

Full Spectrum of Psychiatric Disorders Related to Foreign Migration

A Danish Population-Based Cohort Study

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Importance: Although increased risk for schizophrenia among immigrants is well established, knowledge of the broader spectrum of psychiatric disorders associated with a foreign migration background is lacking.

Objective: To examine the full range of psychiatric disorders associated with any type of foreign migration background among persons residing in Denmark, including foreign-born adoptees, first- and second-generation immigrants, native Danes with a history of foreign residence, and persons born abroad to Danish expatriates.

Design and Setting: Danish population-based cohort study. Persons were followed up from their 10th birthday for the development of mental disorders based on outpatient and inpatient data.

Participants: All persons born between January 1, 1971, and December 31, 2000 (N=1 859 419) residing in Denmark by their 10th birthday with follow-up data to December 31, 2010.

Main Outcome Measures: Incidence rate ratios (IRRs) and cumulative incidences for psychiatric outcomes.

Results: All categories of foreign migration background, except persons born abroad to Danish expatriates, were associated with increased risk for at least 1 psy-

chiatric disorder. Foreign-born adoptees had increased IRRs for all psychiatric disorders and had the highest IRRs for these disorders compared with other foreign migration categories. First- and second-generation immigrants having 2 foreign-born parents had significantly increased IRRs for schizophrenia and schizophrenia spectrum disorders and had similar risk magnitudes. Second-generation immigrants having 1 foreign-born parent had significantly increased IRRs for all psychiatric disorders. Native Danes with a history of foreign residence had increased IRRs for bipolar affective disorder, affective disorders, personality disorders, and schizophrenia spectrum disorders.

Conclusions and Relevance: The extent to which a background of foreign migration confers an increased risk for the broad spectrum of psychiatric disorders varies according to parental origin, with greatest risks for foreign-born adoptees. The spectrum of psychiatric disorders showed greater variation within the second-generation immigrant group than between first-generation vs second-generation immigrants, and the spectrum differed according to whether individuals had 1 or 2 foreign-born parents.

JAMA Psychiatry. 2013;70(4):427-435.

Published online February 27, 2013.

doi:10.1001/jamapsychiatry.2013.441

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A GROWING NUMBER OF POPULATION-BASED studies¹⁻⁵ have found increased incidence rates of nonaffective and affective psychoses in first- and second-generation immigrants, firmly establishing a link between foreign migration and higher risk for the development of schizophrenia and other psychotic disorders. The mechanisms underlying this association remain unclear, although potential explanations encompass a broad range of factors, including selective migration of predisposed individuals and exposure to risk factors, such as cannabis use, perinatal complications, low levels of vitamin D,

childhood trauma, and urban upbringing.^{1,6,7} To date, none of the potential explanations have been confirmed or ruled out. Aspects of social stress have been increasingly highlighted in recent years because of the especially high rates of schizophrenia found in immigrants having dark skin^{1,2,8} or marked differences in culture and appearance compared with the host culture.^{9,10} The increased risk for psychotic disorders found in second-generation immigrants suggests that post-migration aspects of the social context (eg, socioeconomic deprivation or long-term experiences of social defeat) may be more important risk mediators than the migration

process itself.^{6,11} Although early data emphasized generational differences, with higher rates of psychotic disorders found in second-generation immigrants compared with first-generation immigrants,¹ a recent meta-analysis⁴ showed no overall generational differences but found considerable consistency in increased risk for psychotic disorders across a diversity of immigrant or racial/ethnic minority groups, with the greatest risks for such disorders in migrants from countries where the predominant skin color is black. Although other factors cannot be ruled out, converging evidence suggests that adverse aspects of the social environment may be important contributors to the development of psychotic disorders in immigrants.

However, adverse social circumstances (eg, low socioeconomic status, unemployment, and stressful life events) are known contributors to psychiatric disorders more generally.¹²⁻¹⁴ The question remains whether the increased risks associated with migration regarding schizophrenia and other psychotic disorders^{2,3} extend to a broader range of psychiatric outcomes. To date, few population-based studies have examined the risk for the development of the broad spectrum of psychiatric disorders in first- and second-generation immigrants. Also, a recent meta-analysis¹⁵ that examined the risk for bipolar affective disorder, unipolar depressive disorder, and mood disorders of unspecified polarity in immigrants found comparatively moderately elevated risks for mood disorders and concluded that immigrants' risk for mood disorders was not as high as their risk for schizophrenia. Population-based investigations of the risk for substance use disorders in immigrants are scarce and tend to lack data from outpatient services, although a recent study¹⁶ from the Netherlands that included inpatient and outpatient data showed that immigrant groups found to be at increased risk for schizophrenia (ie, persons from Surinam, Morocco, and the Dutch Antilles) also had increased risk for developing drug use disorder. Therefore, the specificity of the association between migration and an increased risk for developing psychotic disorders remains unclear. Moreover, the term *migrant* has been used variously to denote experiences ranging from shifting one's country of residence to having foreign-born parentage (racial/ethnic minority status). Thus, the extent to which the relevant aspect with regard to psychiatric disorder is place of birth, foreign-born parentage, or residence abroad is unknown and requires further examination.

Denmark is an optimal setting for the examination of the full spectrum of psychiatric disorders associated with migration. Migration and migration policy have been increasingly on the political agenda in Denmark during the last decade, in part due to an increasing flow of immigrants and refugees from less developed countries compared with immigrants from other countries. Labor market integration of those migrants arriving since the middle of the 1980s has been problematic.¹⁷ Unemployment rates among immigrants and refugees from low-income countries are 3 times higher than those among Danish-born citizens, a ratio that is larger than that in other Organisation for Economic Co-operative and Development countries.¹⁷ Moreover, previous population-based studies in Denmark have shown increased risk for developing

schizophrenia in first-generation immigrants,¹⁸ second-generation immigrants,⁵ foreign-born adoptees,¹⁹ and native Danes with a history of foreign residence.¹⁸ The present study examines the incidence rate ratios (IRRs) and the lifetime risks for a broad spectrum of psychiatric disorders in a large representative national cohort of persons who were residing in Denmark by their 10th birthday and whose parents were living in Denmark at that time. The younger follow-up age (ie, from the 10th birthday) used in the present study design represents a more stringent strategy than previous strategies¹⁸ in that it minimizes the risk that some first-generation immigrants may have migrated because of prodromal symptoms. Risk for psychiatric disorders was examined across a comprehensive range of categories of foreign migration background (personal or parental), including foreign-born adoptees residing in Denmark and 2 groups of Danes with a history of migration (ie, native Danes with a period of residence abroad before their 10th birthday and persons of Danish parentage born to Danish mothers when these women were living abroad). As outlined earlier, residence abroad among Danes may be considered a type of foreign migration. To the extent that migration per se rather than race/ethnicity is the salient background characteristic, these 2 groups of Danes may potentially be informative as to mechanisms underlying associations between foreign migration and adverse psychiatric outcomes.

METHODS

STUDY POPULATION

We used data from the Danish Civil Registration System²⁰ to obtain a large and representative data set of residents in Denmark 10 years or older born in Denmark or abroad. Our study population (N=1 859 419) included all persons who had information on country of birth who were born between January 1, 1971, and December 31, 2000; who were living in Denmark by their 10th birthday; and whose parents were living in Denmark at that time. In total, 989 persons (0.1%) were excluded from the sample on the basis of unknown country of birth. The Danish Civil Registration System was established in 1968, when all people alive and living in Denmark were registered. Among other variables, it contains information on the personal identifier, sex, date and country of birth, the person's parents' identifiers, and continuously updated data on place of residence and vital status. The personal identifier is used in all national registers, enabling accurate record linkage between registers. The links to the parents are based on the legal relationship, such that for each person registered, the parental links registered represent the legal parents. This information is updated whenever changes occur.

ASSESSMENT OF MENTAL DISORDERS IN PERSONS AND THEIR PARENTS

Persons within the study cohort and their parents and siblings were linked via their personal identifier to the Danish Psychiatric Central Research Register,²¹ which contains data relating to all admissions to psychiatric hospitals since April 1, 1969, and all outpatient contact data since January 1, 1995. From April 1, 1969, to December 31, 1993, the diagnostic system used by physicians in routine practice was the ICD-8,²² and from Janu-

ary 1, 1994, the diagnostic system used was the *ICD-10*.²³ Persons were classified as having a mental disorder if they had been admitted to a psychiatric hospital or had received outpatient care.

The full spectrum of possible mental disorders was considered, including the following: schizophrenia (*ICD-10* code F20; equivalent *ICD-8* code 295 [excluding 295.79]), schizoaffective disorder (*ICD-10* code F25; equivalent *ICD-8* codes 295.79 and 296.89), bipolar affective disorder (*ICD-10* codes F30-31; equivalent *ICD-8* codes 296.19 and 296.39), substance use disorders (*ICD-10* codes F10-19; equivalent *ICD-8* codes 291, 294.30, 294.38, 303, and 304), anxiety and somatoform disorders (*ICD-10* codes F40-45 and F48; equivalent *ICD-8* codes 300, 305, and 307.99), schizophrenia spectrum disorders (*ICD-10* codes F21-23 and F29; equivalent *ICD-8* codes 297, 298.39, and 301.83), affective disorders (*ICD-10* codes F32-34 and F38-39; equivalent *ICD-8* codes 296.09, 296.29, 296.89, 296.99, 298.09, 298.19, 300.49, and 301.19), and personality disorders (*ICD-10* codes F60-69; equivalent *ICD-8* codes 301 [excluding 301.83], 302.19, 302.29, 302.39, 302.49, 302.89, and 302.99). The National Hospital Register²¹ was established January 1, 1977, and information about all admissions to public hospitals in Denmark was prospectively recorded. Since January 1, 1995, outpatient visits have also been registered. Because some patients with substance abuse are treated only in somatic departments, we decided to include patients in the National Hospital Register who had a diagnosis of substance use disorders. We also examined any psychiatric contact (a category representing contact with psychiatric services for any reason). For each mental disorder outcome, the date of onset was defined as the first day of the first contact (inpatient or outpatient) with the diagnosis of interest. Multiple disorders were recorded if developed by the individual. Parents and siblings were classified as having a history of mental disorder if they had been admitted to a psychiatric hospital or had been in outpatient treatment for any reason. This study was approved by the Danish Data Protection Agency.

ASSESSMENT OF FOREIGN MIGRATION BACKGROUND

Foreign migration background was classified according to the person and his or her parents' country of birth, as well as the mother's country of residence at the time of the person's birth. Foreign migration background was classified as the following 8 categories: (1) foreign-born adoptees (Among persons whose legal mother and father were born in Denmark, we identified intercountry adoptees as persons born abroad at the time when the legal mother was residing in Denmark. The classification of children as intercountry adoptees was more stringent but otherwise was identical to that used previously.¹⁹), (2) first-generation immigrants (persons born abroad having both parents born abroad), (3) second-generation immigrants by mother only (persons born in Denmark having a mother born abroad), (4) second-generation immigrants by father only (persons born in Denmark having a father born abroad), (5) second-generation immigrants by both parents (persons born in Denmark having both parents born abroad), (6) persons born abroad to Danish expatriates (Among persons whose mother and father were born in Denmark, we identified persons born to expatriates as persons born abroad at the time when the mother lived abroad), (7) native Danes with a history of foreign residence (persons who were born in Denmark and whose parents were born in Denmark and for whom such a person had a history of foreign residence before the 10th birthday), and (8) native Danes (persons who were born in Denmark and whose parents were born in Denmark).

Persons who were not classified in the 8 categories were included in the analyses and treated separately in "missing" categories ($n=20\ 603$). Most of these were persons born in Denmark for whom either parent had unknown country of birth ($n=8952$) or persons born abroad having 1 parent born in Denmark and 1 parent born abroad ($n=10\ 167$).

STATISTICAL ANALYSIS

For each psychiatric disorder, individuals were followed up from their 10th birthday or January 1, 1995 (whichever came last), until death, emigration from Denmark, onset of the outcome in question, or December 31, 2010 (whichever came first). Because persons were followed up from January 1, 1995, onward only, those having diagnoses before that date were excluded. Therefore, the findings were based entirely on incident cases diagnosed according to the more operational *ICD-10* diagnostic classification system and during a period when both inpatient and outpatient information was used, except that the *ICD-8* classification was used to censor persons with a diagnosis before January 1, 1995.

The IRRs for each mental disorder outcome were estimated by log-linear Poisson regression.^{24,25} All IRRs were adjusted for age, sex, calendar period, and the interaction between age and sex. Age and calendar period were treated as time-dependent variables,²⁶ whereas all others were treated as variables independent of time. *P* values and 95% CIs were based on likelihood ratio tests.²⁶ In total, we consider 9 different outcomes subdivided by 7 different categories of foreign migration background. Because of the many tests performed, in the text that follows, we denote estimates as statistically significant if $P < .005$ using native Danes as the unexposed group, approximating a Bonferroni correction for multiple testing within each outcome category.

Using competing risks survival analyses,^{27,28} the absolute risks (or cumulative incidences) of any psychiatric contact were calculated as the percentages of persons in the population who had contact with psychiatric services for any reason, considering that people may migrate or die. These analyses were made separately for each sex and immigration status. Cumulative incidence by the 40th birthday was also calculated for each of the outcomes separately for men and women.²⁸

RESULTS

DESCRIPTIVE FINDINGS

A total of 1 859 419 persons born between January 1, 1971, and December 31, 2000, and residing in Denmark by their 10th birthday were included in the study. More than 170 countries of foreign birth were represented in the cohort; the most frequent countries of origin were Turkey, Iraq, Lebanon, Bosnia-Herzegovina, and Somalia. The eTable (<http://www.jamapsych.com>) gives a detailed description of regions of birth by migration status. The cohort was followed up for a total of 19 984 628 person-years; the longest individual follow-up period was 16 years. Follow-up age ranged from 10 to 40 years; 45.5% of the follow-up time involved persons aged 10 to 19 years, 39.5% involved persons aged 20 to 29 years, and 15.0% involved persons aged 30 to 39 years. Approximately 7.5% of persons ($n=138\ 694$) had at least 1 contact with inpatient or outpatient psychiatric services in Denmark during the follow-up period. The most common psychiatric outcome was substance use disorders, followed by anxiety and somatoform disorders.

Table 1. Incidence Rate Ratios (IRRs) for ICD-10 Psychiatric Disorders According to Foreign Migration Background Among Persons Born Between 1971 and 2000, Residing in Denmark at Their 10th Birthday, and Followed Up Using Outpatient and Inpatient Information From 1995 to 2010^a

	Foreign-Born Adoptees (n = 15 360)	First-Generation Immigrants (n = 34 555)	Second-Generation Immigrants			Persons Born Abroad to Danish Expatriates (n = 8046)	Native Danes With a History of Foreign Residence (n = 21 280)	Native Danes (n = 1 576 396)
			By Mother Only (n = 53 906)	By Father Only (n = 57 933)	By Both Parents (n = 71 340)			
Any Psychiatric Contact								
No. of cases	1913	2305	4271	4932	3258	557	1604	118 219
IRR	1.65 (1.58-1.73) ^b	0.97 (0.93-1.01) ^b	1.19 (1.15-1.23)	1.29 (1.25-1.33)	0.81 (0.78-0.83) ^b	0.98 (0.90-1.06)	1.05 (1.00-1.11)	1 [Reference]
P value	<.0001	.14	<.0001	<.0001	<.0001	.58	.04	...
Schizophrenia								
No. of cases	159	254	317	334	331	40	104	6827
IRR	2.52 (2.14-2.94)	2.10 (1.84-2.37) ^b	1.63 (1.46-1.83)	1.65 (1.47-1.83)	1.95 (1.74-2.18) ^b	1.25 (0.90-1.67)	1.20 (0.98-1.45)	1 [Reference]
P value	<.0001	<.0001	<.0001	<.0001	<.0001	.18	.07	...
Schizophrenia Spectrum Disorders								
No. of cases	199	310	390	433	427	58	144	8595
IRR	2.47 (2.13-2.83)	1.96 (1.75-2.19) ^b	1.56 (1.41-1.73)	1.64 (1.49-1.81)	1.81 (1.64-1.99) ^b	1.43 (1.09-1.83)	1.31 (1.11-1.54)	1 [Reference]
P value	<.0001	<.0001	<.0001	<.0001	<.0001	.01	.0020	...
Schizoaffective Disorder								
No. of cases	19	19	46	32	26	5	18	781
IRR	2.40 (1.47-3.67)	1.56 (0.95-2.39)	2.14 (1.57-2.85)	1.43 (0.99-2.00)	1.52 (1.00-2.20)	1.35 (0.48-2.92)	1.82 (1.10-2.81)	1 [Reference]
P value	.0009	.07	<.0001	.06	.05	.52	.02	...
Bipolar Affective Disorder								
No. of cases	60	42	106	119	58	16	53	2719
IRR	2.15 (1.65-2.75)	0.98 (0.71-1.32)	1.41 (1.16-1.70)	1.52 (1.26-1.82)	0.94 (0.72-1.21)	1.26 (0.74-1.98)	1.54 (1.16-1.99)	1 [Reference]
P value	<.0001	.92	.0009	<.0001	.65	.38	.0038	...
Affective Disorders								
No. of cases	518	492	1067	1260	573	156	491	32 990
IRR	1.47 (1.35-1.60)	0.81 (0.74-0.89)	1.11 (1.04-1.18)	1.24 (1.17-1.31)	0.61 (0.56-0.66)	1.00 (0.85-1.16)	1.17 (1.07-1.28)	1 [Reference]
P value	<.0001	<.0001	.0010	<.0001	<.0001	.97	.0008	...
Anxiety and Somatoform Disorders								
No. of cases	899	1183	2054	2456	1632	267	761	58 707
IRR	1.47 (1.38-1.57)	1.05 (0.99-1.12)	1.17 (1.12-1.23)	1.32 (1.27-1.38)	0.89 (0.85-0.94)	0.95 (0.84-1.07)	1.01 (0.94-1.08)	1 [Reference]
P value	<.0001	.08	<.0001	<.0001	<.0001	.40	.79	...
Personality Disorders								
No. of cases	576	392	977	1076	463	134	387	26 099
IRR	2.07 (1.90-2.25) ^b	0.85 (0.77-0.94) ^b	1.32 (1.23-1.40)	1.38 (1.30-1.47)	0.69 (0.63-0.76) ^b	1.09 (0.91-1.28)	1.18 (1.06-1.30)	1 [Reference]
P value	<.0001	.0011	<.0001	<.0001	<.0001	.35	.0021	...
Substance Use Disorders								
No. of cases	823	1025	2071	2256	1296	282	771	57 808
IRR	1.55 (1.44-1.65)	0.89 (0.83-0.94) ^b	1.21 (1.15-1.26)	1.23 (1.18-1.29)	0.73 (0.69-0.77) ^b	1.03 (0.91-1.16)	1.04 (0.97-1.12)	1 [Reference]
P value	<.0001	<.0001	<.0001	<.0001	<.0001	.62	.29	...

Abbreviation: ICD-10, International Classification of Diseases, 10th Revision.

^aAll IRRs were adjusted for sex, age, calendar year, and the interaction between age and sex. The numbers in parentheses indicate 95% CIs.

^bSignificant difference ($P < .005$) by sex (highest risk for men).

IRRs ACCORDING TO FOREIGN MIGRATION BACKGROUND

Table 1 gives the IRRs for each of 9 psychiatric outcomes across 7 categories of foreign migration background compared with native Danes (ie, persons born in Denmark whose parents were born in Denmark). Among 63 estimates of relative risks summarized, 34 risk estimates were significantly increased, 8 risk estimates were significantly decreased, and 21 risk estimates were non-significant. There was a general tendency for IRRs for schizophrenia and schizophrenia spectrum disorders to be almost similar in magnitude within any given foreign

migration category and to be significantly increased across all categories of migration, except for persons born abroad to Danish expatriates. The IRRs for schizoaffective disorder, bipolar affective disorder, and affective disorders showed a less consistent pattern across foreign migration categories. The IRRs for any psychiatric contact were significantly increased for foreign-born adoptees and second-generation immigrants having 1 foreign-born parent and were significantly decreased for second-generation immigrants having 2 foreign-born parents. Significant sex differences were mostly observed among first- and second-generation immigrants having 2 foreign-born parents, and they mostly concerned schizophrenia, schizophrenia spec-

trum disorders, personality disorders, and substance use disorders. When significant sex differences were observed, men had higher IRRs than women.

Foreign-born adoptees had significantly increased IRRs for all outcomes. Furthermore, they had by far the highest IRRs for all outcomes compared with those in the other migrant status categories.

First-generation immigrants had significantly increased IRRs solely for schizophrenia and schizophrenia spectrum disorders. The IRRs were significantly decreased for affective disorders, personality disorders, and substance use disorders.

Second-generation immigrants having 1 foreign-born parent (by mother or by father) and 1 native Danish parent had significantly increased IRRs for all outcomes. In contrast, second-generation immigrants having 2 foreign-born parents had significantly increased IRRs solely for schizophrenia and schizophrenia spectrum disorders. Moreover, second-generation immigrants having 2 foreign-born parents had significantly decreased IRRs for any psychiatric contact, affective disorders, anxiety and somatoform disorders, personality disorders, and substance use disorders. Therefore, the pattern of risk estimates observed for this group resembles the pattern observed for first-generation immigrants.

Persons born abroad to Danish expatriates had no significantly increased IRRs for any psychiatric outcome. However, native Danes with a history of foreign residence had significantly increased IRRs for schizophrenia spectrum disorders, bipolar affective disorder, affective disorders, and personality disorders. Further adjustment for a history of mental illness in a parent or sibling had limited influence on the IRRs presented.

CUMULATIVE INCIDENCE PATTERNS

In addition to the results summarized in Table 1 for any psychiatric contact, the cumulative incidence for any psychiatric outcome is shown in the **Figure**. The figure shows the cumulative incidences for males and females from the 10th birthday to the 40th birthday. The cumulative incidence measures the probability of having developed the disorder at a specified age. Therefore, the cumulative incidences are more informative than IRRs regarding the prediction of a person's probability of developing the disease in question.

Cumulative incidences by the 40th birthday for all psychiatric outcomes according to foreign migration status are summarized separately for men and women in **Table 2**. In general, the cumulative incidences resembled the pattern of IRRs given in Table 1 but are expressed as the probability of having developed the disorder in question by the 40th birthday. For example, among foreign-born adoptees, the probability of having developed schizophrenia before the 40th birthday is 3.77% for men and 1.95% for women.

COMMENT

To our knowledge, this is the first study to consider the full spectrum of psychiatric outcomes in relation to a for-

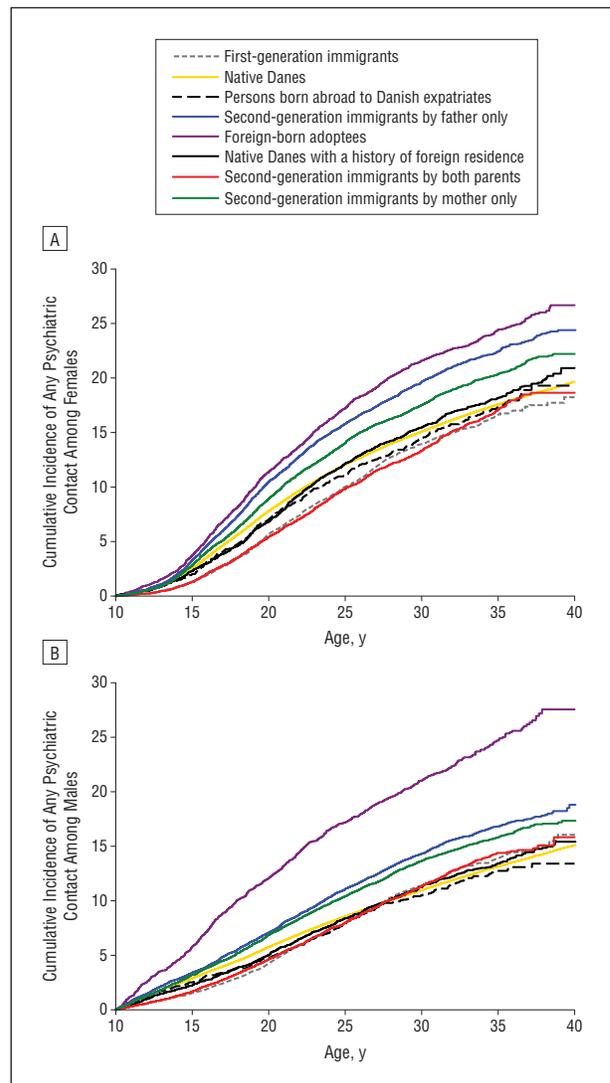


Figure. Cumulative incidence of psychiatric contact according to foreign migration background by age among females (A) and males (B). The cumulative incidence measures the probability of having had a psychiatric contact at a given age.

eign migration background. In this study of 1 859 419 persons, foreign-born adoptees had the most consistently elevated risks compared with native Danes for all psychiatric outcomes. Foreign-born adoptees and first- and second-generation immigrants having 1 or 2 foreign-born parents showed significantly increased risk for developing schizophrenia or schizophrenia spectrum disorders but differed with regard to increased risk for the other disorders. Native Danes with a history of foreign residence had increased risk for several disorders, including schizophrenia spectrum disorders, schizoaffective disorder, and bipolar affective disorder, suggesting that residence abroad, rather than having foreign-born parents or racial/ethnic minority status, may increase the risk for developing psychotic disorders.

STRENGTHS AND LIMITATIONS

The main strengths of this study are the detailed levels of information about residence in Denmark and paren-

Table 2. Cumulative Incidences by the 40th Birthday for All Psychiatric Disorders According to Sex and Foreign Migration Background^a

Sex	% (95% CI)								
	Foreign-Born Adoptees	First-Generation Immigrants	Second-Generation Immigrants			Persons Born Abroad to Danish Expatriates	Native Danes With a History of Foreign Residence	Native Danes	
			By Mother Only	By Father Only	By Both Parents				
			Any Psychiatric Contact						
Men	27.55 (25.48-29.79)	16.06 (14.65-17.61)	17.34 (16.49-18.24)	18.81 (17.69-20.00)	15.83 (14.11-17.76)	13.41 (11.77-15.28)	15.42 (14.23-16.70)	15.10 (14.92-15.29)	
Women	26.68 (25.18-28.26)	18.25 (16.70-19.95)	22.21 (21.30-23.16)	24.39 (23.45-25.37)	18.64 (17.47-19.89)	19.30 (17.19-21.66)	20.91 (19.43-22.50)	19.64 (19.45-19.83)	
			Schizophrenia						
Men	3.77 (2.99-4.76)	3.07 (2.53-3.71)	1.96 (1.67-2.31)	2.23 (1.91-2.60)	2.74 (2.34-3.20)	1.26 (0.82-1.92)	1.56 (1.21-2.00)	1.22 (1.17-1.26)	
Women	1.95 (1.50-2.53)	1.24 (0.89-1.71)	1.32 (1.09-1.61)	1.17 (0.94-1.46)	1.41 (0.97-2.06)	1.07 (0.65-1.76)	0.86 (0.56-1.32)	0.81 (0.78-0.85)	
			Schizophrenia Spectrum Disorders						
Men	4.15 (3.20-5.37)	3.10 (2.56-3.76)	2.07 (1.78-2.40)	2.37 (2.04-2.75)	3.45 (2.94-4.04)	1.51 (1.04-2.18)	2.01 (1.53-2.64)	1.55 (1.48-1.62)	
Women	2.76 (2.20-3.48)	1.96 (1.51-2.53)	1.89 (1.60-2.23)	1.94 (1.61-2.33)	1.97 (1.52-2.55)	2.14 (1.44-3.20)	1.69 (1.07-2.65)	1.12 (1.07-1.16)	
			Schizoaffective Disorder						
Men	0.33 (0.16-0.68)	0.16 (0.08-0.32)	0.20 (0.13-0.32)	0.15 (0.09-0.24)	0.13 (0.05-0.30)	0.16 (0.05-0.50)	0.09 (0.04-0.22)	0.12 (0.10-0.14)	
Women	0.27 (0.14-0.50)	0.12 (0.06-0.24)	0.26 (0.17-0.39)	0.14 (0.09-0.23)	0.30 (0.13-0.71)	0.17 (0.04-0.72)	0.33 (0.19-0.59)	0.14 (0.13-0.16)	
			Bipolar Affective Disorder						
Men	0.95 (0.45-2.01)	0.69 (0.35-1.36)	0.70 (0.45-1.07)	0.57 (0.42-0.76)	0.23 (0.14-0.38)	0.40 (0.19-0.85)	1.04 (0.62-1.75)	0.44 (0.40-0.48)	
Women	1.45 (1.00-2.10)	0.48 (0.28-0.83)	0.83 (0.61-1.13)	0.91 (0.65-1.27)	0.79 (0.43-1.47)	0.70 (0.33-1.48)	0.60 (0.40-0.91)	0.63 (0.59-0.68)	
			Affective Disorders						
Men	5.61 (4.64-6.78)	3.93 (2.99-5.17)	3.82 (3.36-4.34)	4.93 (3.98-6.10)	3.38 (2.70-4.23)	3.80 (2.94-4.91)	4.67 (3.87-5.63)	3.89 (3.76-4.03)	
Women	9.99 (8.93-11.19)	7.25 (5.91-8.90)	7.91 (7.29-8.59)	8.75 (8.09-9.46)	6.08 (5.03-7.34)	7.18 (5.55-9.28)	8.47 (7.36-9.74)	7.36 (7.22-7.50)	
			Anxiety and Somatoform Disorders						
Men	11.59 (9.94-13.52)	7.52 (6.40-8.84)	7.75 (7.10-8.45)	8.13 (7.51-8.80)	8.36 (6.72-10.39)	5.85 (4.80-7.13)	6.65 (5.68-7.79)	6.96 (6.83-7.09)	
Women	15.21 (13.94-16.60)	11.71 (10.34-13.27)	13.12 (12.34-13.95)	15.27 (14.31-16.30)	12.44 (11.43-13.55)	10.18 (8.66-11.97)	11.82 (10.68-13.08)	11.38 (11.23-11.54)	
			Personality Disorders						
Men	6.29 (5.35-7.41)	2.55 (2.12-3.06)	3.18 (2.84-3.56)	4.02 (3.58-4.52)	2.80 (2.31-3.40)	2.59 (1.92-3.49)	2.74 (2.22-3.39)	2.72 (2.66-2.79)	
Women	9.77 (8.75-10.91)	3.75 (3.05-4.62)	6.65 (6.12-7.24)	6.56 (6.06-7.11)	3.91 (3.04-5.02)	5.12 (4.17-6.29)	6.10 (5.39-6.90)	5.23 (5.13-5.33)	
			Substance Use Disorders						
Men	15.49 (13.97-17.18)	10.16 (9.23-11.17)	11.71 (10.90-12.58)	11.85 (11.15-12.60)	9.86 (8.81-11.04)	10.35 (8.85-12.12)	10.21 (9.01-11.57)	10.13 (10.00-10.26)	
Women	9.83 (8.57-11.29)	4.67 (3.91-5.58)	8.26 (7.55-9.04)	8.52 (7.89-9.20)	5.04 (4.06-6.25)	5.99 (4.92-7.30)	7.54 (6.63-8.59)	7.00 (6.88-7.12)	

^aThe cumulative incidence measures the probability (percentage) of having developed the psychiatric disorder in question at the 40th birthday, taking into account that persons may emigrate or die.

tal origin and the broad range of psychiatric disorders, including inpatient and outpatient contact. This is a national study, and the Danish registers have almost complete coverage and follow-up data, with virtually no loss of individuals in the records.²⁰ Also, high agreement between genotypic profile and foreign country of birth as recorded in the registers has been documented.²⁹ Although the present information is based on routine clinical reporting rather than research-guided diagnostic procedures, the validity of the Danish national registers has been shown to be high.²¹ Moreover, the information in the Danish national registers, including inpatient and outpatient contact for the total follow-up period for all cohort members, enables the estimation of incidence rates of disorders not necessarily requiring inpatient treatment such as personality disorders or anxiety and somatoform disorders. The inclusion of information concerning outpatient contact with psychiatric services is especially essential in countries in which psychiatric services have become less institutionalized and more outpatient oriented. Moreover, all participants were residing in Denmark by their 10th birthday, which enables the ascertainment of disorders with early onset and eliminates the risk for bias due to the selective migration of the individuals themselves. An additional strength is the restriction of the cohort to persons whose parents were alive and living in Denmark at the person's 10th birth-

day. This eliminates any potential bias due to differential rates of parental death in migrants during childhood, as well as separation from parents due to parental foreign residence during childhood, events that have been shown to increase the risk for mental disorders.^{5,30}

The results are based on treatment, and a possible limitation is that differential treatment-seeking behavior among persons with a foreign background may lead to differential coverage in the registers, especially for less severe psychiatric disorders. Persons having 2 foreign-born parents may be less likely to seek treatment for such disorders,³¹ or they may preferentially seek treatment among general or private practitioners and not be covered in the outpatient registers. Nevertheless, it is implausible that persons from more than 170 different countries of origin would share the same treatment-seeking behavioral pattern. All persons recorded in the Danish Civil Registration System are residents of Denmark and are entitled to full and free health benefits. However, the possibility that persons with a foreign background may be misdiagnosed by Danish psychiatrists cannot be entirely excluded.³² Finally, our findings may apply only to persons with onset of psychiatric disorder before age 40 years. Also, psychiatric outcomes regarding any of these disorders may potentially differ in persons migrating as adults.

MAIN FINDINGS

The present results show that first- and second-generation immigrants in Denmark have almost a 2-fold risk for developing schizophrenia and schizophrenia spectrum disorders. These results agree with previous findings in other European settings (eg, the United Kingdom and the Netherlands^{2,3,9}), albeit the present risk magnitudes are somewhat lower. Although comparisons across studies are difficult because of methodological differences, the lower risk magnitudes for schizophrenia in this Danish cohort may be due to fewer persons originating from Africa, the Caribbean, and Morocco (ie, groups that have previously shown especially high risks for psychotic disorders elsewhere in Europe⁴). The overall findings indicate that migration is associated with a range of psychiatric disorders. In contrast, North American investigations of migration and mental illness tend to emphasize the “healthy migrant effect,”³³ whereby foreign birth seems to be protective against psychiatric disorder. However, the more stringent regulation of migration to the United States and Canada may favor the migration of healthier persons.

Moreover, first- and second-generation immigrants having 2 foreign-born parents showed a striking specificity of outcomes (ie, significantly elevated IRRs solely for schizophrenia and schizophrenia spectrum disorders). In contrast, second-generation immigrants having 1 native Danish parent showed a broader range of psychiatric disorders, including significantly elevated IRRs for bipolar affective disorder. Increased risk for a broader range of psychiatric disorders associated with mixed parentage has been found previously in a Swedish study.³⁴ Although the presence of a Danish parent in the household might lead to greater acceptance of treatment-seeking behavior per se, it is also possible that the selection of a non-Danish mate by a native Dane represents some aspect of vulnerability for psychiatric disorder that could lead to a broader range of psychiatric outcomes in the offspring. Furthermore, although common psychiatric disorders, such as depression, have been found to be associated with socioeconomic adversity,³⁵ it is unlikely that families with mixed parentage would necessarily have poorer socioeconomic circumstances than families in which both parents are foreign born. Moreover, higher and lower parental socioeconomic status has been shown to be related to the development of schizophrenia in offspring.³⁶ Unfortunately, information about socioeconomic circumstances during upbringing was unavailable for any of the groups studied. However, families with mixed parentage might be more prone to internal conflict, and long-term exposure to conflict may negatively affect their offspring’s mental health.

The particular vulnerability for schizophrenia and schizophrenia spectrum disorders among persons having 2 foreign-born parents, born abroad or in Denmark, remains paradoxical, and it cannot be ruled out that their risks for less severe psychiatric disorders may have been underestimated. However, all cohort members were residing in Denmark by their 10th birthday. Persons with foreign-born parents attend Danish schools and learn Dan-

ish, a process that might facilitate adjustment and reduce the development of less severe psychiatric disorders related to acculturation difficulties. Yet, reduction of acculturation difficulties may not necessarily lead to greater acceptance of persons with foreign-born parentage by Danish society, and exposure to a more long-term type of psychosocial adversity (ie, social defeat) has been suggested to contribute to greater risk for schizophrenia among migrants.^{1,4,5,10} In this respect, persons having 2 foreign-born parents may have greater visibility than persons having mixed parentage because of greater differences in physical or behavioral characteristics and might be particularly vulnerable to chronic social defeat. Therefore, some migrants may be especially challenged by their greater visibility or “otherness” in Danish society, and contextual factors may seem increasingly relevant.

Overall, the pattern of results obtained for any specific foreign migration category could be attributable to the combined effects of several factors, including racial/ethnic density, differential treatment seeking, exposure to chronic psychosocial adversity, or biological factors such as low levels of vitamin D.³⁷ For example, a protective effect of racial/ethnic density has been shown to be related to the incidence of psychotic disorders among immigrants^{38,39} as well as to depression among visible minorities.⁴⁰ Finally, it cannot be ruled out that subtle selection factors are operating, whereby parental characteristics transmitted to offspring may influence the results. However, further adjustment of the IRRs for a history of psychiatric disorder in parents and in siblings had no influence on the findings. The completeness of information concerning parental psychiatric history would not expect to differ within the cohort because the study population included only persons who themselves and both parents were living in Denmark at the person’s 10th birthday. Although information might be missing for parents with mental disorders before migration to Denmark, individuals with mental illness have a lower rate of foreign migration compared with healthy persons.⁷ Therefore, the potential bias introduced will be minor.

To our knowledge, this is the first study of psychiatric outcomes among persons born abroad to expatriates, and such individuals did not have significantly elevated risks for any of the psychiatric conditions studied. However, the results for this migrant group were based on a small population, implicating power limitations. In contrast, native Danes with a history of foreign residence before the 10th birthday had elevated risks for several psychiatric outcomes. Possible differences represented by these 2 categories of foreign migration with regard to any potential association with psychiatric outcomes would require further study.

The increased risks for all psychiatric outcomes found in foreign-born adoptees confirm our previous findings of increased risk for schizophrenia in this group¹⁹ and extend those data to include a broader range of psychiatric disorders. Foreign-born adoptees are generally regarded as a vulnerable group and have high rates of suicide and severe mental disorders.^{41,42} It is likely that a complex interplay of factors, including heritability, poor perinatal care, unwanted pregnancy, and social adversities before and possibly after arrival in Denmark, con-

tributes to the high rates of all psychiatric disorders in foreign-born adoptees, among whom 72.9% originate from Asia and 14.6% from South America (eTable). Nevertheless, the cumulative incidence for the development of schizophrenia in these adoptees is high (3.81 for men and 1.97 for women) and might suggest a parental history of psychiatric illness in the biological parents.⁴³

Considering the broad range of psychiatric outcomes studied, it would be difficult to draw any conclusions about the extent to which the elevated risk for psychiatric disorders associated with migration is mostly due to exposure to social adversity, other types of nongenetic factors, or aspects of parental vulnerability. The extent to which parental choice of residence per se might be influenced by genetic determinants cannot be entirely ruled out as a contributing factor.⁷ Moreover, each of the categories of foreign migration represented in the present study involves a complex set of circumstances that might affect the outcomes observed herein. Nevertheless, against a background of minor between-generational differences in psychiatric outcomes among immigrants in general, it is important to note the large differences within the broad category of second-generation immigrants when further subdivided by 1 or 2 foreign-born parents, suggesting that clues as to the mechanisms contributing to increased risk for schizophrenia and schizophrenia spectrum disorders may be found especially within this group. Further work is needed to characterize what the experiences of immigrants are and how these findings may relate to the development of schizophrenia.

Submitted for Publication: February 28, 2012; final revision received August 15, 2012; accepted August 26, 2012.

Published Online: February 27, 2013. doi:10.1001/jamapsychiatry.2013.441

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Conflict of Interest Disclosures: None reported.

Funding/Support: Dr Pedersen was supported by the Stanley Medical Research Institute, Bethesda, Maryland, and by grants from The Lundbeck Foundation, Denmark.

Role of the Sponsor: The funders had no involvement in any aspect of the study.

Online-Only Material: The eTable is available at <http://www.jamapsych.com>.

REFERENCES

- Cantor-Graae E, Selten JP. Schizophrenia and migration: a meta-analysis and review. *Am J Psychiatry*. 2005;162(1):12-24.
- Fearon P, Kirkbride JB, Morgan C, Dazzan P, Morgan K, Lloyd T, Hutchinson G, Tarrant J, Fung WL, Holloway J, Mallett RM, Harrison G, Leff JP, Jones PB, Murray RM; AESOP Study Group. Incidence of schizophrenia and other psychoses in ethnic minority groups: results from the MRC AESOP Study. *Psychol Med*. 2006;36(11):1541-1550.
- Coid JW, Kirkbride JB, Barker D, Cowden F, Stamps R, Yang M, Jones PB. Raised incidence rates of all psychoses among migrant groups: findings from the East London First Episode Psychosis study [published correction appears in *Arch Gen Psychiatry*. 2009;66(2):161]. *Arch Gen Psychiatry*. 2008;65(11):1250-1258.
- Bourque F, van der Ven E, Malla A. A meta-analysis of the risk for psychotic disorders among first- and second-generation immigrants. *Psychol Med*. 2011;41(5):897-910.
- Cantor-Graae E, Pedersen CB. Risk of schizophrenia in second-generation immigrants: a Danish population-based cohort study. *Psychol Med*. 2007;37(4):485-494.
- Cantor-Graae E. The contribution of social factors to the development of schizophrenia: a review of recent findings. *Can J Psychiatry*. 2007;52(5):277-286.
- Pedersen CB, Mortensen PB, Cantor-Graae E. Do risk factors for schizophrenia predispose to emigration? *Schizophr Res*. 2011;127(1-3):229-234.
- Cantor-Graae E, Zolkowska K, McNeil TF. Increased risk of psychotic disorder among immigrants in Malmö: a 3-year first-contact study. *Psychol Med*. 2005;35(8):1155-1163.
- Veling W, Selten JP, Veen N, Laan W, Blom JD, Hoek HW. Incidence of schizophrenia among ethnic minorities in the Netherlands: a four-year first-contact study. *Schizophr Res*. 2006;86(1-3):189-193.
- Weiser M, Werbeloff N, Vishna T, Yoffe R, Lubin G, Shmushkevitch M, Davidson M. Elaboration on immigration and risk for schizophrenia. *Psychol Med*. 2008;38(8):1113-1119.
- Selten JP, Cantor-Graae E, Kahn RS. Migration and schizophrenia. *Curr Opin Psychiatry*. 2007;20(2):111-115.
- Bruce ML, Takeuchi DT, Leaf PJ. Poverty and psychiatric status: longitudinal evidence from the New Haven Epidemiologic Catchment Area study. *Arch Gen Psychiatry*. 1991;48(5):470-474.
- Ford E, Clark C, McManus S, Harris J, Jenkins R, Bebbington P, Brugha T, Meltzer H, Stansfeld SA. Common mental disorders, unemployment and welfare benefits in England. *Public Health*. 2010;124(12):675-681.
- Faravelli C, Catena M, Scarpato A, Ricca V. Epidemiology of life events: life events and psychiatric disorders in the Sesto Fiorentino study. *Psychother Psychosom*. 2007;76(6):361-368.
- Swinen SG, Selten JP. Mood disorders and migration: meta-analysis. *Br J Psychiatry*. 2007;190:6-10.
- Selten JP, Wiersma A, Mulder N, Burger H. Treatment seeking for alcohol and drug use disorders by immigrants to the Netherlands: retrospective, population-based, cohort study. *Soc Psychiatry Psychiatr Epidemiol*. 2007;42(4):301-306.
- Pedersen PJ, Smith N. *International Migration and Migration Policy in Denmark*. Århus, Denmark: Centre for Labour Market and Social Research; 2001. Working paper 01-05.
- 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.
- Cantor-Graae E, Pedersen CB. Risk for schizophrenia in intercountry adoptees: a Danish population-based cohort study. *J Child Psychol Psychiatry*. 2007;48(11):1053-1060.
- Pedersen CB, Gøtzsche H, Møller JO, Mortensen PB. The Danish Civil Registration System: a cohort of eight million persons. *Dan Med Bull*. 2006;53(4):441-449.
- Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. *Scand J Public Health*. 2011;39(7)(suppl):54-57.
- World Health Organization. *International Classification of Diseases, Eighth Revision (ICD-8)*. Geneva, Switzerland: World Health Organization; 1967.
- World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva, Switzerland: World Health Organization; 1992.
- Breslow NE, Day NE. *The Design and Analysis of Cohort Studies*. Vol 2. Lyon, France: International Agency for Research on Cancer; 1987.
- SAS Institute Inc. *The GENMOD Procedure: SAS/STAT 9.1 User's Guide*. Cary, NC: SAS Institute Inc; 2004:1609-1730.
- Clayton D, Hills M. *Statistical Models in Epidemiology*. Oxford, England: Oxford University Press; 1993.
- Andersen PK, Borgan Ø, Gill RD, Keiding N. *Statistical Models Based on Counting Processes*. New York, NY: Springer; 1997.
- Rosthøj S, Andersen PK, Abildstrom SZ. SAS macros for estimation of the cumulative incidence functions based on a Cox regression model for competing risks survival data. *Comput Methods Programs Biomed*. 2004;74(1):69-75.
- Pedersen CB, Demontis D, Pedersen MS, Agerbo E, Mortensen PB, Borglum AD, Hougaard DM, Hollegaard MV, Mors O, Cantor-Graae E. Risk of schizophrenia in relation to parental origin and genome-wide divergence. *Psychol Med*. 2012;42(7):1515-1521.
- Laursen TM, Munk-Olsen T, Nordentoft M, Mortensen PB. A comparison of selected risk factors for unipolar depressive disorder, bipolar affective disorder,

- schizoaffective disorder, and schizophrenia from a Danish population-based cohort. *J Clin Psychiatry*. 2007;68(11):1673-1681.
31. Lay B, Nordt C, Rössler W. Mental hospital admission rates of immigrants in Switzerland. *Soc Psychiatry Psychiatr Epidemiol*. 2007;42(3):229-236.
 32. Hickling FW, McKenzie K, Mullen R, Murray R. A Jamaican psychiatrist evaluates diagnoses at a London psychiatric hospital. *Br J Psychiatry*. 1999;175:283-285.
 33. Grant BF, Stinson FS, Hasin DS, Dawson DA, Chou SP, Anderson K. Immigration and lifetime prevalence of *DSM-IV* psychiatric disorders among Mexican Americans and non-Hispanic whites in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry*. 2004;61(12):1226-1233.
 34. Saraivo Leão T, Sundquist J, Johansson LM, Johansson SE, Sundquist K. Incidence of mental disorders in second-generation immigrants in Sweden: a four-year cohort study. *Ethn Health*. 2005;10(3):243-256.
 35. Lorant V, Deliège D, Eaton W, Robert A, Philippot P, Ansseau M. Socioeconomic inequalities in depression: a meta-analysis. *Am J Epidemiol*. 2003;157(2):98-112.
 36. Selten JP, Cantor-Graae E. Schizophrenia and migration. In: Gattaz W, Häfner H, eds. *Search for the Cause of Schizophrenia*. Vol 5. Darmstadt, Germany: Steinkopff/Springer; 2004:3-25.
 37. McGrath JJ, Burne TH, Féron F, Mackay-Sim A, Eyles DW. Developmental vitamin D deficiency and risk of schizophrenia: a 10-year update. *Schizophr Bull*. 2010;36(6):1073-1078.
 38. Veling W, Susser E, van Os J, Mackenbach JP, Selten JP, Hoek HW. Ethnic density of neighborhoods and incidence of psychotic disorders among immigrants. *Am J Psychiatry*. 2008;165(1):66-73.
 39. Kirkbride JB, Morgan C, Fearon P, Dazzan P, Murray RM, Jones PB. Neighbourhood-level effects on psychoses: re-examining the role of context. *Psychol Med*. 2007;37(10):1413-1425.
 40. Stafford M, Newbold BK, Ross NA. Psychological distress among immigrants and visible minorities in Canada: a contextual analysis. *Int J Soc Psychiatry*. 2011;57(4):428-441.
 41. Hjern A, Lindblad F, Vinnerljung B. Suicide, psychiatric illness, and social maladjustment in intercountry adoptees in Sweden: a cohort study. *Lancet*. 2002;360(9331):443-448.
 42. van der Vegt EJ, Tieman W, van der Ende J, Ferdinand RF, Verhulst FC, Tiemeier H. Impact of early childhood adversities on adult psychiatric disorders: a study of international adoptees. *Soc Psychiatry Psychiatr Epidemiol*. 2009;44(9):724-731.
 43. Gottesman II, Laursen TM, Bertelsen A, Mortensen PB. Severe mental disorders in offspring with 2 psychiatrically ill parents. *Arch Gen Psychiatry*. 2010;67(3):252-257.