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Incidence of Schizophrenia Among Second-Generation Immigrants in the Jerusalem Perinatal Cohort

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***Objective*: Increased incidence of schizophrenia is observed among some immigrant groups in Europe, with the offspring of immigrants, ie "second-generation" immigrants particularly vulnerable. Few contemporary studies have evaluated the risk of schizophrenia among second-generation immigrants in other parts of the world. *Methods*: We studied the incidence of schizophrenia in relation to parental immigrant status in a population-based cohort of 88 829 offspring born in Jerusalem in 1964–1976. Parental countries of birth were obtained from birth certificates and grouped together as (1) Israel, (2) Other West Asia, (3) North Africa, and (4) Europe and industrialized countries. Cox proportional hazards methods were used in adjusting for sex, parents' ages, maternal education, social class, and birth order. *Results*: Linkage with Israel's Psychiatric Registry identified 637 people admitted to psychiatric care facilities with schizophrenia-related diagnoses, before 1998. Incidence of schizophrenia was not increased among second-generation immigrants in this birth cohort, neither overall nor by specific group. *Conclusions*: The difference in risk of schizophrenia among second-generation immigrants in Europe and in this Israeli birth cohort suggests that the nature of the immigration experience may be relevant to risk, including reasons for migration, the nature of entry, and subsequent position in the host country for immigrants and their offspring. Minority status may be of importance as, in later studies, immigrants to Israel from Ethiopia had increased risk of schizophrenia.**

Key words: immigration/risk/Israel/birth cohort/longitudinal

Introduction

Immigrant status has consistently been associated with an increased risk of schizophrenia, with the offspring of immigrants, ie "second-generation immigrants" particularly vulnerable.[1] In the United Kingdom, the increased risk for schizophrenia among migrants from the Caribbean is amplified in their offspring, born in England.[2–4] Likewise, in the Netherlands, the heightened risk for schizophrenia observed among migrants from Morocco and the former Dutch colony of Surinam persists into the second generation.[5,6] Similar transgenerational elevation in risk for schizophrenia among immigrants is found in studies from Denmark[7] and Sweden.[8,9] Overall, a meta-analysis of 18 independent population-based incidence studies yielded a mean weighted relative risk of schizophrenia of 4.5 (95% confidence interval [CI] 1.5–13.1) for "second-generation" immigrants (ie, the native born offspring of immigrants), higher than that observed for the original immigrants: 2.7 (95% CI 2.3–3.2).[1]

These epidemiological studies, primarily focused on Europe (with one study in Israel), reported the risk of schizophrenia to vary by ethnicity, being greatest among selected groups of immigrants and their children.[1,10] For example, the incidence of schizophrenia is increased among African-Caribbean migrants to the United Kingdom (incidence rate ratio [IRR] = 9.1)[11] and among Moroccans in the Netherlands (IRR = 3.7).[12] In a later wave of immigration to Israel, an elevated risk for schizophrenia was found among first- (hazard ratio = 1.6) and second- (hazard ratio = 1.4) generation immigrant adolescents, particularly among those who were Ethiopian (adjusted HR = 2.95).[10] These studies suggest that when individuals become part of a discriminated minority in a host society to which they are not acculturated, their risk for schizophrenia increases. This is consistent

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with the migration effect on risk of schizophrenia persisting and even increasing in the offspring of migrants, ie second-generation immigrants.

Waves of immigration to Israel brought refugees from Europe after World War II, from West Asia in the late 1940s and 1950s and from North Africa in the 1950s and 1960s. Jews who had been ''minorities'' in their home countries became members of the majority culture in the newly formed state of Israel. The experience of migrants to Israel therefore differed from those immigrants to European countries, who with their offspring came to constitute religious and ethnic minorities. Although some groups in Israel, such as North Africans, did face some discrimination,[13,14] it was arguably not as great as what ethnic Moroccans have faced in the Netherlands.[15]

We evaluated a prospective birth cohort in Jerusalem to examine the incidence of schizophrenia in second-generation immigrants, of whom at least one parent had immigrated to Israel prior to their birth. We expected that given the circumstances and experiences of mass immigration following the establishment of the State of Israel, there would be no increased incidence of schizophrenia among second-generation immigrants, neither generally nor within any individuals from any specific region.

Methods

This study relies on a population-based research cohort known as the Jerusalem Perinatal Study. In 1964–1976, all 92 408 births were recorded for mothers resident in a defined geographic area of Jerusalem. Demographic data, including the parents' countries of birth, were copied from the birth notification. Other data were added from surveillance of obstetric and pediatric inpatient departments, well-baby clinics, and interviews with mothers. Descriptions of the study have been published over the past 4 decades.[16–18]

To study schizophrenia and its related diagnoses in offspring in this cohort, the database was linked to that of Israel's National Psychiatric Registry. This registry, established in 1950, receives all psychiatric diagnoses, including reports from patients admitted to specialized psychiatric hospitals, psychiatric wards within general hospitals and psychiatric day care facilities.[18] The diagnoses for individuals with psychosis have been validated.[19] For this study, the Registry defined schizophrenia broadly using the *International Classification of Diseases, 10th Revision*, as diagnoses of F20–F29 (schizophrenia, schizotypal disorder, delusional disorders, nonaffective psychoses, and schizoaffective disorders). The date of incidence was defined as the date of the first admission to a psychiatric facility. The Registry removed the names, identity numbers, and other identifying information from the linked file, which was then analyzed collaboratively in New York and Israel. The study was approved by the Institutional Review Boards in both countries.

Data Analysis

Of the 92 408 births in 1964–1976, 91 479 were born alive and of these, 88 829 (97.1%) were available for study, having been traced and followed to December 31, 1997, and 637 were admitted to psychiatric facilities with a schizophrenia-related diagnosis before that date. Life table estimates of the cumulative incidence were 0.35% at age 20 and 0.91% at age 30.[20] Offspring were followed from birth until the date of diagnosis, death, or end of the follow-up period; at this point, they were of ages 21–33. Cox proportional hazards methods were used to estimate the relative risk (hazard ratio) of schizophrenia associated with immigrant parents, taking into account potential confounding variables, using the PHREG procedure available in SAS 9.0.[21] Alpha was set at .05, and tests were 2 tailed. We defined confounding variables as those whose addition to an unadjusted (crude) model caused the hazard ratio to change by 10% or more. We included additional covariates if they independently improved the otherwise full regression model's fit (by comparison of the full model with and without the specific variable of interest).

All variables relate to their values at the time of the offspring's birth. Offspring were categorized by their parents' status as immigrants (vs born in Israel) as follows: both parents, only the father, only the mother vs neither parent (referent). The parents' countries of birth were available from birth certificates; we grouped them according to the following broad categories: Israel, other West Asia (including Iraq, Iran, Afghanistan, Turkey, Syria, Lebanon, and Yemen), North Africa (mainly Morocco), or Europe (mainly Poland, Union of Soviet Socialist Republic, and Eastern Europe), the latter including the Americas and other industrially developed countries, hereafter ''Europe, etc.'' Parents born before 1948 in the British-controlled region that was to become the state of Israel were considered to have been born in Israel.

Paternal age was modeled as a continuous variable for adjustment in other models and was expressed in decades from the mean (age 30) with unknowns (0.8%) assigned to this age. For adjustment in models, maternal age was categorized as 30–34 and 35+ vs <30; unknowns for maternal age (0.1%) were assigned the mean age of 27.7. Maternal education was modeled as a dichotomous variable in years, ($\leq$8, $\geq$9). Duration of marriage in years was categorized as 2–4, 5–9, and 10+ vs <2; unknown duration of marriage (1.7%) was set to the median of 5 years. Birth order was also modeled in categories (4–6 and 7+ vs 1–3). Social class ranks were determined by levels of education observed for paternal occupations (Corcoran C, Perrin M, Harlap S, Deutsch L, Fennig S, Manor O, Nahon D, Kimhy, D, Malaspina D, Susser E, unpublished

data). All other variables were described and used as dichotomies (sex, urban/rural, maternal employment, and birth weight [<2500 g vs ≥2500 g]). No information was available on family history of psychiatric disorders.

Results

Table 1 shows the characteristics of the cohort, comparing the distributions of various categories of demographic variables in each category of parental immigrant status. In families in which both parents were immigrants, parents were older, less educated, married longer, and had more children. They were more likely to live in a rural setting and be in the lower social classes. There were no differences in sex or birth weight of offspring of immigrant parents, as compared with those of native-born parents.

Table 2 shows the crude and adjusted relative risks of schizophrenia for offspring of immigrant parents, as compared with the referent group of Israeli-born parents. There was no change in risk of schizophrenia for offspring of immigrants, including those who had only 1 immigrant parent and those who had 2 immigrant parents. There was no association between length of time in Israel since immigration and risk of schizophrenia in the offspring (data not shown).

Table 3 demonstrates that no combinatorial arrangements of maternal and paternal countries of birth were related to increased risk for schizophrenia in offspring.

Discussion

As expected, in this birth cohort, there was no increased incidence of schizophrenia among second-generation immigrants born in Jerusalem during this era, either overall or within specific groups. The comparison of findings of this study with European studies can help us to better understand the effect of immigration on risk of schizophrenia observed for certain ethnic groups in some countries of Europe, notably in the United Kingdom and the Netherlands.

Advantages of this study include (1) a large, population-based cohort, (2) a validated method for the diagnosis of schizophrenia through a national registry of admissions to psychiatric facilities, (3) identification of parental immigrant status prior to birth, (4) follow-up data required for the use of appropriate statistical methods (proportional hazards regression models), taking into account varying length of follow-up and controlling for covariates, and (5) adjustment for paternal age, a known risk factor for schizophrenia which could be related to age structure among the populations of immigrants vs native-born parents of offspring in the cohort. There was a follow-up period of 21–33 years, which although long potentially represents a limitation of this study if second-generation immigrants have a later age of onset of schizophrenia. Also, these findings should be interpreted with caution in respect to risk of schizophrenia in immigrant women as many women have an onset of schizophrenia at ages beyond 21 through 33.

Social causation is the leading hypothesis for explaining the increased risk of schizophrenia found among second-generation immigrants in contemporary European studies.[22] Social factors considered include low social class and adversity, discrimination encountered, and the challenge of acculturation. A description of patterns of immigration to Israel during this era, and their contrast with those observed later in Israel and in Western Europe, can help clarify which of these factors may account for the phenomenon of dramatic increases in schizophrenia among second-generation immigrants in European studies.[1,6,10] As for Israel, Weiser and colleagues[10] found increased schizophrenia specifically among immigrants from Ethiopia and the former Soviet Union, whose influx occurred after the period of 1964–1976, when the present birth cohort was ascertained.

Of particular use is a comparison of the experiences of North African immigrants to Israel with that of North Africans who emigrated to the Netherlands. Some investigators have suggested that the increased risk of schizophrenia among second-generation immigrants in Europe may be related to their low social class.[22,23] In the Netherlands, second-generation Moroccan immigrants are among the lowest social classes; they have less education, lower income, and more unemployment.[24] Likewise, in this current study, immigrants from Islamic countries, ie, those from West Asia and North Africa were of lower social class than Israelis of European origin (or ethnicity). The absence of an increased risk of schizophrenia among these less advantaged immigrants in Israel, however, argues against low socioeconomic status as the primary explanation for an effect of immigration/ethnicity on schizophrenia, as proposed by Hjern and colleagues.[8]

Other social factors include issues of cultural identity and discrimination faced by second-generation immigrants.[25] The experience of interpersonal and institutional discrimination has been associated with increased risk for psychosis.[26,27] In the Netherlands, Moroccans face considerable discrimination,[15] and ecological studies show an association of risk of schizophrenia with degree of discrimination experienced.[12] Although North African immigrants to Israel and their offspring also faced discrimination,[28] it was arguably much less than that encountered by ethnic Moroccans in the Netherlands.

A closer examination of the context and circumstances of immigration for North Africans in Israel, as compared with the Netherlands, may be illustrative. Moroccans in the Netherlands are Muslims in a secular state whose population is primarily Christian; second-generation Moroccan immigrants are not considered to be "native Dutch." By contrast, North Africans coming to Israel

Table 1. Numbers of offspring of immigrants and nonimmigrants and percent distribution of selected variables

Characteristic	Paternal and Maternal Immigration Status					
	Both Parents	Father Only	Mother Only	Neither Parent	Total	
Offspring, N	37 443	12 707	10 924	27 755	88 829	
Percent	100	100	100	100	100	*P* Value
Sex						
Male	51.8	50.9	51.3	52	45 872	.2
Female	48.2	49.1	48.7	48	42 957	
Paternal age						
<25	8.9	14.9	13	18.2	11 700	<.0001
25–34	52.8	61.6	62.3	60.2	51 112	
35–44	30.9	20.2	22.5	19.9	22 120	
45+	7.4	3.3	2.3	1.7	3897	
Maternal age						
<25	27.6	40.9	33.9	39	30 062	<.0001
25–29	31.2	31.3	37.3	32.7	28 768	
30–34	22.6	17.3	19	18.7	17 914	
35+	18.7	10.5	9.9	9.7	12 085	
Paternal education (yrs)						
Unknown	9	4.6	6.6	6.5	6446	<.0001
0–4	12	1.6	1.2	1.3	5198	
8-May	30	19.4	17.6	14.1	19 539	
12-September	28.5	37.8	40.5	38.5	30 573	
13+	20.6	36.6	34.2	39.6	27 073	
Maternal education (yrs)						
Unknown	8.5	4.2	5.1	6.2	5979	<.0001
0–4	18.8	1.5	4.2	2.3	8319	
8-May	29.4	21.4	21.1	20	21 596	
12-September	25.6	41.9	38.2	39.4	30 035	
13+	17.7	31	31.3	32.1	22 900	
Duration of parents' marriage (yrs)						
<2	14.8	24.8	20.9	21.2	16 680	<.0001
4-February	23.7	33.5	32.4	31.7	25 434	
9-May	28.4	26	30.7	28.2	25 105	
10+	33.2	15.7	16.1	18.9	21 430	
Birth order						
3-January	58.5	82.1	78.9	77.4	62 407	<.0001
6-April	25.7	14.3	17.4	16.7	17 955	
7+	15.9	3.7	3.8	6	8467	
Urban/rural						
Urban	95.5	95.8	97.6	97	85 511	<.0001
Rural	4.5	4.2	2.4	3	3318	
Socioeconomic status						
1 (high)	8.2	13.6	11.8	12.5	9538	<.0001
2	11.7	22.8	23.7	31.3	18 548	
3	12.4	17.5	17.8	16.5	13 393	
4	16.7	21.2	20.3	18	16 165	
5	29.2	18.1	18.9	14.7	19 396	
6 (low)	21.8	6.9	7.5	7	11 789	
Maternal employment outside the home						
No	67.9	50.6	55.4	50.7	36 853	<.0001
Yes	32.1	49.4	44.6	49.3	51 976	
Birth weight						
<2500 g	6.1	6.7	6.5	6.3	5587	0.1
≥2500 g	93.9	93.3	93.5	93.7	83 242	

Table 2. Numbers of Offspring With and Without Schizophrenia, Crude and Adjusted RRs, and 95% CI Associated With Immigration Status of the Parents

Parental Immigration Status	Schizophrenia		Crude RR	95% CI	Adjusted RR[a]	95% CI	Adjusted RR[b]	95% CI	*P* Value
	−	+							
Neither parent	27 563	192	1		1		1		
Father only	12 622	85	1	0.8–1.2	1	0.7–1.2	0.9	0.7–1.2	0.7
Mother only	10 843	81	1.1	0.8–1.4	1	0.8–1.3	1	0.8–1.3	0.9
Both parents	37 164	279	1	0.8–1.2	0.9	0.8–1.1	0.9	0.7–1.1	0.2

Note: RR, relative risk; CI, confidence interval.
[a]Adjusted for paternal age.
[b]Adjusted for paternal and maternal age, maternal education, paternal social class, sex, and birth order.

were Jewish migrants moving to a Jewish state, frequently escaping anti-Semitic discrimination in their homelands. Moving to Israel may have relieved preimmigration stress for many migrants. Israel, a young country of mass immigration, was a haven for Jews from other countries and their children. Jews have a long history of migration, and most native-born Israelis also have immigrants in their recent ancestry. Therefore, in Israel, immigrants and their children may not be perceived as "outsiders," especially as immigrants were not in the minority.

Additionally, immigrants to Israel, especially from Islamic countries, often arrived together as whole villages or communities and were often housed together, allowing the maintenance of cultural practices and family support structures.[29] This maintenance of "ethnic density" may have been protective, buffering the effects of discrimination and other social stresses which might increase risk of schizophrenia in offspring of immigrants. Ethnic density has been observed to moderate the risk of schizophrenia among immigrants, both in early ecological studies in the United States[30] and in more contemporary studies in Europe.[31,32] However, ethnic density did not have an apparent protective effect for adolescents who later immigrated to Israel from Ethiopia, whose families also emigrated en masse as communities from rural Ethiopia.[10] Data on ethnic density during the wave of immigration in the 1960s–1970s were not available for this article but would be of interest to explore in future studies.

Table 3. Numbers of Offspring With and Without Schizophrenia Based on Parental Birth Places

Maternal and Paternal Birthplace		Schizophrenia		Adjusted Relative Risk[a]	95% Confidence Interval	*P* Value
Maternal	Paternal	−	+			
Israel	Israel	27 563	192	1		
Israel	Other West Asia	4427	29	0.9	0.6–1.3	0.6
Israel	North Africa	2615	15	0.9	0.5–1.5	0.7
Israel	Europe, etc.	5580	41	1	0.7–1.4	1
Other West Asia	Israel	3231	28	1.1	0.7–1.6	0.8
Other West Asia	Other West Asia	11 721	88	0.8	0.6–1.1	0.2
Other West Asia	North Africa	843	5	0.7	0.3–1.8	0.5
Other West Asia	Europe, etc.	541	7	1.4	0.7–3.0	0.4
North Africa	Israel	2454	24	1.3	0.9–2.0	0.2
North Africa	Other West Asia	1374	6	0.6	0.3–1.3	0.2
North Africa	North Africa	13 040	110	1	0.7–1.2	0.8
North Africa	Europe, etc.	802	8	1.2	0.6–2.4	0.6
Europe, etc.	Israel	5158	29	0.8	0.6–1.2	0.3
Europe, etc.	Other West Asia	603	3	0.7	0.2–2.2	0.5
Europe, etc.	North Africa	726	3	0.6	0.2–1.9	0.4
Europe, etc.	Europe, etc.	7514	49	0.9	0.6–1.2	0.3

[a]Adjusted for paternal and maternal age, maternal education, paternal social class, sex, and birth order.

Methodological differences could potentially explain the difference in findings between this prospective birth cohort study and European studies of schizophrenia incidence which rely on census and municipal registry data. The question of the ''denominator'' in such studies has been raised, with concern as to the accuracy of these databases in enumerating base populations of immigrants.[13] However, estimates from these registries are likely to be reliable as registration is obligatory and necessary for access to benefits and medical care.[1] Possible underenumeration, especially of single male immigrants,[33] has been accounted for in studies.[34] Also, although some migrants are transient[35] and may not register officially while in Europe,[36] undercounting is unlikely to account for the robust IRR seen among immigrant groups in large population-based cohorts.[6,7]

A number of proposed etiological factors for schizophrenia have also been evaluated and found to be unlikely to explain the immigration effect on schizophrenia as they are not significantly increased among immigrants to Europe; these include cannabis and other drug use,[37–39] infections,[40,41] and obstetric complications.[42,43] Vitamin D insufficiency has been considered[44,45] and requires further study[1] as it potentially could explain why nonwhite minorities in Europe have an increased risk of schizophrenia (though could not account for increased schizophrenia among adolescents who emigrated from Ethiopia to Israel).[10]

Conclusion

In this large birth cohort study, there was no increased risk of schizophrenia among second-generation immigrants, as has been found in many contemporary studies for nonwhite ethnic groups in Europe and Israel. A comparison of context and patterns of migration to Israel with that in other Western countries suggests that the issue of cultural identity and disparities in physical appearance may influence risk of schizophrenia in second-generation immigrants. The examination of schizophrenia incidence among second-generation immigrants would be of use to explore in other parts of the world in order to understand better the dramatic increased risk seen among some ethnic groups in European countries. Potential populations of interest include Mexican-Americans and ethnic Koreans in Japan and China.

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