



# Schizophrenia and birthplace of paternal and maternal grandfather in the Jerusalem perinatal cohort prospective study

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## ARTICLE INFO

### Article history:

Received 13 November 2008

Received in revised form 11 March 2009

Accepted 16 March 2009

Available online 9 April 2009

### Keywords:

Schizophrenia

Jews

Cohort studies

Incidence

Relative risk

Maternal

Paternal

Grandfathers

## ABSTRACT

Some forms of epigenetic abnormalities transmitted to offspring are manifested in differences in disease incidence that depend on parent-of-origin. To explore whether such phenomena might operate in schizophrenia spectrum disorders, we estimated the relative incidence of these conditions in relation to parent-of-origin by considering the two grandfathers' countries of birth. In a prospective cohort of 88,829 offspring, born in Jerusalem in 1964–76 we identified 637 cases through Israel's psychiatric registry. Relative risks (RR) were estimated for paternal and maternal grandfathers' countries of birth using proportional hazards methods, controlling for parents' ages, low social class and duration of marriage. After adjusting for multiple observations, we found no significant differences between descendants of maternal or paternal grandfathers born in Iraq, Iran, Turkey, Syria, Yemen, Morocco, Algeria, Tunisia, Libya/Egypt, Poland, USSR, Czechoslovakia, Germany or the USA. Those with paternal grandfathers from Romania (RR = 1.9, 95% CI = 1.3–2.8) or Hungary (1.6, 1.0–2.6) showed an increased incidence; however, those with maternal grandfathers from these countries experienced reduced incidence (RR = 0.5, 0.3–0.8 and 0.4, 0.2–0.8). In post-hoc analyses we found that results were similar whether the comparison groups were restricted to descendants of other Europeans or included those from Western Asia and North Africa; and effects of paternal grandfathers from Romania/Hungary were more pronounced in females, while effects of maternal grandfathers from these countries were similar in males and females. These post-hoc "hypothesis-generating" findings lead one to question whether some families with ancestors in Romania or Hungary might carry a variant or mutation at a parentally imprinted locus that is altering susceptibility to schizophrenia. Such a locus, if it exists, might involve the X chromosome.

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## 1. Introduction

There is increasing interest in the hypothesis that epigenetic alterations might contribute to the causes of schizophrenia (Petronis et al., 1999; Crow, 2007; Huang et al., 2007; Crespi, 2008; Isles and Wilkinson, 2008). Epigenetics refers to the changes in gene expression brought about by methylation of DNA and/or by modifications of

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chromatin structure (Keverne and Curley, 2008). Several peculiarities of epigenetics may be relevant to psychosis and other psychiatric conditions. First, certain genes are expressed from only one allele, activation or suppression depending on the parent-of-origin; some such genes are important in growth, development and neuroendocrine function (Wilkinson et al., 2007). Examples include the cluster of parentally imprinted loci on chromosome 15q11–q13 associated with Prader–Willi and Angelman syndromes (Horsthemke and Wagstaff, 2008) and with autism (Dimitropoulos and Schultz, 2007); and those on chromosome 7q21 associated with OCD, alcohol abuse and other psychiatric conditions (Hess et al., 2007). Second, many genes on the X chromosome are epigenetically inactivated in females (Payer and Lee, 2008); diverse loci on the X chromosome are important in brain development (Nguyen and Disteche, 2006) and some may reflect parent-of-origin effects (Davies et al., 2008). Third, genetically vulnerable individuals may be shaped by the social or physical environment at a critical period of fetal life or childhood; such influence may alter the individual's "program" of further development (Szyf et al., 2008). Examples of phenotypes associated with such gene–environment interactions include violent and antisocial personality in males (due to inactivating mutation in X-linked MAO-A combined with abuse in childhood) and affective disorders (due to variants in the 5HTT promoter combined with other stresses in life) (Craig, 2007).

That parentally imprinted loci might be involved in schizophrenia is suggested by the parent-of-origin effects observed in some studies (Crow et al., 1989; Husted et al., 1998; Ohara et al., 1997; Petronis, 2000; Corradi et al., 2005; Francks et al., 2007). To search for evidence of this, we used conventional epidemiologic methods to estimate the risk of schizophrenia in Jews in relation to parent-of-origin, picking parents according to their ancestral geographic origin. To our knowledge, there have been no previous studies taking this approach. Elsewhere, we have reported that for offspring born in this cohort, neither immigration of the parents nor their broad geographic origin affected the incidence of schizophrenia (Corcoran et al., *in press*).

## 2. Methods

In 1964–76, the Jerusalem Perinatal Study surveyed all 92,408 births to mothers resident in Western (Israeli) Jerusalem. Items abstracted from the birth certificate included demographic information on the parents and both grandfathers; these were supplemented with data abstracted from medical records, interviews and surveillance of pediatric inpatients. The methods, characteristics of the population, tracing and verification have been described in detail (Davies et al., 1969; Harlap et al., 1977, 2007; Malaspina et al., 2001). The cohort was linked to Israel's national Psychiatric Registry of persons hospitalized for psychiatric conditions. This registry, established in 1950, receives information from multiple sources, including inpatient wards in psychiatric and general hospitals, and psychiatric day-care facilities. Diagnoses of psychoses have been validated (Weiser et al., 2005). Because the data base was prepared by government employees as a pilot/preliminary study, schizophrenia was defined broadly, taking schizophrenia-related diagnostic

codes F20–F29 (ICD-10) at discharge, hereafter termed "schizophrenia". The date of onset was taken as the date of the first admission episode in the registry. Names, identity numbers and other identifying information were removed and the anonymous file was analyzed collaboratively in New York and Israel. The study was approved by the Institutional Review Boards Hadassah Medical Center, Jerusalem, New York University Medical Center and Columbia University Medical Center, New York, and exempted from the requirement for informed consent.

### 2.1. Countries of origin

Offspring were classified according to the countries of birth of grandfathers, as recorded on the birth notification. No information was available on grandmothers or on associations within families. The coding system used in the Jerusalem Perinatal Study was the one used by the Israel government in the mid-1960s; this did not provide individual codes for the separate components of the former Soviet Union. Similarly, our study cannot separate Kurdish Jews, who at that time made up a substantial but unknown proportion of Jerusalem's immigrants from Iraq, from other Jews from Iraq, Iran, Syria or Turkey.

### 2.2. Data analysis

We used SAS® version 9.1 to analyze the data, studying time to diagnosis with Kaplan–Meyer and proportional hazards methods. Offspring were followed from birth until date of diagnosis, death or censoring (December 31, 1997); the survivors were then aged 21–33. Results are given as relative risks (RR, i.e. hazard ratios) and 95% confidence intervals, relative to a stated comparison group. Unless otherwise mentioned, the *p*-values refer to raw, two-tailed tests. To limit the probability of false discovery, we arbitrarily restricted the countries for analysis to those for which there were at least 1000 offspring with either a maternal or a paternal grandfather born there. In addition, we present adjusted *p*-values, calculated both by Hochberg's (Hochberg, 1988) modification of the Bonferroni method and by the method of Benjamini and Hochberg (Benjamini, 1995). Proportional hazards assumptions were verified by inspecting log-negative log plots and by testing each variable (coded 0, 1) as a time-dependent variable constructed from its product with the length of follow-up. Variables included in the models were those we found to be significantly related both to broad ethnic groups (unadjusted *p* < .05) and to schizophrenia and/or variables that altered the crude estimates of relative risks for ethnic groups by at least 10%. Included were paternal age (treated as a continuous variable, in deviations from the mean (age 31) with unknowns (0.8%) being assigned to the mean); duration of marriage (1.7% unknowns were assigned to the mean (5 years)); and a series of dichotomies coded 1 (if present) or 0 (if absent) for maternal age (30–34, 35+ versus younger); sex (male); and lower paternal social class at birth based on our previously described classification of occupations (Harlap et al., 1977). Other variables tested, but not included in the final models, were categories of religion, parents' status as immigrants or Israeli-born; the immigrants' broad areas of origin (Western Asia, North Africa or Europe/America), rural versus urban

**Table 1**

Number of traced offspring in the Jerusalem cohort (N) and cases of schizophrenia (Schiz), by country of birth of at least one grandfather.

Country	N	Schiz	Country	N	Schiz	Country	N	Schiz
Israel	21,350	156						
Turkey	5030	36						
Cyprus	334	4	USSR, Baltic states	8192	59	Canada	174	2
Syria	2585	28	Poland	13,831	90	USA	2273	11
Lebanon	297	–	Romania	5637	42	Mexico	26	–
Jordan	29	–	Yugoslavia	998	12	Cuba	7	–
Iraq	17,176	130	Bulgaria	692	8	Panama	2	–
Saudi Arabia	13	–	Greece	442	4	Central America, remainder	2	–
Yemen	3655	26	Albania	2	–	Venezuela	3	–
Aden	172	1	Germany	4444	22	Colombia	15	–
Iran	8735	60	Austria	1363	10	Ecuador	2	–
Afghanistan	672	7	Switzerland, Lichtenstein	261	2	Peru	3	–
India (Pakistan, Ceylon, Burma, Thailand, Malaysia)	749	6	Czechoslovakia	2624	17	Bolivia	7	–
Singapore, Laos, Cambodia	13	–	Hungary	4235	24	Brazil	57	–
Indonesia, Philippines	10	–	Finland	45	–	Uruguay	13	–
China, Hong Kong	32	–	Sweden	41	–	Argentina	427	1
Japan	3	–	Norway	15	–	Chile	29	–
Asia, remaining countries	18	–	Denmark, Iceland	64	–	South America, remainder	12	–
Asia, unknown	1	–	United Kingdom	851	4	Australia	50	1
			Eire	40	–	New Zealand	6	–
Morocco, Tangier, Spanish Morocco	19,838	145	Netherlands	482	4	Oceania	75	1
Algeria	1619	15	Belgium	180	4			
Tunisia	2333	26	Luxembourg	5	–	Continent of origin unknown	313	3
Libya	578	4	France, Monaco	525	3			
Egypt, Sudan	1558	15	Portugal	10	–			
Ethiopia, Eritrea, Somalia	14	1	Spain, Gibraltar, Andorra	501	5			
Rhodesia, Zambia	6	1	Italy	267	2			
South Africa	227	–	Europe unknown	3	–	Total offspring	88,829	637
Africa, remaining countries	25	–						
Africa unknown	10	–						

residence, birth weight, birth order, year of birth, season (month of birth), categories of education of either parent and the offspring of rabbis or students in Talmud academies. The relationship of schizophrenia to fathers' social class has been described separately (Corcoran et al., 2009) as has the absence of any influence of parents' immigration (Corcoran et al., in press).

### 3. Results

The cohort of 88,829 included 637 offspring hospitalized with schizophrenia spectrum disorders during the period of observation. The cumulative life-table estimate of incidence was 0.96% before age 35 (Malaspina et al., 2001). Adjusted relative risks (RRs) were 1.39 (95% confidence interval 1.20–1.61,  $p < .0001$ ) for each decade of paternal age; 1.35 (1.15–1.58  $p < .0002$ ) in males versus females; 1.32 (1.07–1.62,  $p = .0093$ ) for low social class and 0.80 (0.73–0.89,  $p < .0001$ ) per five years of parents' duration of marriage. Compared with maternal age  $<30$ , the RRs for offspring of mothers aged 30–34 and 35+ were 1.19 (0.95–1.50) and 1.53 (1.12–2.08,  $p = .0070$ ). Each of these estimates was adjusted for the others mentioned.

Table 1 lists the countries of origin of grandfathers, showing the raw numbers of offspring, and numbers of cases of schizophrenia spectrum disorders. Nearly a quarter of this population had at least one grandfather born in Israel. Those from West Asia were predominantly from Iraq and Iran, with more limited numbers coming from Yemen, Turkey, Syria and Lebanon. North Africans came mainly from Morocco, while ancestries in Europe were mainly from Poland and USSR, with

somewhat smaller numbers from central Europe. Some 98.0% were Jewish. Non-Jews (mainly Muslim Arabs) are included in this study, most having grandparents born in Israel or nearby countries; their incidence of schizophrenia (to be reported in detail separately) was similar to that of Jews.

Table 2 compares risk estimates for maternal and paternal ancestries in groups of countries, calculated separately for each of the three continents. The control group for each continent consists of offspring with no grandfathers from that continent and the estimates for each type of grandfather take into account effects of other grandfathers from the same countries shown in that section of the table. Results (not shown) were similar to those in Table 2 if the data were re-analyzed to compare each country individually with all other countries combined, if males and females were analyzed separately, or if the grandfathers were divided into three mutually exclusive groups from each country, i.e. "only maternal", "only paternal" and "both" grandfathers. Among offspring with at least one ancestor from a specific country, the proportions with both grandfathers born in the same country varied in the West Asian group from 64% for Yemen to 23% for Turkey. In the North African group it varied from 74% for Morocco and 49% for Tunisia, to approximately 28% for the remaining countries; while in the European group the proportions whose two grandfathers were from the same country varied from 34% for the USSR to 20% for the USA.

Table 2 shows significant heterogeneity only in the European groups, after allowing for multiple tests. For the West Asian countries, there is no obvious pattern of differences comparing this group with all others, or comparing different countries within the group. Other researchers have sometimes grouped

**Table 2**

Numbers of offspring (*N*), cases of schizophrenia spectrum disorders (Schiz), adjusted relative risk (RR) and 95% confidence intervals (CI), with raw and adjusted *p*-values, by maternal and paternal grandfathers' countries of birth.

Country of birth of grandfather	Type of grandfather	N	Schiz	RR <sup>a</sup>	95% CI	Raw p	Adjusted p-values	
							Hocberg 1988 (30)	Benjamini and Hochberg (31)
<i>Western Asia</i>								
Iraq	Maternal	11,817	94	1.22	0.92–1.61	0.1663	0.976	0.333
	Paternal	12,643	85	0.78	0.58–1.04	0.0861	0.775	0.333
Iran	Maternal	5942	39	0.88	0.59–1.30	0.5123	0.976	0.854
	Paternal	6270	44	0.93	0.64–1.36	0.7205	0.976	0.929
Turkey	Maternal	2920	19	0.92	0.57–1.49	0.7429	0.976	0.929
	Paternal	2757	21	0.95	0.60–1.50	0.8372	0.976	0.930
Syria	Maternal	1470	16	1.46	0.86–2.49	0.1611	0.775	0.333
	Paternal	1527	14	0.99	0.56–1.75	0.9756	0.976	0.333
Yemen	Maternal	2705	20	1.55	0.88–2.75	0.1327	0.976	0.333
	Paternal	2772	14	0.50	0.25–0.98	0.0436	0.436	0.333
None of the above		69,936	485	1	reference group			
<i>North Africa</i>								
Morocco	Maternal	15,935	122	1.13	0.85–1.50	0.4038	0.996	0.646
	Paternal	15,261	112	0.90	0.67–1.20	0.4614	0.996	0.646
Algeria	Maternal	1031	10	1.27	0.65–2.50	0.4843	0.996	0.646
	Paternal	817	9	1.32	0.65–2.69	0.4441	0.996	0.646
Tunisia	Maternal	1661	19	1.57	0.91–2.72	0.1046	0.837	0.646
	Paternal	1325	13	1.00	0.52–1.92	0.9963	0.996	0.996
Libya/Egypt	Maternal	1267	12	1.40	0.78–2.52	0.2582	0.996	0.646
	Paternal	1073	7	0.83	0.39–1.79	0.6400	0.996	0.731
None of the above		62,670	428	1	reference group			
<i>Europe etc</i>								
Poland	Maternal	8363	50	0.74	0.54–1.02	0.0598	0.538	0.431
	Paternal	8277	55	1.20	0.88–1.63	0.2438	0.917	0.140
USSR	Maternal	4657	31	0.80	0.54–1.17	0.2460	0.917	0.431
	Paternal	4853	35	1.20	0.83–1.72	0.3360	0.917	0.523
Romania	Maternal	3419	17	0.50	0.30–0.84	0.0088	0.106	0.041
	Paternal	3288	33	1.92	1.31–2.82	0.0008	0.011	0.011
Hungary	Maternal	2317	7	0.36	0.17–0.77	0.0086	0.106	0.041
	Paternal	2470	19	1.61	1.01–2.61	0.0473	0.473	0.132
Czechoslovakia	Maternal	1419	9	0.77	0.39–1.52	0.4548	0.917	0.579
	Paternal	1335	9	1.33	0.68–2.62	0.4003	0.917	0.560
Germany	Maternal	2621	11	0.51	0.28–0.94	0.0320	0.352	0.112
	Paternal	2284	13	1.07	0.61–1.89	0.8178	0.917	0.881
USA	Maternal	1447	8	0.82	0.40–1.71	0.6033	0.917	0.704
	Paternal	1222	6	0.96	0.41–2.21	0.9165	0.917	0.917
None of the above		63,518	459	1	reference group			

<sup>a</sup> Adjusted for maternal age (30–34, 35+, versus younger), paternal age (continuous), duration of marriage and low social class.

Aden with Yemen, and Afghanistan with Iran, but doing so did not alter our conclusions (data not shown). In the North African group, there were somewhat raised risks of schizophrenia associated with maternal grandfathers from these countries, but no consistent pattern associated with paternal grandfathers and no findings were statistically significant. Estimates for paternal grandfathers from Europe were somewhat raised, while most of the estimates for maternal grandfathers from Europe were somewhat lowered. These differences were statistically significant for Romania and Hungary, and because these countries are contiguous we considered it appropriate to explore this association further.

We combined Romania with Hungary and conducted stratified analyses, comparing them with all others in the cohort. Not shown in a table, the summary RR for paternal grandfathers from these countries, stratified by maternal origin, was 1.63 (1.21–2.20,  $p = .0014$ ). For maternal grandfathers from Romania/Hungary, with stratification for paternal grandfathers' origins from the same area or not, we derived a summary RR estimated at 0.51 (0.33–0.79,  $p = .0024$ ).

Table 3 shows analyses separated within additional strata. The altered RRs associated with Romanian/Hungarian grandfathers were observed consistently in offspring of younger and older fathers and at different levels of social class. Among males and females there were similar reductions in risk associated with maternal grandfathers from this region. On the other hand, the raised risk of schizophrenia associated with paternal grandfathers from Romania/Hungary was somewhat stronger in females than in males; however, with overlapping confidence intervals, the difference between males and females was not statistically significant.

Previous researchers have defined a "central European" group of *Ashkenazi* Jews as those with grandparents originating in Austria, Germany, Czechoslovakia, Hungary, Romania and Serbia (Fallin et al., 2004). Our data did not define Serbia; instead, we included the grandfathers from Yugoslavia with this group. The relative risks of schizophrenia spectrum associated with origins in this wider area of Europe were 1.27 (0.99–1.64,  $p = .057$ ) based on paternal grandfather and 0.55 (0.93–0.97,  $p = .031$ ) based on maternal grandfather.

**Table 3**

Numbers of offspring (*N*), cases of schizophrenia spectrum disorders (Schiz), adjusted relative risk (RR) and 95% confidence intervals (CI) by maternal and paternal grandfathers' origins in Romania or Hungary, paternal age, social class and sex of offspring.

	Grandfather born in Romania or Hungary	<i>N</i>	Schiz	RR <sup>a</sup>	95% CI	<i>p</i>
Paternal age <30	Maternal	3174	9	0.46	0.23–0.91	0.0268
	Paternal	3035	19	1.53	0.93–2.50	
	Neither grandfather	34,807	204	1	Reference	
Paternal age 30+	Maternal	2529	15	0.56	0.33–0.98	0.0408
	Paternal	2706	33	1.70	1.16–2.49	
	Neither grandfather	44,040	365	1	Reference	
Social class 4, 5 and 6 (low)	Maternal	1424	8	0.54	0.26–1.20	0.0163
	Paternal	1532	18	1.90	1.13–3.20	
	Neither	45,035	336	1	Reference	
Social class 1, 2 and 3 (high)	Maternal	4312	16	0.48	0.29–0.82	0.0063
	Paternal	4226	34	1.47	1.02–2.13	
	Neither	34,476	238	1	Reference	
Males	Maternal	2982	13	0.51	0.29–0.91	0.0236
	Paternal	3020	26	1.37	0.90–2.08	
	Neither	41,006	342	1	Reference	
Females	Maternal	2753	11	0.52	0.27–0.98	0.0424
	Paternal	2738	26	2.01	1.31–3.09	
	Neither	38,496	232	1	Reference	

<sup>a</sup> Adjusted for maternal age (30–34, 35+, versus younger), paternal age (continuous), duration of marriage and low social class.

Table 4 compares results testing the three mutually exclusive groups derived from different combinations of grandfathers. There was more than a three-fold difference in the risk of schizophrenia spectrum in those with a sole paternal grandfather born in Romania or Hungary compared with those with a sole maternal grandfather from this region. On the other hand, subjects with both grandfathers born in these countries showed no altered risk of schizophrenia, compared with individuals with both grandparents born in other countries. Using the wider definition corresponding to “central Europe” versus all others, the RRs (not shown in a table) were 0.82 (0.55–1.22) when both grandfathers originated in this area, 1.38 (1.04–1.22,  $p = .024$ ) for descendents of a paternal grandfather alone and 0.83 (0.59–1.20) for those of a maternal grandfather alone from central Europe. Comparing the more narrowly focused geographic group with offspring of other fathers born in Europe only, we derived RRs of 1.27 (0.68–2.37 based on 12 cases) for offspring with two grandfathers born in Romania/Hungary, 2.44 (1.57–3.80,  $p < .0001$ ,  $n = 32$ ) for those with only a paternal grandfather from there; and 0.88 (0.32–2.43,  $n = 4$ ) for those with a maternal grandfather from either of these two countries. Thus, the descendents of Romanian/Hungarian grandfathers differed significantly from others whose fathers were born elsewhere in Europe.

While we do not know the birth places of grandmothers, we can assume that for offspring with immigrant parents each pair of grandparents would have had similar origins. With Israeli-born parents, however, it is more than likely that each pair of grandparents' origins differed. We therefore compare analyses for offspring of foreign-born versus Israeli-born parents. For progeny of paternal grandfathers from Romania/Hungary, with immigrant fathers, the RR was 1.88 (1.35–2.62  $p = .0002$ , based on 44 cases in 3943 offspring) compared with a reference group of all others; but the RR was 0.91 (0.45–1.84, 8/1815) if the father was born in Israel. Progeny of maternal grandfathers from Romania/Hungary showed RRs of 0.60 (0.37–0.95,  $p = .031$ , 21/3646) associated with immigrant mothers versus 0.23 (0.07–0.71,  $p = .011$ , 3/2090) associated with Israel-born mothers. So,

while a maternal grandfather's origin in Romania/Hungary was associated with a significantly reduced risk of schizophrenia spectrum regardless of the mother's place of birth, a paternal grandfather's origin from the same region was a risk factor only if the father was an immigrant.

Table 5 compares relative risks associated with various combinations of paternal and maternal grandfathers. A paternal grandfather from Romania/Hungary, in combination with a maternal grandfather of any other origin, was consistently associated with a raised risk of schizophrenia spectrum disorders. This risk was greatest for offspring of mothers who were second-generation Israelis, based on the country of birth of their fathers. Furthermore, there is a marked difference between this group and the corollary group whose fathers were second-generation Israelis but maternal grandfathers were from Romania/Hungary. A maternal grandfather from Romania or Hungary was consistently protective against these disorders, regardless of the origin of the paternal grandfather.

**Table 4**

Numbers of offspring (*N*), cases of schizophrenia spectrum disorders (Schiz), adjusted relative risk (RR) and 95% confidence intervals (CI) by maternal and paternal grandfathers' origins in Romania or Hungary, compared with all other offspring.

Country of birth of grandfather		<i>N</i>	Schiz	RR <sup>a</sup>	95% CI	<i>p</i>
Romania or Hungary	Both grandfathers	2176	13	0.88	0.50–1.52	0.0172
	Maternal grandfather only	3560	11	0.48	0.27–0.88	
	Paternal grandfather only	3582	39	1.60	1.15–2.21	
All other countries	Both grandfathers	79,511	574	1	Reference	0.0050

<sup>a</sup> Adjusted for maternal age (30–34, 35+, versus younger), paternal age (continuous), duration of marriage and low social class.



**Table 5**

Numbers of offspring (*N*), cases of schizophrenia spectrum disorders (Schiz), adjusted relative risk (RR) and 95% confidence intervals (CI) by origins of maternal and paternal grandfathers in Romania or Hungary, versus other countries.

Country of birth of grandfather		<i>N</i>	Schiz	RR <sup>a</sup>	95% CI	<i>p</i>
Paternal	Maternal					
Romania or Hungary	Romania or Hungary	2176	13	0.89	0.52–1.55	
Romania or Hungary	Other Europe	2066	16	1.19	0.72–1.95	
Romania or Hungary	W. Asia, N. Africa, Balkans	696	9	1.73	0.89–3.34	
Romania or Hungary	Israel	812	13	2.51	1.45–4.35	0.0011
Other countries	Any	83,071	585	1	Reference	
Romania or Hungary	Romania or Hungary	2176	13	0.85	0.49–1.48	
Other Europe	Romania or Hungary	1902	9	0.71	0.37–1.37	
W. Asia, N. Africa, Balkans	Romania or Hungary	573	1	0.27	0.04–1.90	
Israel	Romania or Hungary	1062	1	0.15	0.02–1.05	
Any	Other countries	83,093	613	1	Reference	

<sup>a</sup> Adjusted for maternal age (30–34, 35+, versus younger), paternal age (continuous), duration of marriage and low social class.

We also considered the father's year of arrival in Israel, given that immigrants arriving at different times might have been exposed to different environmental stresses. The RR associated with Romanian/Hungarian fathers who immigrated before 1956 was 1.83 (1.24–2.70, based on 28 cases in 2352 offspring); this was similar to the risk estimated for those arriving in 1956 or later (RR = 1.82, 1.03–3.24, 13/1512).

We were unable to identify affected siblings and familial cases of psychiatric disorders, because the file had been made anonymous by removal of names and identity numbers. By sorting the cases hospitalized with schizophrenia spectrum disorders and other causes according to parents' characteristics, however, we identified 55 cases (8.6%) as possible siblings, i.e. probably familial cases. With these 55 excluded, together with 77 additional putative siblings whose parents and grandparents had the same unique combinations of demographic characteristics, the estimated RRs were 1.69 (1.24–2.30,  $p = .0008$ ) for progeny of paternal grandfathers from Romania/Hungary and 0.48 (0.30–0.75,  $p = .0015$ ) for progeny of maternal grandfathers from the same origin. Thus, our results are unlikely to be an artifact due to our being unable to take into account familial correlations.

Last, we considered the RR of schizophrenia spectrum disorders in relation to origin in the Balkans, although with small numbers none of the Balkan countries had met our prior criteria for being studied. The RR associated with maternal and paternal grandfathers from the Balkans were 2.23 (1.35–3.68,  $p = .0019$ ) and 0.86 (0.44–1.68) respectively, the excess risk associated with maternal grandfathers from this region being seen for Yugoslavia (RR = 2.77, 1.42–5.40,  $p = .0027$  based on 9 cases), Greece (RR = 2.03, 0.65–6.34,  $n = 3$ ) and Bulgaria (RR = 1.58, 0.58–4.26,  $n = 4$ ). Descendents of grandmothers of Balkan origin differed significantly from other Europeans ( $p = .0002$ ), from the Romanians and Hungarians

( $p = .004$ ); from West Asians ( $p = .003$ ) and from North Africans ( $p = .03$ ).

Conclusions were unchanged by further controlling for offspring birth order, parents' education, maternal occupation rank, season of birth or urban–rural residence, by excluding the non-Jews or by removing the adjustments for other risk factors.

#### 4. Discussion

This study shows a near doubling of the risk for schizophrenia spectrum disorders for those with paternal grandfathers born in Romania or Hungary. There is a reciprocal reduction in risk for progeny of maternal grandfathers from the same countries. Similar results were observed in offspring of older and younger fathers and at higher and lower social class. Detrimental effects of paternal grandfathers from these areas were restricted to offspring whose fathers had been born abroad and were somewhat stronger in females. Beneficial effects of a maternal grandmother from Romania/Hungary held true regardless of whether the mother had been born abroad or in Israel. These findings suggest the presence of an imprinted locus affecting some families with origins in Romania or Hungary and consistent with the hypothesis attributing schizophrenia to recent mutations, as proposed by Walsh et al. (Walsh et al., 2008). That locus might also interact with a locus on the X chromosome, as others have postulated (DeLisi and Crow, 1989).

A Jewish presence in Romania and Hungary is known from Roman times, and during the Middle Ages. Large influxes of *Sephardim* entered both countries following the Ottoman conquest, and were later augmented by *Ashkenazi* migrants from the west and north. Areas of Transylvania, containing high concentrations of Jews, were alternately conquered or ceded between Romania and Hungary, and other areas of Romania were incorporated into the Ukraine, later the USSR; these, and a history of repeated massacres and deportations makes it difficult to define geographic origins of European Jews with any certainty (Meyer et al., 1953) (<http://www.sephardicstudies.org/romania.html>). In spite of this, our study suggests a focus of altered risk centered on an area involving Romania and Hungary, or less precisely focused on central Europe. Our results, with significant differences associated with parent-of-origin, seem likely to involve sporadic cases, rather than familial ones. The Balkans, although contiguous with Romania and Hungary, show a different pattern of risk that resembles that for descendents of North Africans; this may be consistent with the shared *Sephardic* ancestry of immigrants from both areas. Aside from the findings for Romanians/Hungarians, on the one hand, and the Balkans, on the other, we find little variation between ethnic groups.

A suggestion that schizophrenia might involve abnormalities of epigenetic control of gene expression (Petronis et al., 1999) has been increasingly favored in recent years (Petronis, 2000, 2004; Kan et al., 2004; Petronis et al., 2002; Abdolmaleky et al., 2004; Grayson et al., 2005; Sharma, 2005; Wong et al., 2005). Major support for this hypothesis comes from the intriguing observation that approximately half of monozygotic twins are discordant for schizophrenia, although the risk of schizophrenia in the offspring of such twins is similar (Fischer, 1971). We have postulated that the strong effect of paternal age on risk of schizophrenia might be brought about by epigenetic changes (Perrin et al., 2007)

while Crow has postulated involvement of a locus involved in male meiosis, on the Y and/or X chromosome (Crow, 2007).

Imprinted loci, including hypothetical ones on the X chromosome (Good et al., 2003; Skuse, 2003), play a key role in brain development (Davies et al., 2005), influencing the cognition and behavior, language, social function and brain lateralization that are thought relevant to psychosis (Keverne et al., 1996; Isles and Wilkinson, 2000; Williams et al., 2006). Parent-of-origin effects have been observed at various loci relevant to schizophrenia by some (Husted et al., 1998; Petronis, 2000; Weinstein, 2001a,b; Weinstein et al., 2001; Francks et al., 2003; Corradi et al., 2005) but not others (DeLisi et al., 2000a; Xu et al., 2001; Stober et al., 2000). Parent-of-origin effects have been observed in other neuropsychiatric disorders, including autism (Cook et al., 1997; Schroer et al., 1998), bipolar affective disorder (Stine et al., 1995; McMahon et al., 1995), epilepsy (Gurrieri et al., 1999) and de la Tourette syndrome (Lichter et al., 1995; Eapen et al., 1997). In schizophrenia, parent-of-origin effects, when observed, have included associations with negative symptoms, a more severe course, and greater sibling concordance in those who have inherited schizophrenia paternally (Crow et al., 1989; Ohara et al., 1997). Schizophrenia has also shown genetic linkage to chromosome 15q13–q14 (Leonard and Freedman, 2006), a region near many imprinted genes, including those for the syndromes of Angelman and Prader–Willi (Mann and Bartolomei, 1999). Moreover Prader–Willi syndrome, in which a paternal allele is inactivated, is frequently characterized by a schizophrenia-like psychosis (Clarke and Boer, 1998).

The strong effect of parent-of-origin observed in this study can be consistent with involvement of an imprinted locus. We speculate that some of the families in this cohort, with origins in Romania/Hungary, might carry a variant allele or a mutation that alters susceptibility to schizophrenia. An alternative explanation, however, might be a locus involving repeat DNA, subject to differential expansion and/or contraction on passage through a male or female germ line. As a third option, we postulate the existence of a detrimental allele leading to infertility or fetal loss in females, i.e. not transmitted by mothers, while not altering a man's reproductive capacity. This might explain the lower risk of schizophrenia associated with a maternal grandfather's origin in Romania/Hungary regardless of the mother's place of birth, i.e. regardless of the maternal grandmother's origin.

Our data comparing males and females in Table 3, we speculate, could be consistent with effects of an imprinted allele either at an X-linked locus, or interacting with one. Our finding that female offspring showed a significantly increased risk, while males did not, fits this hypothesis. A detrimental allele would be paternally expressed, i.e. active if transmitted paternally and silent if transmitted maternally; or an allele protective against schizophrenia would be maternally expressed. If the risk-enhancing paternally expressed allele were indeed X-linked, then it would be the geographic origin of the paternal grandmother which would be important, rather than that of the grandfather; however, the two grandparents would often have the same origins. Additional support for this speculation derives from our finding no increased risk in offspring of Romanian/Hungarian fathers born in Israel; in this case the paternal grandmother would be less likely to be of Romanian/Hungarian origin. Others have

found evidence for the existence of X-linked imprinting affecting neurodevelopment and behavior in humans and mice (Davies et al., 2006). While linkage studies have failed to find any region of the X chromosome to be of significance in schizophrenia (DeLisi et al., 2000b), an epigenetically controlled locus has not been excluded (Giouze et al., 2004).

The strength of our prospective study lies in its being based on a well defined cohort with a long duration of follow-up. Information on ethnic origin was ascertained in a uniform manner from vital records, many years before the diagnosis of schizophrenia. Data on place of birth of grandfather is highly reproducible; it is recorded in identity documents prior to or at the point of immigration. Similarly, the ascertainment of schizophrenia depended on a national registry in which the diagnoses of schizophrenia have been validated (Weiser et al., 2005); such diagnoses should be free of ascertainment bias with respect to grandparents' origins. An additional advantage is that 99% of the offspring's parents were married and the population's religious conservatism makes it likely that the legal fathers were indeed the biological fathers. Emigration from this cohort is rare; in parallel studies we identified a current address in Israel or a date of death for 98% of the offspring (Harlap et al., 2007) with no selective loss for those with Romanian or Hungarian grandfathers. Our results are not driven by the choice of the control group – whether restricted to Europeans or excluding other Europeans; in any case, there were no differences in this cohort between offspring of parents or grandparents from different continents, i.e. Western Asia, North Africa or Europe (Corcoran et al., in press).

It is frustrating that we have no information on grandmothers, and are unable to pinpoint origins more specifically than through country of birth of grandfathers; it might have been helpful to study separately the Ukraine and the other countries of the former Soviet Union. Another limitation is the absence of information on family history; it would have been helpful to know whether the prevalence of psychiatric disease is similarly altered in parents originating from Romania/Hungary. Our study is limited to families resident in Jerusalem in 1964–76; in that town there is a lower proportion of immigrants from Romania than pertains in other areas of Israel and very different proportions of origins from those of Jews in the US. The data rely on a broad definition of schizophrenia that includes all schizotypal diagnoses, because this is what was approved by Israel's authorities for linkage during the first cycle of investigation (the pilot study) in this cohort. Furthermore, most of our analyses are post-hoc, so the results should be regarded as “hypothesis-generating” rather than proven. Our findings do suggest that future family-based studies of schizophrenia in *Ashkenazim* might bear fruit through a careful elucidation of parent-of-origin effects and by close attention to geographic origins.

#### Role of the funding source

Funding source had no role.

#### Contributors

SH conceived the study, organized the data analysis and wrote the manuscript. MCP and KK contributed to the data analysis. LD contributed to the data management. SF, DN and AT contributed some of the data. YF oversaw the management team in Israel. DM conceived the study and obtained the funding. All co-authors reviewed and approved the manuscript.

## Conflict of interest

The authors declare no conflicts of interest.

## Acknowledgments

Supported by grants NIMH R01 MH059114-05 (DM), 2K24 MH01699 (DM) and 2R01 CA080197 (SH) from NIH and from the National Alliance for Research on Schizophrenia and Depression (SH, DM, MCP).

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