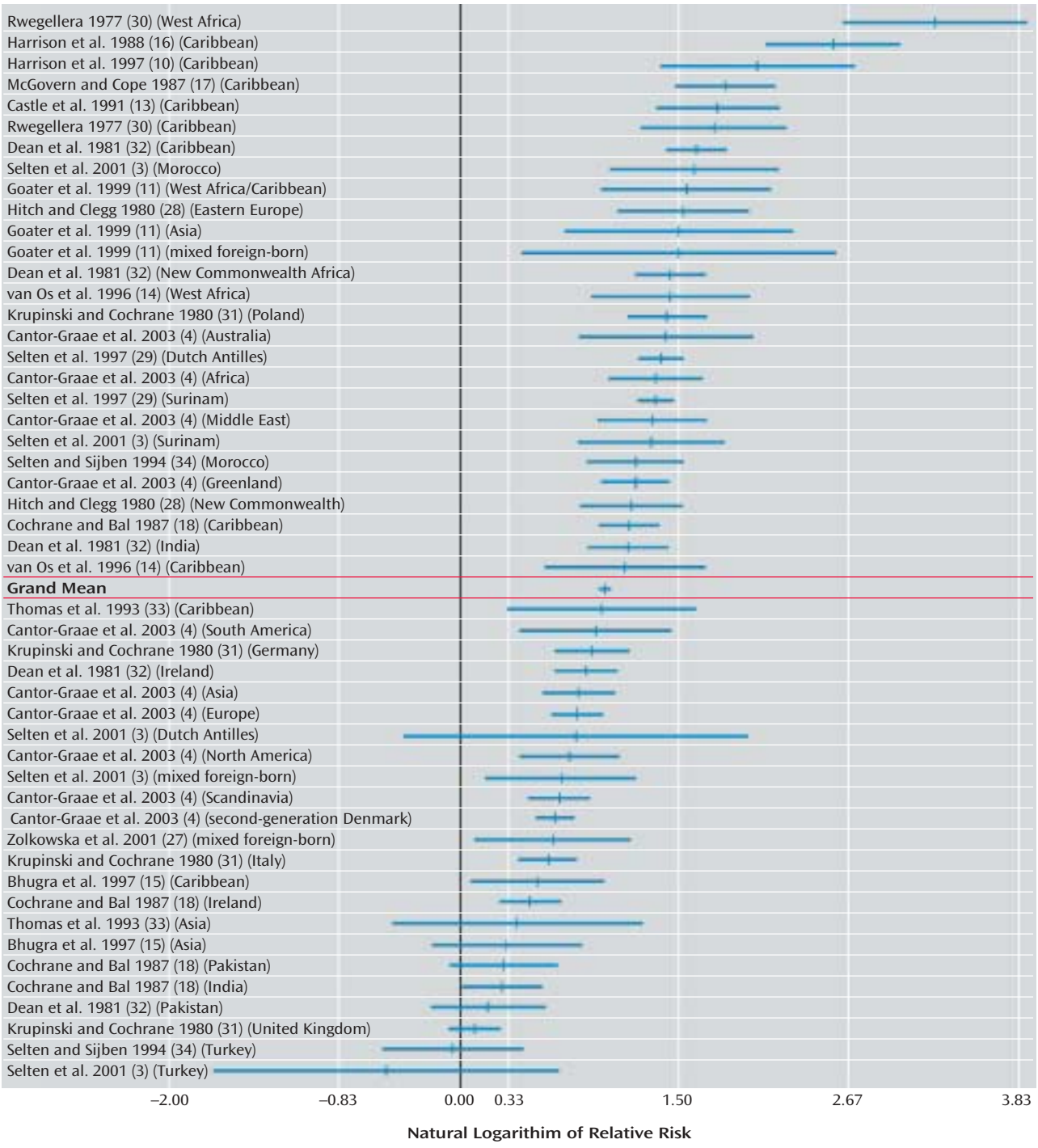
Finally, when the effect sizes for male migrants were compared to those for female migrants (analysis 6), no differences were found (Table 2).

Discussion

How Large an Effect Size Is Indicated by the Migrant Risk Factor?

The most comprehensive of the meta-analyses, which included both first- and second-generation migrants, yielded a mean weighted effect size of 2.9 (95% CI=2.5–3.4) for the risk of developing schizophrenia among migrants. It should be observed that significant heterogeneity was found across studies, indicating that the different migrant groups cannot be regarded as coming from one population having a common effect size. It is important to note that few studies examined all migrant groups in a given country, and most studies were directed at spe-

FIGURE 1. Natural Logarithm of Relative Risk (and 95% Confidence Intervals) for Migrant Groups Included in Population-Based Incidence Studies of Risk for Schizophrenia Associated With Migration[a]



[a] The figure shows the natural logarithms of all effect sizes and the natural logarithm of the grand mean. The effect sizes are for studies that did not distinguish between first- and second-generation migrants, studies from which data for the two generations combined could be extracted, and studies reporting effect sizes for first- or second-generation migrants only.

cific groups with high risks, such as the Surinamese in the Netherlands. However, an overall effect size of this magnitude indicates that there can be little doubt about the existence of an association between migration and schizophrenia.

The largest and most well-documented risk factor related to the development of schizophrenia is a family history of the disease (35). The effect size associated with migration is, however, greater than the effect size associated with most other risk factors putatively implicated in the

etiology of schizophrenia. A recent meta-analytic review showed that the odds ratios for the risk for developing schizophrenia associated with obstetric complications were generally less than 2.0 (36). Winter birth is associated with a 5%–8% increase in the risk for schizophrenia (37), corresponding to a relative risk of 1.05–1.08. The only risk factor with an effect size approaching that of migration would be urbanization, for which relative risks of 2.4 (38) and 2.75 (39) have been reported.

Can the Validity of These Findings Be Questioned?

Diagnostic bias. Some researchers have argued that migrants preferentially receive schizophrenia diagnoses because of cultural misunderstanding and/or language difficulties (e.g., reference 40). Nevertheless, evidence in support of this notion is not convincing. Follow-up studies have shown no evidence of greater diagnostic instability over time among Caribbean versus non-Caribbean patients (e.g., references 41, 42), and most outcome studies reveal few differences in clinical characteristics between these groups. Moreover, similar ages at onset among migrants and native-born patients suggest that schizophrenia is the same disorder in both groups (4, 10).

Methodological concerns. The predominance of studies conducted in Europe partly reflects the feasibility with which incidence data may be collected in these settings. The ascertainment of incident cases is considered to be highly accurate in the Netherlands and in Scandinavia, since private treatment for schizophrenia is virtually nonexistent. Moreover, estimates of the background population are quite reliable, insofar as civil registration is obligatory, registers are updated yearly, and access to benefits such as day care, medical care, and unemployment benefits are dependent on such registration.

In contrast, it may be more difficult to establish correct population denominators where population statistics are based on household censuses, and it has been argued that single African Caribbean men may have been underenumerated (43). To adjust for possible underenumeration of British-born African Caribbeans in the background population, previous researchers have applied 10%–30% correction factors to denominators in calculations involving data for African Caribbeans (e.g., references 10, 14, 17).

An important consideration may be differential paths to treatment, as most studies of migrants are based on rates of treated cases. A review of rates of treated versus untreated cases of severe mental illness found that rates of treated cases were positively related to higher social class (44). Consequently, minority groups may tend to be underrepresented rather than overrepresented in treatment samples. Compulsory admissions are, however, more common among African Caribbeans (45), but these admissions do not necessarily lead to higher incidence per se. Also, although a shorter interval between the emergence of psychosis and first contact with treatment providers among migrants could arguably lead to a higher incidence within a restricted time period, the existing evidence suggests that in migrants this interval is similar to (46) or longer than (3) that in nonmigrants (3). Finally and most importantly, efforts to explain the higher incidence of schizophrenia among migrants on the basis of a lower threshold for treatment alone presuppose a hidden morbidity in the native-born population that exceeds any previously reported finding in population surveys (44, 47).

A limitation in the current method is that assignment to the categories used in analyses 4 and 5 is based on birthplace. The levels of economic development and the skin color of the majority population do not necessarily reflect the individual's actual income or physical appearance.

Selective Migration?

A growing number of empirical findings suggest that Ödegaard's selection hypothesis (5) can be rejected as the sole explanation for the findings on migrants. Findings of fivefold higher incidence rates among Surinamese migrants to the Netherlands than in the native-born population constitute one of the strongest arguments against the selection hypothesis, insofar as more than one-third of the Surinamese population emigrated (6, 29). Moreover, selective migration cannot explain the increased risk for schizophrenia found among second-generation migrants (Table 2) or among migrants residing in Denmark before their 15th birthday (4). Similarly, the median ages of migration for Surinamese and Moroccan-born patients in the study by Selten and colleagues (3) were 9 and 15 years, respectively. Although a role for selective migration cannot be excluded in these migrants' parents, the risk of developing schizophrenia among second-generation migrants in Denmark was lower for those with a parental history of psychiatric disorder than for those without such a parental history (4).

It may be pertinent to note that the premorbid and prodromal characteristics of schizophrenia patients, which include negative symptoms and frontal dysfunction, do not seem compatible with the effort required to emigrate. Considering that even more effort may be required for persons to migrate from developing countries to Europe, such individuals should have lower risks for schizophrenia, contrary to the current findings. Also relevant in this regard, Rosenthal et al. (48) found that emigration rates of adopted children born to a biological parent with schizophrenia spectrum disorder were lower than for children born to parents who did not have a schizophrenia spectrum disorder. It may be further noted that incidence studies conducted in the Caribbean (e.g., reference 49) and Surinam (50) show normal incidence rates for schizophrenia. Thus, genes alone cannot explain why individuals from these countries develop a higher risk for schizophrenia when they migrate.

How Well Do Current Hypotheses Concerning Migrants Fit the Data?

There is still some controversy about whether environmental factors contribute to the etiology of schizophrenia. Nevertheless, meta-analytical evidence from twin studies indicates that schizophrenia has complex multifactorial determinants that would include environmental factors (51). The current findings similarly suggest the operation of environmental factors, albeit their exact nature remains uncertain. Moreover, viable hypotheses concerning migrants must meet the challenge posed by increased rates of schizophrenia found in first-generation *and* in second-generation migrants. Thus, for example, an impaired immunity to a neurotropic virus found in Europe would not explain the findings for second-generation migrants, and impaired intrauterine immunity would not explain the higher rates in first-generation migrants. Studies analyzing the effects of Borna disease and influenza viruses have yielded negative results in migrants (52, 53), but other viral mechanisms are possible. Delayed exposure to a common infectious agent such as Epstein-Barr virus has been suggested as a model for multiple sclerosis, a disorder that also shows migration effects (54). Nevertheless, the intergenerational risk pattern of multiple sclerosis in migrants differs from that of schizophrenia. Migrants from countries with a warm climate generally retain the low risk for multiple sclerosis associated with their country of birth, whereas the risk in their offspring approaches that of the host country population. Moreover, whereas climate and latitude are strongly correlated with multiple sclerosis rates, climate factors seem increasingly unlikely, considering the increased risks for schizophrenia in migrants to Denmark from both Australia and Greenland (4). Prenatal exposure to a vitamin D deficiency associated with dark-skinned migrants living in cold climates might increase the risk for schizophrenia among second-generation migrants but not among first-generation migrants (55). Childhood exposure to animal-borne infectious agents less frequently found in the country of origin, such as *Toxoplasmosis gondii* (e.g., reference 56), might merit further study, since such exposure would affect persons migrating early in life as well as second-generation migrants.

Some data suggest that higher rates of schizophrenia are found in so-called modern countries (57). The mechanism involved in modernization would require further specification, since numerous factors could be involved. Concepts akin to modernization are urban birth and urban upbringing, factors strongly related to higher risk for schizophrenia (38, 39), yet whose specific components are still unknown. The notion that the migrant phenomenon is a manifestation of the urban effect would, however, require that migrants be more intensively exposed to the urban factor or be more sensitive to it. Use of illicit drugs, cannabis in particular, might tentatively fulfill these requirements, in that cannabis use may contribute to the development of schizophrenia (e.g., reference 58). However, it should be noted that the twofold risk associated with cannabis (59) is smaller than the effect size indicated by migration. Moreover, cannabis use would predict a greater risk for schizophrenia among male migrants (60), but a gender difference was not found in the current study. Migrant studies examining illicit drug use in first-onset psychosis patients have failed to find higher rates in African Caribbeans in the United Kingdom (60) or in migrants to the Netherlands (61). Also, a study of schizophrenia risk in Swedish conscripts found that the urban effect remained after adjustment for cannabis use (62).

Aspects of reproduction may be affected by migration. There is some preliminary evidence that greater paternal age contributes to the etiology of schizophrenia (63), and this factor could be further explored in migrants. More speculatively, it has been proposed that cephalopelvic disproportion arising from improved nutritional standards could lead to an elevated incidence of schizophrenia among second-generation migrants (64). Two studies have investigated history of obstetric complications in African Caribbean versus white British-born patients (65, 66). Both studies found fewer obstetric complications in African Caribbean patients, and no differences in first- versus second-generation African Caribbean patients (65). Also, although a decline in breast-feeding among first-generation migrants might lead to a reduction of any putative protective effects in second-generation migrants, data from two national birth cohorts failed to find any protective effect of breast-feeding with regard to risk of schizophrenia (67).

New Directions: Discrimination and Social Defeat

In general, the broad spectrum of migrant groups implicated would seem to refute the notion that any single biological or genetic factor could provide an adequate explanation. Between-population variation of this type does rather strongly support a causal role for aspects of the social environment (68). Explanations that incorporate socioenvironmental elements need not negate the genetic or biological nature of schizophrenia. On the contrary, an approach that seeks to integrate psychology and biology may provide a constructive step forward.

By far the most striking finding in the current meta-analysis is the greater effect size associated with black skin color (relative risk=4.8, 95% CI=3.7–6.2). These findings suggest that despite heterogeneity in birthplace, migrants whose skin color is considerably darker than the background population may share a common risk exposure. Individuals with darker skin are more often discriminated against in Western societies. Experiences of discrimination may foster a paranoid attributional style that facilitates the development of psychotic symptoms (69). A preliminary report from a prospective study conducted in the Netherlands suggests that perceived discrimination predicts the development of psychotic symptoms in healthy persons (70). However, such a hypothesis would also predict a

higher rate of schizophrenia in African Americans, yet evidence in support of this association is generally lacking (e.g., reference 71). Indeed, findings from clinical samples suggest that schizophrenia may be overdiagnosed among African Americans, rather than underdiagnosed (72, 73) (but see reference 74). Nevertheless, prevalence rates based on treated samples may not yield valid estimates, because of differences in service use and diagnostic disparities (e.g., reference 75). Population-based incidence studies utilizing well-defined denominators would be required to resolve this potential anomaly.

It may be argued that aspects other than discrimination could contribute to the observed skin color effect. Persons with dark skin color (and migrants in general) may be more subject to the effects of poverty and low social class. It is, however, unlikely that the higher risks for migrants are explained by their low socioeconomic status. The association found between low socioeconomic status and schizophrenia appears largely attributable to social selection (downward mobility of genetically predisposed persons) rather than to social causation (76). Moreover, no clearcut relationship between parental social class and schizophrenia has been indicated across studies (77), and associations with both higher (e.g., reference 78) and lower parental class (79) have been found. It is important to note that a higher relative risk for schizophrenia has not been found among Turkish migrants to the Netherlands versus native-born persons, although Turkish migrants have lower income, educational, and employment levels than Surinamese migrants, whose relative risk for schizophrenia is high (3, 29). Although none of the studies in the meta-analysis controlled for socioeconomic class, Selten et al. (3) found no effect of neighborhood levels of socioeconomic status.

Ethnic disadvantage, more broadly defined, might make it more difficult for migrants to create a life plan (80), insofar as role models and community institutions may be lacking. Thus, the stress of making decisions concerning adult life, perhaps in combination with weaknesses in executive functioning, might contribute to the development of schizophrenia. Although discrimination and/or difficulties in formulating a life plan would explain the even higher rates of schizophrenia generally found in second-generation migrants, both hypotheses would still need to integrate those aspects of the brain that may be etiologically relevant for schizophrenia. A unifying hypothesis concerning migrants should also be able to explain the risk for schizophrenia associated with internal migration to areas of increased urbanization (39) and the protective effect of ethnic density, i.e., the relatively lower incidence of schizophrenia found in nonwhite ethnic minorities that represent larger proportions of the local population (20).

Such a common mechanism might be the long-term experience of social defeat, i.e., the chronic stressful experience of outsider status (77). Social defeat could arise whenever an individual is forced into a subordinate position in relation to a dominant group and could also arise through internal migration to areas of increased urban density, due to the highly competitive atmosphere in urban areas. Animal experiments using the defeated intruder paradigm show that social dominance has an effect on synaptic dopamine levels. In these experiments, the intruder rat is put into the cage of another rat that attacks him and forces him to show submissive behavior. Male rodents subjected to social defeat stress show elevated levels of dopamine in the nucleus accumbens and the prefrontal cortex (81). Repeated exposure to social defeat stress in rats causes increased self-administration of cocaine and amphetamine and increased sensitivity to these substances (82). Moreover, studies of primates have shown a strong relationship between dopaminergic activity and social rank (83, 84). Thus, disturbed brain dopaminergic function resulting from long-term experiences of social defeat could provide a common pathogenetic mechanism for the increased risk for schizophrenia in urban residents and migrants. Such a notion is purely speculative and based thus far on animal models. Moreover, social defeat is unlikely to be a sufficient cause of schizophrenia, but it could well play a contributory role within a multifactorial model. Although the effect of social defeat on the human brain would require further exploration with neuroimaging techniques, accumulating evidence suggests that stress can be responsible for anatomical changes in the human brain, including hippocampal (85) and gray matter (86) volume reductions. Brains with developmental anomalies may make other, possibly unique adaptations to stress (87).

Specific strategies are needed in order to test the factors putatively involved in the migrant effect. For example, little is known about ethnic groups across settings, e.g., the risk of schizophrenia in African Caribbeans residing in the United States versus those residing in the United Kingdom. A study of dark-skinned migrants who move from developing countries with warm climates to developed countries with warm climates (e.g., Australia) could help differentiate between climate and socioenvironmental factors. The effect of urban versus rural upbringing could be further explored in second-generation migrants. Sibling-pair designs have been successful in other contexts and could be used in studies of migrants to explore the relationship between environmental and genetic factors.

Conclusions

The size of the risk for developing schizophrenia associated with migration is considerable and cannot solely be explained by selection. The aspects of the environment that may contribute to this risk are still poorly understood, but perceptions of social inequality may be important. Further investigations in this area may make a substantial contribution to understanding the etiology of schizophrenia.

Received Nov. 4, 2003; revision received Dec. 23, 2003; accepted March 4, 2004. From the Department of Community Medicine, Hos-

pital UMAS; and Rudolf Magnus Institute of Neuroscience, Department of Psychiatry, University Medical Center Utrecht, Utrecht, the Netherlands. Address correspondence and reprint requests to Dr. Cantor-Graae, Department of Community Medicine, Lund University, University Hospital UMAS, Malmö, Sweden S-205 02; elizabeth.cantor-graae@smi.mas.lu.se (e-mail).

Both authors contributed equally to the article.

Supported by the Stanley Medical Research Institute.

References

1. Murray RM, Hutchinson G: Psychosis in migrants: the striking example of African-Caribbeans resident in England, in Search for the Causes of Schizophrenia, Vol 4: Balance of the Century. Edited by Gattaz WF, Häfner H. Darmstadt, Germany, Steinkopff/Springer, 1999, pp 129–140
2. Sharpley MS, Hutchinson G, McKenzie K, Murray RM: Understanding the excess of psychosis among the African-Caribbean population in England. Br J Psychiatry 2001; 178(suppl 40): S60–S68
3. Selten JP, Veen N, Feller W, Blom JD, Schols D, Camoenië W, Oolders J, van der Velden M, Hoek HW, Vladár Rivero VM, van der Graaf Y, Kahn R: Incidence of psychotic disorders in immigrant groups to the Netherlands. Br J Psychiatry 2001; 178: 367–372
4. Cantor-Graae E, Pedersen CB, McNeil TF, Mortensen PB: Migration as a risk factor for schizophrenia: a Danish population-based cohort study. Br J Psychiatry 2003; 182:117–122
5. Ödegaard Ö: Emigration and insanity. Acta Psychiatr Neurol Scand Suppl 1932; 4:1–206
6. Selten J-P, Cantor-Graae E, Slaets J, Kahn RS: Ødegaard's selection hypothesis revisited: schizophrenia in Surinamese immigrants to the Netherlands. Am J Psychiatry 2002; 159:669–671
7. Malzberg B: Mental disease among the native and foreign-born white populations of New York State, 1939–1941. Ment Hyg 1955; 39:545–563
8. Malzberg B: Mental disease among native and foreign-born whites in New York State, 1949–1951. Ment Hyg 1964; 48:478–499
9. Cochrane R: Mental illness in immigrants to England and Wales: an analysis of mental hospital admissions, 1971. Soc Psychiatry 1977; 12:25–35
10. Harrison G, Glazebrook C, Brewin J, Cantwell R, Dalkin T, Fox R, Jones P, Medley I: Increased incidence of psychotic disorders in migrants from the Caribbean to the United Kingdom. Psychol Med 1997; 27:799–806
11. Goater N, King M, Cole E, Leavey G, Johnson-Sabine E, Blizard R, Hoar A: Ethnicity and outcome of psychosis. Br J Psychiatry 1999; 175:34–42
12. Walvin J: Passage to Britain. London, Penguin Press, 1984
13. Castle D, Wessely S, Der G, Murray RM: The incidence of operationally defined schizophrenia in Camberwell, 1965–84. Br J Psychiatry 1991; 159:790–794
14. van Os J, Castle DJ, Takei N, Der G, Murray RM: Psychotic illness in ethnic minorities: clarification from the 1991 census. Psychol Med 1996; 26:203–208
15. Bhugra D, Leff J, Mallett R, Der G, Corridan B, Rudge S: Incidence and outcome of schizophrenia in whites, African-Caribbeans and Asians in London. Psychol Med 1997; 27:791–798
16. Harrison G, Owens D, Holton A, Neilson D, Boot D: A prospective study of severe mental disorder in Afro-Caribbean patients. Psychol Med 1988; 18:643–657
17. McGovern D, Cope R: First psychiatric admission rates of first and second generation Afro Caribbeans. Soc Psychiatry 1987; 22:139–149
18. Cochrane R, Bal SS: Migration and schizophrenia: an examination of five hypotheses. Soc Psychiatry 1987; 22:181–191
19. Mortensen PB, Cantor-Graae E, McNeil T: Increased rates of schizophrenia among immigrants: some methodological concerns raised by Danish findings. Psychol Med 1997; 27:813–820
20. Boydell J, van Os J, McKenzie K, Allardyce J, Goel R, McCreadie RG, Murray RM: Incidence of schizophrenia in ethnic minorities in London: ecological study into interactions with environment. Br Med J 2001; 323:1–4
21. Carpenter L, Brockington IF: A study of mental illness in Asians, West Indians and Africans living in Manchester. Br J Psychiatry 1980; 137:201–205
22. Lipsey MW, Wilson DB: Practical Meta-Analysis. Thousand Oaks, Calif, Sage Publications, 2001
23. Aleman A, Kahn RS, Selten JP: Sex differences in the risk of schizophrenia: evidence from meta-analysis. Arch Gen Psychiatry 2003; 60:565–571
24. Shadish WR, Haddock CK: Combining estimates of effect size, in The Handbook of Research Synthesis. Edited by Cooper H, Hedges LV. New York, Russell Sage, 1994, pp 261–280
25. Rosenberg MS, Adams DC, Gurevitch J: MetaWin: Statistical Software for Meta-Analysis, Version 2.0. Sunderland, Mass, Sinauer Associates, 2000
26. United Nations: UNCTAD Handbook of Statistics. Geneva, United Nations Conference on Trade and Development, 2002
27. Zolkowska K, Cantor-Graae E, McNeil TF: Increased rates of psychosis among immigrants to Sweden: is migration a risk factor for psychosis? Psychol Med 2001; 31:669–678
28. Hitch PJ, Clegg P: Modes of referral of overseas immigrant and native-born first admissions to psychiatric hospital. Soc Sci Med 1980; 14A:369–374
29. Selten JP, Slaets JP, Kahn RS: Schizophrenia in Surinamese and Dutch Antillean immigrants to the Netherlands: evidence of an increased incidence. Psychol Med 1997; 27:807–811
30. Rwegellera GG: Psychiatric morbidity among West Africans and West Indians living in London. Psychol Med 1977; 7:317–329
31. Krupinski J, Cochrane R: Migration and mental health—a comparative study. J Intercult Stud 1980; 1:49–57
32. Dean G, Walsh D, Downing H, Shelley E: First admissions of native-born and immigrants to psychiatric hospitals in South-East England 1976. Br J Psychiatry 1981; 139:506–512
33. Thomas CS, Stone K, Osborn M, Thomas PF, Fisher M: Psychiatric morbidity and compulsory admission among UK-born Europeans, Afro-Caribbeans and Asians in central Manchester. Br J Psychiatry 1993; 163:91–99
34. Selten JP, Sijben N: First admission rates for schizophrenia in immigrants to the Netherlands. Soc Psychiatry Psychiatr Epidemiol 1994; 29:71–77
35. Gottesman II: Schizophrenia Genesis: The Origins of Madness. New York, WH Freeman, 1991
36. Cannon M, Jones PB, Murray RM: Obstetric complications and schizophrenia: historical and meta-analytic review. Am J Psychiatry 2002; 159:1080–1092
37. Torrey EF, Miller J, Rawlings R, Yolken RH: Seasonality of births in schizophrenia and bipolar disorder: a review of the literature. Schizophr Res 1997; 28:1–38
38. Mortensen PB, Pedersen CB, Westergaard T, Wohlfart J, Ewald H, Mors O, Andersen PK, Melbye M: Effects of family history and place and season of birth on the risk of schizophrenia. N Engl J Med 1999; 340:603–608
39. Pedersen CB, Mortensen PB: Evidence of a dose-response relationship between urbanicity during upbringing and schizophrenia risk. Arch Gen Psychiatry 2001; 58:1039–1046
40. Sashidharan SP: Afro-Caribbeans and schizophrenia: the ethnic vulnerability hypothesis re-examined. Int Rev Psychiatry 1993; 5:129–144
41. Takei N, Persaud R, Woodruff P, Brockington I, Murray RM: First episodes of psychosis in Afro-Caribbean and white people: an

18-year follow-up population-based study. Br J Psychiatry 1998; 172:147–153
42. Harrison G, Amin S, Singh SP, Croudace T, Jones P: Outcome of psychosis in people of African-Caribbean family origin. Br J Psychiatry 1999; 175:43–49
43. Glover GR: Sex ratio errors in census data (letter). Br Med J 1993; 307:506
44. Link B, Dohrenwend BP: Formulation of hypotheses about the ratio of untreated to treated cases in the true prevalence studies of functional psychiatric disorders in adults in the United States, in Mental Illness in the United States: Epidemiologic Estimates. Edited by Dohrenwend BP, Dohrenwend BS, Gould MS, Link B, Neugebauer R, Wunsch-Hirzig R. New York, Praeger; 1980, pp 133–148
45. Bhui K, Stansfeld S, Hull S, Priebe S, Mole F, Feder G: Ethnic variations in pathways to and use of specialist mental health services in the UK. Br J Psychiatry 2003; 182:105–116
46. Harrison G, Holton A, Neilson D, Owens D, Boot D, Cooper J: Severe mental disorder in Afro-Caribbean patients: some social, demographic and service factors. Psychol Med 1989; 19:683–696
47. Von Korff M, Nestadt G, Romanoski A, Anthony J, Eaton W, Merchant A, Chahal R, Kramer M, Folstein M, Gruenberg E: Prevalence of treated and untreated DSM-III schizophrenia. J Nerv Ment Dis 1985; 173:577–581
48. Rosenthal D, Goldberg I, Jacobsen B, Wender PH, Kety SS, Schulsinger F, Eldred CA: Migration, heredity, and schizophrenia. Psychiatry 1974; 37:321–339
49. Mahy GE, Mallett R, Leff J, Bhugra D: First-contact incidence rate of schizophrenia on Barbados. Br J Psychiatry 1999; 175: 28–33
50. Hanoeman M, Selten JP, Kahn RS: Incidence of schizophrenia in Surinam. Schizophr Res 2002; 54:219–221
51. Sullivan PF, Kendler KS, Neale MC: Schizophrenia as a complex trait. Arch Gen Psychiatry 2003; 60:1187–1192
52. Selten JP, van Vliet K, Pleyte W, Herzog S, Hoek HW, van Loon AM: Borna disease virus and schizophrenia in Surinamese immigrants to the Netherlands. Med Microbiol Immunol 2000; 189:55–57
53. Selten JP, Slaets JP, Kahn R: Prenatal exposure to influenza and schizophrenia in Surinamese and Dutch Antillean immigrants to the Netherlands. Schizophr Res 1998; 30:101–103
54. Gale CR, Martyn CN: Migrant studies in multiple sclerosis. Progr Neurobiol 1995; 47:425–448
55. McGrath J: Hypothesis: is low prenatal vitamin D a risk-modifying factor for schizophrenia? Schizophr Res 1999; 40:173–177
56. Yolken RH, Bachmann S, Rouslanova I, Lillehoj E, Ford G, Torrey EF, Schroeder J: Antibodies to *Toxoplasma gondii* in individuals with first-episode schizophrenia. Clin Infect Dis 2001; 32: 842–844; correction, 32:1247
57. Torrey EF, Miller J: The Invisible Plague. New Brunswick, NJ, Rutgers University Press, 2001
58. Zammit S, Allebeck P, Andreasson S, Lundberg I, Lewis G: Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. Br Med J 2002; 325:1199–1203
59. Arseneault L, Cannon M, Witton J, Murray RM: Causal association between cannabis and psychosis: examination of the evidence. Br J Psychiatry 2004; 184:110–117
60. Cantwell R, Brewin J, Glazebrook C, Dalkin T, Fox R, Medley I, Harrison G: Prevalence of substance misuse in first-episode psychosis. Br J Psychiatry 1999; 174:150–153
61. Veen ND, Selten JP, Hoek HW, Feller W, van der Graaf Y, Kahn R: Use of illicit substances in a psychosis incidence cohort: a comparison among different ethnic groups in the Netherlands. Acta Psychiatr Scand 2002; 105:440–443
62. Lewis G, David A, Andreasson S, Allebeck P: Schizophrenia and city life. Lancet 1992; 340:137–140
63. Malaspina D, Harlap S, Fennig S, Heiman D, Nahon D, Feldman D, Susser ES: Advancing paternal age and the risk of schizophrenia. Arch Gen Psychiatry 2001; 58:361–367
64. Warner R: Time trends in schizophrenia: changes in obstetric risk factors with industrialization. Schizophr Bull 1995; 21: 483–500
65. Hutchinson G, Takei N, Bhugra D, Fahy TA, Gilvarry C, Mallett R, Moran P, Leff J, Murray RM: Increased rate of psychosis among African-Caribbeans in Britain is not due to an excess of pregnancy and birth complications. Br J Psychiatry 1997; 171:145–147
66. McKenzie K, Jones P, Lewis S, Williams M, Toone B, Sham P, Murray RM: Lower prevalence of pre-morbid neurological illness in African-Caribbean than White psychotic patients in England. Psychol Med 2002; 32:1285–1291
67. Leask SJ, Done DJ, Crow TJ, Richards M, Jones PB: No association between breast-feeding and adult psychosis in two national birth cohorts. Br J Psychiatry 2000; 177:218–221
68. van Os J, McGuffin P: Can the social environment cause schizophrenia? Br J Psychiatry 2003; 182:291–292
69. Garety PA, Kuipers E, Fowler D, Freeman D, Bebbington PE: A cognitive model of the positive symptoms of psychosis. Psychol Med 2001; 31:189–195
70. Janssen I, Hanssen M, Bak M, Bijl RV, De Graaf R, Vollebergh W, McKenzie K, van Os J: Discrimination and delusional ideation. Br J Psychiatry 2003; 182:71–76
71. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS: Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. Arch Gen Psychiatry 1994; 51:8–19
72. Minsky S, Vega W, Miskimen T, Gara M, Escobar J: Diagnostic patterns in Latino, African American, and European American psychiatric patients. Arch Gen Psychiatry 2003; 60:637–644
73. Mukherjee S, Shukla S, Woodle J, Rosen AM, Olarte S: Misdiagnosis of schizophrenia in bipolar patients: a multiethnic comparison. Am J Psychiatry 1983; 140:1571–1574
74. Sohler NL, Bromet EJ: Does racial bias influence psychiatric diagnoses assigned at first hospitalisation? Soc Psychiatry Psychiatr Epidemiol 2003; 38:463–472
75. Strakowski SM, Flaum M, Amador X, Bracha HS, Pandurangi AK, Robinson D, Tohen M: Racial differences in the diagnosis of psychosis. Schizophr Res 1996; 21:117–124
76. Dohrenwend BP, Levav I, Shrout PE, Schwartz S, Naveh G, Link BG, Skodol AE, Stueve A: Socioeconomic status and psychiatric disorders: the causation-selection issue. Science 1992; 255: 946–952
77. Selten JP, Cantor Graae E: Schizophrenia and migration, in Search for the Cause of Schizophrenia, vol 5. Edited by Gattaz W, Häfner H. Darmstadt, Germany, Steinkopff/Springer, 2004, pp 3–25
78. Jones P, Rodgers B, Murray R, Marmot M: Child developmental risk factors for adult schizophrenia in the British 1946 birth cohort. Lancet 1994; 344:1398–1402
79. Harrison G, Gunnell D, Glazebrook C, Page K, Kwiecinski R: Association between schizophrenia and social inequality at birth: case-control study. Br J Psychiatry 2001; 179:346–350
80. Eaton W, Harrison G: Life chances, life planning, and schizophrenia. Int J Ment Health 2001; 30:58–81
81. Tidey JW, Miczek KA: Social defeat stress selectively alters mesocorticolimbic dopamine release: an in vivo microdialysis study. Brain Res 1996; 721:140–149
82. Covington HE 3rd, Miczek KA: Repeated social-defeat stress, cocaine or morphine: effects on behavioral sensitization and

intravenous cocaine self-administration "binges." Psychopharmacology (Berl) 2001; 158:388–398; erratum, 158:399

83. Kaplan JR, Manuck SB, Fontenot MB, Mann JJ: Central nervous system monoamine correlates of social dominance in cynomolgus monkeys (*Macaca fascicularis*). Neuropsychopharmacology 2002; 26:431–443
84. Morgan D, Grant KA, Gage HD, Mach RH, Kaplan JR, Prioleau O, Nader SH, Buchheimer N, Ehrenkaufer RL, Nader MA: Social dominance in monkeys: dopamine D_2 receptors and cocaine self-administration. Nat Neurosci 2002; 5:169–174
85. Hull AM: Neuroimaging findings in post-traumatic stress disorder. Br J Psychiatry 2002; 181:102–110
86. Yamasue H, Kasai K, Iwanami A, Ohtani T, Yamada H, Abe O, Kuroki N, Fukuda R, Tochigi M, Furukawa S, Sadamatsu M, Sasaki T, Aoki S, Ohtomo K, Asukai N, Kato N: Voxel-based analysis of MRI reveals anterior cingulate gray-matter volume reduction in posttraumatic stress disorder due to terrorism. Proc Natl Assoc Sci USA 2003; 100:9039–9043
87. Weinberger DR, McClure RK: Neurotoxicity, neuroplasticity, and magnetic resonance imaging morphometry. Arch Gen Psychiatry 2002; 59:553–558