

Risk of schizophrenia in second-generation immigrants: a Danish population-based cohort study

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ABSTRACT

Background. Urban birth, a risk factor for schizophrenia, is more frequent among second-generation immigrants. The aim of the current study was to determine whether the increased risk for schizophrenia found in second-generation immigrants is explained by the degree of urbanization of birthplace and/or factors related to parentage, such as geographic origin or history of residence abroad during upbringing.

Method. Using data from the Danish Civil Registration System (CRS), we established a population-based cohort of 2·0 million Danes (persons born in Denmark). Schizophrenia in cohort members was identified by cross-linkage with the Danish Psychiatric Central Register.

Results. The relative risk of developing schizophrenia was 1·93 [95% confidence interval (CI) 1·79–2·08] and 2·96 (95% CI 2·49–3·51) among persons with one or both parents foreign-born respectively compared to native Danes. Adjustment for urbanization of birthplace and parental characteristics reduced these risks slightly. However, urbanization had a lesser effect in second-generation immigrants than in Danes. History of residence abroad was a risk factor for schizophrenia, regardless of whether parents were foreign-born or native Danes.

Conclusion. The increased risk found in second-generation immigrants cannot be explained by urbanization or parental characteristics pertaining to age, mental illness, geographic origin or residence abroad during a child's upbringing.

INTRODUCTION

The increased risk for schizophrenia found among second-generation immigrants is currently unexplained, although social factors seemingly play a contributory role (Hjern *et al.* 2004; Selten & Cantor-Graae, 2005). Using data from a Danish register-based cohort, we investigated whether the increased risk in second-generation immigrants could be explained by other factors, namely urbanization at birth or during upbringing and/or parental characteristics (e.g. geographic origin, residence abroad during a child's upbringing). Urbanization is an important risk

factor for schizophrenia (e.g. Pedersen & Mortensen, 2001*a, b*). No study of second-generation immigrants has explored the potential confounding effect of urbanization, despite the residential clustering of immigrants in urban environments (e.g. Ministry of Internal Affairs, 1999; Singh & Hiatt, 2006). Previous second-generation immigrant studies have measured urbanization implicitly, that is at disease onset rather than at birth (Cantor-Graae & Selten, 2005). We also postulated that clues to underlying mechanisms could be explored by examining the 'risk' parent's identity (father *versus* mother, *versus* both parents foreign-born). Children of dual foreign-born parentage might risk social exclusion due to, for example, poorer Danish language skills or non-Danish physical appearance, whereas children of mixed

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Table 1. *Adjusted relative risk of schizophrenia, according to foreign parent's region of birth, in a population-based cohort of 114 807 second-generation immigrants born in Denmark 1954–1986, of which 905 developed schizophrenia during 1.45 million person-years at risk in 1970–2001*

Foreign parent's region of birth	Only one parent born abroad			Mother and father born abroad in same region ^a		
	No. of cases	Incidence ^b	RR (95% CI) ^c	No. of cases	Incidence ^b	RR (95% CI) ^c
Overall	768	5.90	1.60 (1.49–1.72)	137	9.06	2.32 (1.96–2.76)
Scandinavia	241	5.58	1.51 (1.33–1.72)	9	5.68	1.43 (0.74–2.75)
Europe	327	5.26	1.48 (1.33–1.66)	56	7.56	2.09 (1.61–2.72)
Africa	27	7.52	1.64 (1.12–2.40)	15	18.27	3.83 (2.30–6.37)
Australia	2	4.88	1.44 (0.36–5.75)	0	— ^d	— ^d
South America	12	4.68	1.19 (0.68–2.10)	1	11.77	— ^d
North America	46	7.42	2.05 (1.53–2.74)	1	37.53	— ^d
Middle East	15	8.57	1.78 (1.07–2.95)	3	8.26	1.88 (0.60–5.83)
Asia	31	6.61	1.73 (1.21–2.46)	32	10.69	2.61 (1.84–3.71)
Greenland	67	12.12	2.92 (2.30–3.72)	4	60.21	12.42 (4.66–33.14)

RR, Relative risk; CI, confidence interval.

^a Children whose mother and father were born abroad in different regions (16 cases) were included in the 'Overall' effect but not in the regional effects.

^b Incidence of schizophrenia per 10 000 person-years at risk. The incidence measures the number of new cases that occurred per time period.

^c The reference category was native Danes, that is children born in Denmark and whose parents were both born in Denmark (incidence: 3.03, 9742 cases). Estimates of relative risks were adjusted for age and its interaction with gender, calendar year, maternal and paternal age at time of child's birth, the degree of urbanization at child's birth, and history of mental illness in a parent or sibling. The incidence for children who had unknown information on maternal or paternal place of birth was 3.05 (132 cases).

^d Insufficient information to provide a valid estimate (less than two cases of schizophrenia).

parentage might have difficulties negotiating between dissonant cultural identities.

METHOD

Material

Study population

We used the Danish Civil Registration System (CRS) (Pedersen *et al.* 2006) to obtain a large and representative dataset on Danes. The CRS was established in 1968, when all people living in Denmark were registered. It includes information on personal identification number (CRS-number), gender, date and place of birth, continuously updated information on vital status, and CRS-number of parents. The CRS-number is used as a personal identifier in all national registers, enabling unique linkage between registers. Our study population includes all persons born in Denmark between 1954 and 1986, who were alive at their 15th birthday, and who had maternal and paternal links.

Assessment of parental region of birth

Parental country of birth was classified according to geographical region, as described previously

(Cantor-Graae *et al.* 2003), and subdivided into 30 categories (see Table 1):

- (1) mother born in Denmark, father born abroad (nine categories)
- (2) father born in Denmark, mother born abroad (nine categories)
- (3) mother and father born abroad in the same region (nine categories)
- (4) mother and father born abroad in different regions (one category)
- (5) mother or father's region of birth is unknown (one category)
- (6) mother and father both born in Denmark (one category).

Recall that our study population includes only persons born in Denmark.

Assessment of parental origin

The variable referred to as parental origin is defined as follows: second-generation immigrants by one parent (either by father or by mother only, items 1 and 2 above respectively), second-generation immigrants by both parents (mother and father born abroad, items 3 and 4 above), and native Danes (both parents born in Denmark, item 6 above).

Assessment of developmental level of the parent's country of origin

The developmental level of parental country of origin was categorized as 'developing' or 'developed' (United Nations, 2002), as in our previous study (Cantor-Graae & Selten, 2005).

Assessment of schizophrenia and mental illness in a parent or sibling

The study population and their mothers, fathers and siblings were linked with the Danish Psychiatric Central Register (Munk-Jørgensen & Mortensen, 1997). Computerized since 1969, the register contains data on all admissions to Danish psychiatric in-patient facilities and currently includes data on approximately 450 000 persons and 1.6 million admissions. From 1995 onwards, information on out-patient visits to psychiatric facilities was included in the register. The diagnostic system used in 1969–1993 was the ICD-8 (WHO, 1967) and from 1994 onwards, ICD-10 (WHO, 1992) was used. Cohort members were classified with schizophrenia if they had been admitted to a psychiatric hospital or had been in out-patient care with a diagnosis of the disorder (ICD-8 code 295 or ICD-10 code F20). Date of onset was defined as the first day of the first (in- or out-patient) contact with a diagnosis of schizophrenia. Parents and siblings were categorized hierarchically with a history of schizophrenia, schizophrenia-like psychoses (ICD-8 codes 297, 298.39, 301.83 or ICD-10 codes F21–F29) or other mental disorders (any ICD-8 or ICD-10 diagnosis) if they had been admitted to a psychiatric hospital or had been under out-patient care with one of these diagnoses. The diagnostic categories used were identical to those used previously (Pedersen & Mortensen, 2001a, b, 2006).

Assessment of change of residence, urbanicity at birth and during upbringing

Municipalities in Denmark were classified according to the degree of urbanization (Statistics Denmark, 1997), as described previously (Pedersen & Mortensen, 2001b), yielding the following categories: capital (Copenhagen), capital suburb, provincial city, provincial town, and rural area. For each cohort member, we compiled information on the degree of urbanization of birthplace. For persons born in 1971

or later, information was accessible on residence in Denmark during upbringing. For those persons we compiled information on the accumulated number of years each person had been living in each degree of urbanization from birth to their 15th birthday, and the number of changes in municipality at various ages (0–3, 4–9, 10–12 and 13–14 years), as before (Pedersen & Mortensen, 2001a).

Assessment of residence abroad

For each cohort member, we compiled information on the family's (mother, father, cohort member) residence at the time of the child's 15th birthday, as an indicator of history of foreign residence at the family level (moving in and out of Denmark during upbringing). This was categorized as:

- (a) All living in Denmark: the child, child's mother and child's father reside in Denmark at the child's 15th birthday.
- (b) Only the mother is living abroad: the child and the child's father reside in Denmark at the child's 15th birthday.
- (c) Only the father is living abroad: the child and the child's mother reside in Denmark at the child's 15th birthday.
- (d) Family is living abroad: the child and both parents reside abroad at the child's 15th birthday.
- (e) Other: any other combination, such as the child plus a parent (father or mother) reside abroad at the child's 15th birthday.

A personal history of foreign residence (accessible only for persons born in 1969 or later) was categorized as ever living abroad from birth to the 15th birthday *versus* never living abroad, as described previously (Cantor-Graae *et al.* 2003).

Study design

A total of 2 090 260 persons were followed during residence in Denmark from their 15th birthday or 1 April 1970, whichever came later, until onset of schizophrenia, death or 31 December 2001, whichever came first.

Statistical analyses

The relative risk of schizophrenia was estimated by Poisson regression (Breslow & Day, 1987; SAS Institute, 2004). All relative risks were

adjusted for age and its interaction with gender, calendar year and parental age. Further adjustments were made for history of mental illness in a parent or sibling, degree of urbanization at place of birth and during upbringing, and change of residence. Age, calendar year, and history of mental illness in siblings were treated as time-dependent variables (Clayton & Hills, 1993), whereas all other variables were treated as independent of time. *p* values were based on likelihood ratio tests and 95% confidence intervals (CIs) were calculated by Wald's test (Clayton & Hills, 1993). The adjusted-score test (Breslow, 1996) suggested that the regression models were not subject to over-dispersion.

RESULTS

Our cohort included 2 090 260 persons born in Denmark 1954–1986 followed for the development of schizophrenia 1970–2001, contributing 34.1 million person-years at risk. In total, 10 779 persons developed schizophrenia: 9742 (90.4%) native Danes, 436 (4.0%) second-generation immigrants by mother only, 332 (3.1%) second-generation immigrants by father only, 137 (1.3%) second-generation immigrants by both parents, and 132 (1.2%) persons lacking information on a parent's country of birth.

Effects of risk parent, birth region and developmental level

Table 1 shows the distribution of cases and the relative risks of developing schizophrenia among second-generation immigrants by one and by both parents foreign-born, compared to native Danes. The crude incidence for native Danes was 3.03 per 10 000 person-years at risk. Second-generation immigrants (irrespective of parents' birth region) had a greater crude incidence rate and a greater relative risk of schizophrenia compared to native Danes.

Among second-generation immigrants with one parent foreign-born, the risk of schizophrenia did not differ significantly according to which parent was foreign-born ($p=0.86$), that is the risk for children with a Danish mother and a Scandinavian father equals the risk for children with a Scandinavian mother and a Danish father, etc. (results not shown).

The risks of schizophrenia among second-generation immigrants differed significantly

according to parental region of birth ($p<0.001$, one parent foreign-born; $p=0.02$, both parents foreign-born). Risks were greater for second-generation immigrants with one or both parents from developing *versus* developed countries ($p=0.01$, results not shown). When developmental level and regional differences were mutually adjusted for, the regional differences remained significant ($p=0.02$), whereas the developmental level no longer had a significant effect ($p=0.70$).

Although significant regional effects were obtained, further analyses concern the effect of parental origin solely, irrespective of region. We considered the following potential confounders and/or effect modifiers: the family's residence at the child's 15th birthday, urbanization at birth and during upbringing, change of residence during upbringing, parental age at birth, and history of mental illness in a parent or sibling.

Effects of the family's residence at the child's 15th birthday

Among second-generation immigrants, 5.75% had a family member not residing in Denmark at the child's 15th birthday, whereas among native Danes, only 0.71% had a family member not residing in Denmark at the child's 15th birthday (results not shown). A family member living abroad (child, mother, father or the entire family) *versus* the entire family living in Denmark at the child's 15th birthday increased the risk of developing schizophrenia ($p<0.0001$) (Table 2). This risk did not differ according to parental origin, that is one or both parents foreign-born, or both parents born in Denmark ($p=0.22$), and remained significant after adjustment for parental region of birth ($p=0.0008$). In addition, a personal history of foreign residence increased the risk 1.23-fold (95% CI 1.03–1.46), regardless of parental origin ($p=0.39$).

Overall effect of parental origin adjusted for potential confounders

The overall effect of parental origin obtained using different adjustment models is shown in Table 3. Adjustment for the degree of urbanization of child's birthplace in Denmark reduced the risk associated with parental origin to a slightly greater degree than adjustment for

Table 2. *Adjusted relative risk of schizophrenia according to the family's residence at the child's 15th birthday in a population-based cohort of 2.0 million people born in Denmark 1954–1986, of which 10 779 people developed schizophrenia during 34.1 million person-years at risk 1970–2001*

Family's residence at child's 15th birthday	No. of cases	Incidence ^a	RR (95% CI) ^b
Overall	10 779	3.16	
All alive at child's 15th birthday			
All live in Denmark	9995	3.06	1.00 (reference)
Mother only lives abroad	22	8.53	1.86 (1.23–2.84)
Father only lives abroad	122	6.72	1.56 (1.30–1.87)
All live abroad	42	6.38	1.50 (1.11–2.04)
Other residence	29	9.19	1.83 (1.27–2.63)
Parent not alive at child's 15th birthday			
Mother dead	147	4.84	1.27 (1.08–1.49)
Father dead	359	5.01	1.27 (1.14–1.41)
Mother and father dead	16	10.08	1.97 (1.20–3.22)
Unknown information at child's 15th birthday	47	5.24	1.17 (0.88–1.57)

RR, Relative risk; CI, confidence interval.

^a Incidence of schizophrenia per 10 000 person-years at risk. The incidence measures the number of new cases that occurred per time period.

^b Estimates were adjusted for age and its interaction with gender, calendar year, maternal and paternal age at time of child's birth, urbanization at child's birth and parental origin.

Table 3. *Overall adjusted relative risks for 114 807 second-generation immigrants born in Denmark 1954–1986, of which 905 developed schizophrenia during 1.45 million person-years at risk 1970–2001*

Adjustment model	Relative risk (95% confidence interval) ^a	
	Second-generation immigrant by one parent	Second-generation immigrant by both parents
Full cohort, born 1954–1986		
Basic model (1)	1.93 (1.79–2.08)	2.96 (2.49–3.51)
History of mental illness in a parent or sibling (2)	1.77 (1.65–1.91)	2.83 (2.39–3.35)
Urbanization at place of birth (3)	1.70 (1.57–1.83)	2.31 (1.95–2.75)
Family's residence at child's 15th birthday (4)	1.85 (1.72–2.00)	2.80 (2.36–3.33)
History of mental illness in a parent or sibling and urbanization at place of birth (5)	1.60 (1.49–1.72)	2.32 (1.96–2.76)
Fully adjusted model (6)	1.55 (1.44–1.68)	2.24 (1.89–2.66)
Cohort for which information on residence during upbringing is accessible, born 1971–1986		
Basic model (1)	1.96 (1.73–2.23)	2.70 (2.22–3.30)
History of mental illness in a parent or sibling (2)	1.77 (1.56–2.02)	2.62 (2.15–3.19)
Urbanization at place of birth (3)	1.74 (1.53–1.98)	2.08 (1.70–2.54)
Urbanization during upbringing (3a)	1.62 (1.42–1.84)	1.91 (1.55–2.34)
Family's residence at child's 15th birthday (4)	1.87 (1.64–2.13)	2.61 (2.13–3.18)
History of mental illness in a parent or sibling and urbanization at place of birth (5)	1.63 (1.43–1.85)	2.17 (1.77–2.65)
History of mental illness in a parent or sibling and urbanization during upbringing (5a)	1.55 (1.36–1.77)	2.00 (1.63–2.45)
Fully adjusted model (6)	1.57 (1.37–1.79)	2.11 (1.72–2.59)
Fully adjusted model (6a)	1.53 (1.34–1.74)	1.99 (1.62–2.45)

^a The reference category was native Danes, that is children born in Denmark whose parents were also both born in Denmark (9742 cases born 1954–1986, 2428 cases born 1971–1986).

(1) Estimates were adjusted for age and its interaction with gender, calendar year, maternal and paternal age at time of child's birth.

(2) Estimates were adjusted for all variables in the basic model and history of mental illness in a parent or sibling.

(3) Estimates were adjusted for all variables in the basic model and urbanization at child's birth; (3a) also adjusting for urbanization and change of residence during upbringing.

(4) Estimates were adjusted for all variables in the basic model and the family's residence at the child's 15th birthday.

(5) Estimates were adjusted for all variables in the basic model, history of mental illness in a parent or sibling and urbanization at child's birth. These estimates are identical to the overall estimates presented in Table 1; (5a) also adjusting for urbanization and change of residence during upbringing.

(6) Estimates were adjusted for all variables in the basic model, history of mental illness in a parent or sibling, urbanization at child's birth, and the family's residence at the child's 15th birthday; (6a) also adjusting for urbanization and change of residence during upbringing.

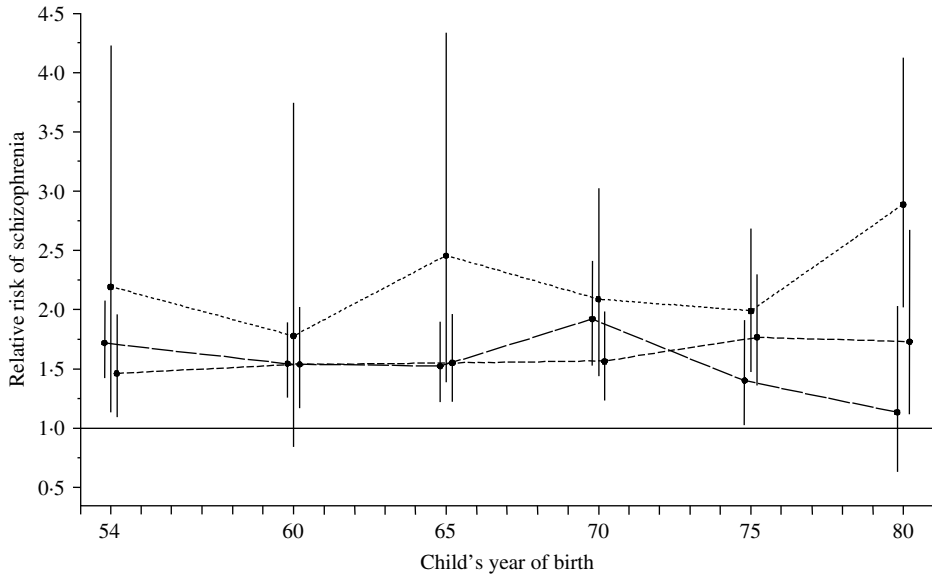


FIG. 1. Adjusted relative risks of schizophrenia associated with parental origin subdivided by birth cohort. Native Danes born at the same time were chosen as the reference category. Estimates of relative risks were adjusted for age and its interaction with gender, calendar year, parental age at birth, history of mental illness in a parent or sibling, and urbanization at place of birth in Denmark. —, Native Dane; — — —, foreign-born mother; - - - -, foreign-born father; · · · · ·, foreign-born parents.

mental illness in a parent or sibling. It may be noted that 31.9% of second-generation immigrants, compared with only 15.6% of the native Danes, were born in the capital. However, the effect of parental origin was not reducible to urbanization of birthplace. Among people born in 1971 or later, we had accessible information on residence during upbringing. In this restricted cohort, adjustment for urbanization during upbringing and change of residence during upbringing (Pedersen & Mortensen, 2001a) resulted in a similar, albeit slightly greater, reduction of the overall risk (see Table 3). The results comparing the two overlapping cohorts are strikingly similar.

When adjusted for age and its interaction with gender, calendar year, parental age at birth, mental illness in a parent or sibling, and the degree of urbanization of the child's birthplace, the overall risk for second-generation immigrants, whether by one or by both parents foreign-born, was 1.68 (95% CI 1.57–1.80). The effect of parental origin, whether by one or by both parents foreign-born, remained constant over time, regardless of birth year (Fig. 1).

Differing effect of urbanization of birthplace in Danes and in second-generation immigrants

Table 4 shows the relative risk of schizophrenia subdivided by parental origin and the degree of urbanization of birthplace in Denmark. The risk associated with parental origin was modified by the degree of urbanization at birth. Among children born in a rural area, second-generation immigrants by one parent had a risk of 1.90 (95% CI 1.52–2.36) compared to native Danes (reference category), while second-generation immigrants by both parents had a risk of 4.15 (95% CI 1.86–9.25) compared to native Danes. Summarizing this dose-response association as a trend, the risk of schizophrenia was 1.92 (95% CI 1.59–2.34) for second-generation immigrants by one parent born in a rural area compared to native Danes born in a rural area (Table 4, Trend). Among children born in the capital, native Danes had a risk of 1.99 (95% CI 1.87–2.11), second-generation immigrants by one parent had a risk of 2.85 (95% CI 2.52–3.22), and second-generation immigrants by both parents had a risk of 3.94 (95% CI

Table 4. *Adjusted relative risk^a (and 95% confidence interval) associated with parental origin and place of birth in Denmark*

Place of birth in Denmark	Native Danes	Second-generation immigrant by one parent	Second-generation immigrant by both parents	Trend ^b
Capital	1.99 (1.87–2.11)	2.85 (2.52–3.22)	3.94 (3.08–5.06)	1.42 (1.30–1.55)
Capital suburb	1.50 (1.39–1.62)	2.58 (2.14–3.12)	4.06 (2.86–5.76)	1.68 (1.47–1.92)
Provincial city	1.42 (1.32–1.52)	1.90 (1.49–2.43)	2.68 (1.34–5.37)	1.35 (1.10–1.65)
Provincial town	1.15 (1.09–1.22)	2.11 (1.82–2.44)	3.32 (2.25–4.89)	1.78 (1.59–2.00)
Rural area	1.00 (reference)	1.90 (1.52–2.36)	4.15 (1.86–9.25)	1.92 (1.59–2.34)
Trend ^c	1.98 (1.88–2.09)	1.52 (1.26–1.84)	1.22 (0.72–2.06)	

^a Estimates were adjusted for age and its interaction with gender, calendar year, maternal and paternal age at time of child's birth, and history of mental illness in a parent or sibling. There was significant interaction between parental origin and place of birth in Denmark ($p = 0.03$).

^b We used trends to summarize the risk associated with parental origin, scoring native Danes as 0, second-generation immigrants by one parent as 1, and second-generation immigrants by both parents as 2. For each place of birth in Denmark, the trend summarizes the risk of schizophrenia among second-generation immigrants by one parent compared to native Danes (which by definition equals the risk of schizophrenia among second-generation immigrants by both parents compared to second-generation immigrants by one parent).

^c We used trends to summarize the risk associated with place of birth in Denmark, scoring a rural area as 0, a provincial town as 0.25, a provincial city as 0.5, a capital suburb as 0.75, and the capital as 1. For each category of parental origin, the trend summarizes the risk of schizophrenia associated with birth in the capital compared to birth in a rural area.

3.08–5.06). Summarizing this dose–response association as a trend, the risk of schizophrenia was 1.42 (95% CI 1.30–1.55) for second-generation immigrants by one parent born in the capital compared to native Danes born in the capital (Table 4, Trend).

Moreover, as indicated by the interaction between these two variables/exposures, the risk associated with urban birthplace was modified by parental origin. Among native Danes, the risk of schizophrenia was 1.99 (95% CI 1.87–2.11) when born in the capital compared to the rural area (reference category). Among native Danes, the greater the degree of urbanization at birth, the greater was the risk of schizophrenia. Summarizing this dose–response association as a trend, the risk of schizophrenia was 1.98 (95% CI 1.88–2.09) for native Danes born in the capital compared to native Danes born in a rural area (Table 4, Trend).

Among second-generation immigrants by one parent, the greater the degree of urbanization at birth, the greater was the risk of schizophrenia. Summarizing this dose–response association as a trend, the risk of schizophrenia was 1.52 (95% CI 1.26–1.84) for second-generation immigrants by one parent born in the capital compared to second-generation immigrants by one parent born in a rural area (Table 4, Trend).

Among second-generation immigrants by both parents, there was no evidence of a dose–response association between risk of schizophrenia and the degree of urbanization. Summarizing this association as a trend, the risk of schizophrenia was 1.22 (95% CI 0.72–2.06) for second-generation immigrants by both parents born in the capital compared to second-generation immigrants by both parents born in a rural area.

DISCUSSION

Main findings

This Danish cohort study examined a number of potential confounders of the increased risk of developing schizophrenia in second-generation immigrants. None of these factors appeared to be explanatory. Thus, the increased risks of schizophrenia in second-generation immigrants remained significant after adjustment for a family member residing abroad at the time of the child's 15th birthday, the degree of urbanization at birth and during upbringing in Denmark, change of residence during upbringing, parental age at child's birth, and history of mental illness in a parent or sibling. Furthermore, the increased risk of developing schizophrenia among second-generation immigrants remained constant over time (Fig. 1), despite

social and environmental changes in Denmark during this period.

Differential effect of urbanization at birth: what is the mechanism?

The most striking results in the current study were revealed by examining the co-action of urbanization and second-generation immigrant status (Table 4). Urbanization at birth/up-bringing has previously been shown to be associated with an increased risk for developing schizophrenia (e.g. Pedersen & Mortensen, 2001*a, b*). Yet in the current sample, no effect of urbanization at birth was seen in second-generation immigrants by both parents, and only some effect of urbanization was seen in second-generation immigrants by one parent. Thus, the dose–response relationship previously shown between urbanization at birth and during upbringing and schizophrenia (Pedersen & Mortensen, 2001*a*) could be replicated only among persons with both parents born in Denmark. The current findings seemingly indicate that the more ‘Danish’ the family is, the greater is the urbanization effect. Urban-born second-generation immigrants by both parents, that is individuals having maximum exposure to both risk factors, showed no evidence that their dual exposure resulted in substantially greater risks of developing schizophrenia with increasing levels of urbanization.

One possible interpretation of the lack of urbanization effect among second-generation immigrants by both parents foreign-born is that they are ‘protected’ by the increased level of ethnic density presumably associated with increasing levels of urbanization. Although, in this regard, the results might resemble the protective effect of ethnic density shown by Boydell *et al.* (2001), the current study concerns birth-place rather than ethnic density effects measured on the neighbourhood level at the time of schizophrenia onset, and may thus be more suitable for identifying risk factors causally associated with schizophrenia. In addition, the ‘ethnic density/protection’ interpretation presupposes that urbanization exerts its influence primarily through environmental or psychosocial factors. An alternative explanation is that Danish parents-to-be who settle in urban areas are preselected for some trait (genetic and/or

environmental) that may be related to the development of schizophrenia in their offspring (Pedersen & Mortensen, 2006), whereas urban immigrant parents-to-be are not.

Effects of geographic origin

Our findings show that parental region of origin is more important for the second-generation immigrant effect than the developmental level of the country. However, the regional divisions are based solely on geographic proximity. Thus, the ‘concept’ underlying the regional effect remains obscure. Nevertheless, persons originating from the same geographic region might share characteristics, such as similar physical appearance (e.g. skin colour) and/or cultural and geographical distance from Denmark. It may be observed that persons whose parents were born in Greenland had the greatest risks of developing schizophrenia, whereas incidence rates in Greenland are not markedly elevated (Lyngé *et al.* 1999). Consumption of alcohol is greater among Greenlandic immigrants in Denmark than residents of Greenland (Madsen *et al.* 2005). Alcohol usage among parents could possibly be a destabilizing influence, contributing to the further development of social adversity in the household. A dose–response relationship between social adversity during childhood and the risk of developing schizophrenia has been shown by Wicks *et al.* (2005). Alternative explanations for the increased risks associated with Greenlandic parentage are nevertheless possible.

Risk parent or risk parents?

The risk of developing schizophrenia among second-generation immigrants was substantially increased when both parents were foreign-born, suggesting that dual foreign-born parentage represents an increased parental ‘disadvantage’. The nature of this disadvantage is currently unknown. In the study by Hjern *et al.* (2004), adjustment for parental socio-economic household indicators reduced slightly the schizophrenia risks obtained in second-generation immigrants. Although low parental socioeconomic status *per se* is not associated with an increased risk of developing schizophrenia (e.g. Byrne *et al.* 2004; Wicks *et al.* 2005), recent findings indicate a role for specific types of parental disadvantage, such as parental

unemployment/disability pension (Byrne *et al.* 2004; Wicks *et al.* 2005) and parents receiving social welfare (Wicks *et al.* 2005). A common denominator underlying these and other types of parental disadvantage may be increased risk for social exclusion or social defeat in the offspring.

Recently, it has been proposed that chronic and long-term experience of social defeat may contribute to the development of schizophrenia, through sensitization (or increased baseline activity) of the mesolimbic dopamine system (Selten & Cantor-Graae, 2005). Perceived discrimination has been shown to predict the development of psychotic symptoms in previously healthy individuals (Janssen *et al.* 2003). Thus, children who are born and raised in Denmark, yet who are regarded as 'foreigners' and subjected to chronic social exclusion or discrimination, may be prone to social defeat. In this respect, children having dual foreign-born parentage might encounter more barriers than if one parent is Danish because of, for example, poorer Danish language skills or non-Danish physical characteristics. These notions are speculative and require further investigation. However, the current findings do seem to exclude the notion that the second-generation immigrant effect is mediated by a risk transmitted preferentially through one parent, such as obstetric complications via the mother or sperm mutation via the father.

Residence abroad: a type of migration?

Family's residence abroad at the child's 15th birthday was a risk factor for developing schizophrenia. Thus, periods of emigration, or the emigration process, may confer an increased risk for schizophrenia regardless of whether the parents are foreign-born or native Danes. These results are consistent with previous findings implicating personal history of foreign residence before age 15 as a risk factor in native Danes (Cantor-Graae *et al.* 2003). It is not known whether the risk associated with residence abroad is mediated by selection (e.g. parents who emigrate being preselected for certain traits) or by 'exposure', such as exposure to uncommon infectious agents or separation from a parent. Upbringing in a single-parent household is associated with an increased risk of schizophrenia (Wicks *et al.* 2005). Mallett *et al.*

(2002) also found that Afro-Caribbean patients were more likely to have long-term separation from one or both parents during upbringing. It should be noted that although family's residence abroad was more frequent in second-generation immigrants, adjustment for this factor had little impact on the effect of parental origin (Table 3).

Methodological concerns

Although the use of register-based diagnostic data may represent a possible limitation, the Danish Psychiatric Central Register has shown good diagnostic validity (Munk-Jørgensen, 1995). However, insofar as the current findings are based on patients admitted for treatment (in- and out-patient), some early episode patients may be overlooked. Nevertheless, most early episode patients will eventually present for treatment and be registered. Although a possible source of bias may be selective referral of immigrants, this has previously been shown to be of little importance for psychosis rates in Denmark (Mortensen *et al.* 1997). In addition, service provision in Denmark is equivalent in rural and urban areas, and even in rural areas distances are small.

Unfortunately, detailed demographic information, such as socio-economic background, was not accessible for the cohort because of constraints concerning data usage from Statistics Denmark (Frank, 2000). In addition, such information only exists from 1981 onwards. Thus, it was not possible to make adjustments for the potential influence of household circumstances during upbringing.

Nevertheless, our study has several major strengths. In this population-based sample, 99% of all people have accessible information on their parental country of birth. Estimates of relative risk were calculated using a cohort study including only incident cases of schizophrenia (Pedersen, 2006). The study is large and representative of the Danish population, with power sufficient for subdivision of second-generation immigrants by 'risk' parent (by mother, father or both parents) and by parental region of birth. All cohort members are born in Denmark. Thus, any potential influences of selective migration pertain only to the parents, and not to the cohort members themselves (Pedersen & Mortensen, 2006).

CONCLUSION

Further study of the mechanisms contributing to the development of schizophrenia in second-generation immigrants is clearly needed. Our findings suggest that such study may also have important implications for current conceptualizations of the urbanization effect in schizophrenia.

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DECLARATION OF INTEREST

None.

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