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SCHIZOPHRENIA AND BIRTHPLACE OF PATERNAL AND MATERNAL GRANDFATHER IN THE JERUSALEM PERINATAL COHORT PROSPECTIVE STUDY

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Abstract

Some forms of epigenetic abnormalities transmitted to offspring are manifest 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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Keywords

schizophrenia; Jews; cohort studies; incidence; relative risk; maternal; paternal; grandfathers

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 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 & 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 Disteché, 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 & 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.*, 2008b).

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; Malaspina *et al.*, 2001; Harlap *et al.*, 2007). 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.

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.

Data analysis

We used SAS[®] version 9.1 to analyze the data, studying time to diagnosis with Kaplan-Meier 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 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.*, 2008a) as has the absence of any influence of parents' immigration (Corcoran *et al.*, 2008b).

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 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 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.

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.

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.P *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; Kan *et al.*, 2004; Petronis *et al.*, 2002; Petronis, 2004; 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, 2001b; Weinstein, 2001a; 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 (Giouzei *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.*, 2008b).

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.

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REFERENCES

- Abdolmaleky HM, Smith CL, Faraone SV, Shafa R, Stone W, Glatt SJ, Tsuang MT. Methylomics in psychiatry: Modulation of gene-environment interactions may be through DNA methylation. *Am J Med Genet B Neuropsychiatr Genet* 2004;127:51–59. [PubMed: 15108180]
- Benjamini YH, Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J.R.Statist.Soc* 1995;B:289–300.
- Clarke DJ, Boer H. Problem behaviors associated with deletion Prader-Willi, Smith-Magenis, and cri du chat syndromes. *Am.J Ment.Retard* 1998;103:264–271. [PubMed: 9833657]

- Cook EH Jr, Lindgren V, Leventhal BL, Courchesne R, Lincoln A, Shulman C, Lord C, Courchesne E. Autism or atypical autism in maternally but not paternally derived proximal 15q duplication. *Am.J Hum.Genet* 1997;60:928–934. [PubMed: 9106540]
- Corcoran C, Perrin M, Harlap S, Deutsch L, Fennig S, Manor O, Nahon D, Kimhy D, Malaspina D, Susser E. Effect of socioeconomic status and parents' education at birth on risk of schizophrenia in offspring. *Social psychiatry and psychiatric epidemiology*. 2008a
- Corcoran C, Perrin M, Harlap S, Deutsch L, Fennig S, Manor O, Nahon D, Kimhy D, Malaspina D, Susser E. Incidence of Schizophrenia Among Second-Generation Immigrants in the Jerusalem Perinatal Cohort. *Schizophrenia bulletin*. 2008b
- Corradi JP, Ravyn V, Robbins AK, Hagan KW, Peters MF, Bostwick R, Buono RJ, Berrettini WH, Furlong ST. Alternative transcripts and evidence of imprinting of GNAL on 18p11.2. *Mol.Psychiatry* 2005;10:1017–1025. [PubMed: 16044173]
- Craig IW. The importance of stress and genetic variation in human aggression. *Bioessays* 2007;29:227–236. [PubMed: 17295220]
- Crespi B. Genomic imprinting in the development and evolution of psychotic spectrum conditions. *Biol Rev Camb Philos Soc* 2008;83:441–493. [PubMed: 18783362]
- Crow TJ. How and why genetic linkage has not solved the problem of psychosis: review and hypothesis. *The American journal of psychiatry* 2007;164:13–21. [PubMed: 17202538]
- Crow TJ, DeLisi LE, Johnstone EC. Concordance by sex in sibling pairs with schizophrenia is paternally inherited. Evidence for a pseudoautosomal locus. *Br.J Psychiatry* 1989;155:92–97. [PubMed: 2605438]
- Davies AM, Prywes R, Tzur B, Weiskopf P, Sterk VV. The Jerusalem Perinatal Study: 1. Design and organization of a continuing, community-based, record-linked survey. *Israel J Med Sci* 1969;5:1095–1106. [PubMed: 5365594]
- Davies W, Isles AR, Burgoyne PS, Wilkinson LS. X-linked imprinting: effects on brain and behaviour. *Bioessays* 2006;28:35–44. [PubMed: 16369947]
- Davies W, Isles AR, Humby T, Wilkinson LS. What are imprinted genes doing in the brain? *Adv Exp Med Biol* 2008;626:62–70. [PubMed: 18372791]
- Davies W, Isles AR, Wilkinson LS. Imprinted gene expression in the brain. *Neurosci.Biobehav.Rev* 2005;29:421–430. [PubMed: 15820547]
- DeLisi LE, Crow TJ. Evidence for a sex chromosome locus for schizophrenia. *Schizophr.Bull* 1989;15:431–440. [PubMed: 2683040]
- DeLisi LE, Razi K, Stewart J, Relja M, Shields G, Smith AB, Wellman N, Larach VW, Loftus J, Vita A, Comazzi M, Crow TJ. No evidence for a parent-of-origin effect detected in the pattern of inheritance of schizophrenia. *Biol.Psychiatry* 2000a;48:706–709. [PubMed: 11032983]
- DeLisi LE, Shaw S, Sherrington R, Nanthakumar B, Shields G, Smith AB, Wellman N, Larach VW, Loftus J, Razi K, Stewart J, Comazzi M, Vita A, De Hert M, Crow TJ. Failure to establish linkage on the X chromosome in 301 families with schizophrenia or schizoaffective disorder. *Am.J Med Genet* 2000b;96:335–341. [PubMed: 10898911]
- Dimitropoulos A, Schultz RT. Autistic-like symptomatology in Prader-Willi syndrome: a review of recent findings. *Curr Psychiatry Rep* 2007;9:159–164. [PubMed: 17389128]
- Eapen V, O'Neill J, Gurling HM, Robertson MM. Sex of parent transmission effect in Tourette's syndrome: evidence for earlier age at onset in maternally transmitted cases suggests a genomic imprinting effect. *Neurology* 1997;48:934–937. [PubMed: 9109880]
- Fallin MD, Lasseter VK, Wolynec PS, McGrath JA, Nestadt G, Valle D, Liang KY, Pulver AE. Genomewide linkage scan for bipolar-disorder susceptibility loci among Ashkenazi Jewish families. *Am.J Hum.Genet* 2004;75:204–219. [PubMed: 15208783]
- Fischer M. Psychoses in the offspring of schizophrenic monozygotic twins and their normal co-twins. *Br.J Psychiatry* 1971;118:43–52. [PubMed: 5103549]
- Francks C, DeLisi LE, Shaw SH, Fisher SE, Richardson AJ, Stein JF, Monaco AP. Parent-of-origin effects on handedness and schizophrenia susceptibility on chromosome 2p12-q11. *Hum.Mol.Genet* 2003;12:3225–3230. [PubMed: 14583442]
- Francks C, Maegawa S, Lauren J, Abrahams BS, Velayos-Baeza A, Medland SE, Colella S, Groszer M, McAuley EZ, Caffrey TM, Timmusk T, Pruunsild P, Koppel I, Lind PA, Matsumoto-Itaba N, Nicod

- J, Xiong L, Joobor R, Enard W, Krinsky B, Nanba E, Richardson AJ, Riley BP, Martin NG, Strittmatter SM, Moller HJ, Rujescu D, St Clair D, Muglia P, Roos JL, Fisher SE, Wade-Martins R, Rouleau GA, Stein JF, Karayiorgou M, Geschwind DH, Ragoussis J, Kendler KS, Airaksinen MS, Oshimura M, DeLisi LE, Monaco AP. LRRTM1 on chromosome 2p12 is a maternally suppressed gene that is associated paternally with handedness and schizophrenia. *Mol Psychiatry* 2007;12:1129–1139. 1057. [PubMed: 17667961]
- Giouze M, Williams NA, Lonie LJ, DeLisi LE, Crow TJ. ProtocadherinX/Y, a candidate gene-pair for schizophrenia and schizoaffective disorder: a DHPLC investigation of genomic sequence. *Am.J Med Genet B Neuropsychiatr.Genet* 2004;129:1–9. [PubMed: 15274028]
- Good CD, Lawrence K, Thomas NS, Price CJ, Ashburner J, Friston KJ, Frackowiak RS, Orelund L, Skuse DH. Dosage-sensitive X-linked locus influences the development of amygdala and orbitofrontal cortex, and fear recognition in humans. *Brain* 2003;126:2431–2446. [PubMed: 12958079]
- Grayson DR, Jia X, Chen Y, Sharma RP, Mitchell CP, Guidotti A, Costa E. Reelin promoter hypermethylation in schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America* 2005;102:9341–9346. [PubMed: 15961543]
- Gurrieri F, Battaglia A, Torrisi L, Tancredi R, Cavallaro C, Sangiorgi E, Neri G. Pervasive developmental disorder and epilepsy due to maternally derived duplication of 15q11-q13. *Neurology* 1999;52:1694–1697. [PubMed: 10331703]
- Harlap S, Davies AM, Deutsch L, Calderon-Margalit R, Manor O, Paltiel O, Tiram E, Yanetz R, Perrin MC, Terry MB, Malaspina D, Friedlander Y. The Jerusalem Perinatal Study cohort, 1964–2005: methods and a review of the main results. *Paediatr Perinat Epidemiol* 2007;21:256–273. [PubMed: 17439536]
- Harlap S, Davies AM, Grover NB, Prywes R. The Jerusalem Perinatal study: the first decade 1964–73. *Isr.J.Med.Sci* 1977;13:1073–1091. [PubMed: 591301]
- Hess CW, Raymond D, Aguiar Pde C, Frucht S, Shriberg J, Heiman GA, Kurlan R, Klein C, Bressman SB, Ozelius LJ, Saunders-Pullman R. Myoclonus-dystonia, obsessive-compulsive disorder, and alcohol dependence in SGCE mutation carriers. *Neurology* 2007;68:522–524. [PubMed: 17296918]
- Hochberg Y. A sharper Bonferroni procedure for multiple significance testing. *Biometrika* 1988;75:800–803.
- Horsthemke B, Wagstaff J. Mechanisms of imprinting of the Prader-Willi/Angelman region. *Am J Med Genet A* 2008;146A:2041–2052. [PubMed: 18627066]
- Huang HS, Matevossian A, Whittle C, Kim SY, Schumacher A, Baker SP, Akbarian S. Prefrontal dysfunction in schizophrenia involves mixed-lineage leukemia 1-regulated histone methylation at GABAergic gene promoters. *J Neurosci* 2007;27:11254–11262. [PubMed: 17942719]
- Husted J, Scutt LE, Bassett AS. Paternal transmission and anticipation in schizophrenia. *Am.J.Med.Genet* 1998;81:156–162. [PubMed: 9613855]
- Isles AR, Wilkinson LS. Imprinted genes, cognition and behaviour. *Trends Cogn Sci* 2000;4:309–318. [PubMed: 10904255]
- Isles AR, Wilkinson LS. Epigenetics: what is it and why is it important to mental disease? *British medical bulletin* 2008;85:35–45. [PubMed: 18281695]
- Kan PX, Pependikyte V, Kaminsky ZA, Yolken RH, Petronis A. Epigenetic studies of genomic retroelements in major psychosis. *Schizophr.Res* 2004;67:95–106. [PubMed: 14741329]
- Keverne EB, Curley JP. Epigenetics, brain evolution and behaviour. *Front Neuroendocrinol* 2008;29:398–412. [PubMed: 18439660]
- Keverne EB, Fundele R, Narasimha M, Barton SC, Surani MA. Genomic imprinting and the differential roles of parental genomes in brain development. *Brain Res.Dev.Brain Res* 1996;92:91–100.
- Leonard S, Freedman R. Genetics of chromosome 15q13-q14 in schizophrenia. *Biol.Psychiatry* 2006;60:115–122. [PubMed: 16843094]
- Lichter DG, Jackson LA, Schachter M. Clinical evidence of genomic imprinting in Tourette's syndrome. *Neurology* 1995;45:924–928. [PubMed: 7746408]
- Malaspina D, Harlap S, Fennig S, Heiman D, Nahon D, Feldman D, Susser ES. Advancing paternal age and the risk of schizophrenia. *Arch.Gen.Psychiatry* 2001;58:361–367. [PubMed: 11296097]
- Mann MR, Bartolomei MS. Towards a molecular understanding of Prader-Willi and Angelman syndromes. *Hum.Mol.Genet* 1999;8:1867–1873. [PubMed: 10469839]

- McMahon FJ, Stine OC, Meyers DA, Simpson SG, DePaulo JR. Patterns of maternal transmission in bipolar affective disorder. *Am.J Hum.Genet* 1995;56:1277–1286. [PubMed: 7762550]
- Meyer, P.; Weirby, BD.; Duschinsky, E.; Sylvain, N. *The Jews in Soviet Satellites*. Syracuse University Press Syracuse; 1953.
- Nguyen DK, Distech CM. High expression of the mammalian X chromosome in brain. *Brain research* 2006;1126:46–49. [PubMed: 16978591]
- Ohara K, Xu HD, Mori N, Suzuki Y, Xu DS, Ohara K, Wang ZC. Anticipation and imprinting in schizophrenia. *Biol.Psychiatry* 1997;42:760–766. [PubMed: 9347124]
- Payer B, Lee JT. X chromosome dosage compensation: how mammals keep the balance. *Annu Rev Genet* 2008;42:733–772. [PubMed: 18729722]
- Perrin MC, Brown AS, Malaspina D. Aberrant epigenetic regulation could explain the relationship of paternal age to schizophrenia. *Schizophrenia bulletin* 2007;33:1270–1273. [PubMed: 17712030]
- Petronis A. The genes for major psychosis: aberrant sequence or regulation? *Neuropsychopharmacology* 2000;23:1–12. [PubMed: 10869881]
- Petronis A. The origin of schizophrenia: genetic thesis, epigenetic antithesis, and resolving synthesis. *Biol.Psychiatry* 2004;55:965–970. [PubMed: 15121478]
- Petronis A, Paterson AD, Kennedy JL. Schizophrenia: an epigenetic puzzle? *Schizophr.Bull* 1999;25:639–655. [PubMed: 10667737]
- Petronis A, Pependikyte V, Kan P, Sasaki T. Major psychosis and chromosome 22: genetics meets epigenetics. *CNS.Spectr* 2002;7:209–214. [PubMed: 15211284]
- Schroer RJ, Phelan MC, Michaelis RC, Crawford EC, Skinner SA, Cuccaro M, Simensen RJ, Bishop J, Skinner C, Fender D, Stevenson RE. Autism and maternally derived aberrations of chromosome 15q. *Am.J Med Genet* 1998;76:327–336. [PubMed: 9545097]
- Sharma RP. Schizophrenia, epigenetics and ligand-activated nuclear receptors: a framework for chromatin therapeutics. *Schizophr.Res* 2005;72:79–90. [PubMed: 15560954]
- Skuse D. X-linked genes and the neural basis of social cognition. *Novartis.Found.Symp* 2003;251:84–98. [PubMed: 14521189]
- Stine OC, Xu J, Koskela R, McMahon FJ, Gschwend M, Friddle C, Clark CD, McInnis MG, Simpson SG, Breschel TS, Vishio E, Riskin K, Feilott H, Chen E, Shen S, Folstein S, Meyers DA, Botstein D, Marr TG, DePaulo JR. Evidence for linkage of bipolar disorder to chromosome 18 with a parent-of-origin effect. *Am.J Hum.Genet* 1995;57:1384–1394. [PubMed: 8533768]
- Stober G, Meyer J, Nanda I, Wienker TF, Saar K, Knapp M, Jatzke S, Schmid M, Lesch KP, Beckmann H. Linkage and family-based association study of schizophrenia and the synapsin III locus that maps to chromosome 22q13. *Am.J.Med.Genet* 2000;96:392–397. [PubMed: 10898920]
- Szyf M, McGowan P, Meaney MJ. The social environment and the epigenome. *Environ Mol Mutagen* 2008;49:46–60. [PubMed: 18095330]
- Walsh T, McClellan JM, McCarthy SE, Addington AM, Pierce SB, Cooper GM, Nord AS, Kusenda M, Malhotra D, Bhandari A, Stray SM, Rippey CF, Rocanova P, Makarov V, Lakshmi B, Findling RL, Sikich L, Stromberg T, Merriman B, Gogtay N, Butler P, Eckstrand K, Noory L, Gochman P, Long R, Chen Z, Davis S, Baker C, Eichler EE, Meltzer PS, Nelson SF, Singleton AB, Lee MK, Rapoport JL, King MC, Sebat J. Rare Structural Variants Disrupt Multiple Genes in Neurodevelopmental Pathways in Schizophrenia. *Science*. 2008
- Weinstein LS. The role of tissue-specific imprinting as a source of phenotypic heterogeneity in human disease. *Biol.Psychiatry* 2001a;50:927–931. [PubMed: 11750888]
- Weinstein LS. The stimulatory G protein alpha-subunit gene: mutations and imprinting lead to complex phenotypes. *J Clin.Endocrinol.Metab* 2001b;86:4622–4626. [PubMed: 11600514]
- Weinstein LS, Yu S, Warner DR, Liu J. Endocrine manifestations of stimulatory G protein alpha-subunit mutations and the role of genomic imprinting. *Endocr.Rev* 2001;22:675–705. [PubMed: 11588148]
- Weiser M, Kanyas K, Malaspina D, Harvey PD, Glick I, Goetz D, Karni O, Yakir A, Turetsky N, Fennig S, Nahon D, Lerer B, Davidson M. Sensitivity of ICD-10 diagnosis of psychotic disorders in the Israeli National Hospitalization Registry compared with RDC diagnoses based on SADS-L. *Compr.Psychiatry* 2005;46:38–42. [PubMed: 15714193]
- Wilkinson LS, Davies W, Isles AR. Genomic imprinting effects on brain development and function. *Nat Rev Neurosci* 2007;8:832–843. [PubMed: 17925812]

- Williams NA, Close JP, Giouzei M, Crow TJ. Accelerated evolution of Protocadherin11X/Y: a candidate gene-pair for cerebral asymmetry and language. *Am.J Med Genet B Neuropsychiatr.Genet* 2006;141:623–633. [PubMed: 16874762]
- Wong AH, Gottesman II, Petronis A. Phenotypic differences in genetically identical organisms: the epigenetic perspective. *Hum.Mol.Genet* 2005;14 Spec No 1:R11–R18. [PubMed: 15809262]
- Xu J, Pato MT, Torre CD, Medeiros H, Carvalho C, Basile VS, Bauer A, Dourado A, Valente J, Soares MJ, Macedo AA, Coelho I, Ferreira CP, Azevedo MH, Macciardi F, Kennedy JL, Pato CN. Evidence for linkage disequilibrium between the alpha 7-nicotinic receptor gene (CHRNA7) locus and schizophrenia in Azorean families. *Am.J Med Genet* 2001;105:669–674. [PubMed: 11803513]

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	5,030	36						
Cyprus	334	4	USSR, Baltic states	8,192	59	Canada	174	2
Syria	2,585	28	Poland	13,831	90	USA	2,273	11
Lebanon	297	-	Romania	5,637	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	3,655	26	Albania	2	-	Venezuela	3	-
Aden	172	1	Germany	4,444	22	Colombia	15	-
Iran	8,735	60	Austria	1,363	10	Ecuador	2	-
Afghanistan	672	7	Switzerland, Liechtenstein	261	2	Peru	3	-
India (Pakistan, Ceylon, Burma, Thailand, Malaysia)	749	6	Czechoslovakia	2,624	17	Bolivia	7	-
Singapore, Laos, Cambodia	13	-	Hungary	4,235	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	1,619	15	Belgium	180	4			
Tunisia	2,333	26	Luxembourg	5	-	Continent of origin unknown	313	3
Libya	578	4	France, Monaco	525	3			
Egypt, Sudan	1,558	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	-			
Africa, remaining countries	25	-				Total offspring	88,829	637

Country	N	Schiz	Country	N	Schiz
Africa unknown	10	-			

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 grand-father	N	Schiz	RR*	95% CI	raw p	adjusted p values	
							Hochberg 1988 (30)	Benjamini & Hochberg (31)
Western Asia								
Iraq	Maternal	11,817	94	1.22	0.92–1.61	.1663	.976	.333
	Paternal	12,643	85	0.78	0.58–1.04	.0861	.775	.333
Iran	Maternal	5,942	39	0.88	0.59–1.30	.5123	.976	.854
	Paternal	6,270	44	0.93	0.64–1.36	.7205	.976	.929
Turkey	Maternal	2,920	19	0.92	0.57–1.49	.7429	.976	.929
	Paternal	2,757	21	0.95	0.60–1.50	.8372	.976	.930
Syria	Maternal	1,470	16	1.46	0.86–2.49	.1611	.775	.333
	Paternal	1,527	14	0.99	0.56–1.75	.9756	.976	.333
Yemen	Maternal	2,705	20	1.55	0.88–2.75	.1327	.976	.333
	Paternal	2,772	14	0.50	0.25–0.98	.0436	.436	.333
None of the above		69,936	485	1	reference group			
North Africa								
Morocco	Maternal	15,935	122	1.13	0.85–1.50	.4038	.996	.646
	Paternal	15,261	112	0.90	0.67–1.20	.4614	.996	.646
Algeria	Maternal	1,031	10	1.27	0.65–2.50	.4843	.996	.646
	Paternal	817	9	1.32	0.65–2.69	.4441	.996	.646
Tunisia	Maternal	1,661	19	1.57	0.91–2.72	.1046	.837	.646
	Paternal	1,325	13	1.00	0.52–1.92	.9963	.996	.996
Libya/Egypt	Maternal	1,267	12	1.40	0.78–2.52	.2582	.996	.646
	Paternal	1,073	7	0.83	0.39–1.79	.6400	.996	.731
None of the above		62,670	428	1	reference group			
Europe etc								
Poland	Maternal	8,363	50	0.74	0.54–1.02	.0598	.538	.431
	Paternal	8,277	55	1.20	0.88–1.63	.2438	.917	.140

Country of birth of grandfather	Type of grand-father	N	Schiz	RR*	95% CI	raw p	adjusted p values	
							Hochberg 1988 (30)	Benjamini & Hochberg (31)
USSR	Maternal	4,657	31	0.80	0.54–1.17	.2460	.917	.431
	Paternal	4,853	35	1.20	0.83–1.72	.3360	.917	.523
Romania	Maternal	3,419	17	0.50	0.30–0.84	.0088	.106	.041
	Paternal	3,288	33	1.92	1.31–2.82	.0008	.011	.011
Hungary	Maternal	2,317	7	0.36	0.17–0.77	.0086	.106	.041
	Paternal	2,470	19	1.61	1.01–2.61	.0473	.473	.132
Czechoslovakia	Maternal	1,419	9	0.77	0.39–1.52	.4548	.917	.579
	Paternal	1,335	9	1.33	0.68–2.62	.4003	.917	.560
Germany	Maternal	2,621	11	0.51	0.28–0.94	.0320	.352	.112
	Paternal	2,284	13	1.07	0.61–1.89	.8178	.917	.881
USA	Maternal	1,447	8	0.82	0.40–1.71	.6033	.917	.704
	Paternal	1,222	6	0.96	0.41–2.21	.9165	.917	.917
None of the above		63,518	459	1	reference group			

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

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	N	Schiz	RR [*]	95% CI	p
Paternal age						
<30	Maternal	3,174	9	0.46	0.23–0.91	.0268
	Paternal	3,035	19	1.53	0.93–2.50	
	Neither grandfather	34,807	204	1	reference	
Paternal age						
30+	Maternal	2,529	15	0.56	0.33–0.98	.0408
	Paternal	2,706	33	1.70	1.16–2.49	.0063
	Neither grandfather	44,040	365	1	reference	
Social class						
4, 5 & 6	Maternal	1,424	8	0.54	0.26–1.20	
(low)	Paternal	1,532	18	1.90	1.13–3.20	.0163
	Neither	45,035	336	1	reference	
Social class						
1, 2 & 3	Maternal	4,312	16	0.48	0.29–0.82	.0063
(high)	Paternal	4,226	34	1.47	1.02–2.13	.0409
	Neither	34,476	238	1	reference	
Males	Maternal	2,982	13	0.51	0.29–0.91	.0236
	Paternal	3,020	26	1.37	0.90–2.08	
	Neither	41,006	342	1	reference	
Females	Maternal	2,753	11	0.52	0.27–0.98	.0424
	Paternal	2,738	26	2.01	1.31–3.09	.0015
	Neither	38,496	232	1	reference	

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

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	N	Schiz	RR*	95% CI	p
Romania or Hungary					
Both grandfathers	2,176	13	0.88	0.50–1.52	
Maternal grandfather only	3,560	11	0.48	0.27–0.88	.0172
Paternal grandfather only	3,582	39	1.60	1.15–2.21	.0050
All other countries	79,511	574	1	reference	

* 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		N	Schiz	RR*	95% CI	p
Paternal	Maternal					
Romania or Hungary	Romania or Hungary	2,176	13	0.89	0.52–1.55	
Romania or Hungary	Other Europe	2,066	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	.0011
Other countries	Any	83,071	585	1	reference	
Romania or Hungary	Romania or Hungary	2,176	13	0.85	0.49–1.48	
Other Europe	Romania or Hungary	1,902	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	1,062	1	0.15	0.02–1.05	
Any	Other countries	83,093	613	1	reference	

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