Family history, place and season of birth as risk factors for schizophrenia in Denmark: a replication and reanalysis

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Background Although a family history of schizophrenia is the strongest individual risk factor for schizophrenia, environmental factors related to urbanicity may contribute to a substantial proportion of the population occurrence of the disease.

Aims This study replicates previous findings in four mutually exclusive Danish study populations, including out-patient information, ICD–10 diagnoses of schizophrenia, and a broader adjustment for mental illness in family members.

Method We established a population-based cohort of 2.66 million Danish people using data from the Civil Registration System linked with the Psychiatric Case Register.

Results Overall, 10 264 persons developed schizophrenia during the 50.7 million person-years of follow-up. The risk of schizophrenia was increased by urbanicity of place of birth and by family history of schizophrenia or other mental disorders.

Conclusions Urban–rural differences of schizophrenia risk were replicated and could not be associated with the potential sources of bias we assessed. Environmental factors underlying the effect of place of birth are major determinants of schizophrenia occurrence at the population level, although the effect of family history is the strongest at the individual level.

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A family history of schizophrenia is the strongest and best documented risk factor for the disease (Gottesman, 1991), but season and place of birth or upbringing have also been demonstrated to increase schizophrenia risk (Lewis *et al*, 1992; Marcelis *et al*, 1999; Mortensen *et al*, 1999). Mortensen *et al* (1999) indicated that environmental factors related to urbanicity may contribute to a substantial proportion of the population occurrence of schizophrenia. This finding was controversial (McGuffin & Gottesman, 1999) and our finding regarding attributable risk had a number of limitations, as it has not been replicated in other populations; was based on ICD–8 criteria, as opposed to the more operational ICD–10 criteria; was based only on in-patients, who may not be representative of the populations of patients with schizophrenia seen in psychiatry today; and was adjusted only for schizophrenia in family members, which may not account for urban–rural differences in other mental disorders related to schizophrenia. This study uses a large population-based sample to validate the previous findings by examining the influence of these potential sources of error.

METHOD

Study population

We used data from the Danish Civil Registration System (Malig, 1996) to obtain a large and representative data-set on Danish people. We identified all persons with known maternal identity born in Denmark between 1 January 1950 and 31 December 1993. The study population and their mothers, fathers and siblings were linked with the Danish Psychiatric Central Register (Munk-Jørgensen & Mortensen, 1997), which contains data on all admissions to Danish psychiatric in-patient facilities since April 1969 and on out-patient visits to psychiatric departments since 1995. From April 1969 to December 1993 the diagnostic system used was the ICD–8 (World Health Organization, 1967). From January 1994 the diagnostic system used was the ICD–10 (World Health Organization, 1992).

Study design

Overall, 2.66 million people were followed from their fifth birthday or 1 April 1970 (whichever came later) until onset of schizophrenia, death, emigration or 31 December 1998 (whichever came first). Cohort members were recorded as having schizophrenia if they had been admitted to a psychiatric hospital or received out-patient care with a diagnosis of schizophrenia (ICD–8 code 295 or ICD–10 code F20). Onset was defined as the first day of the first contact leading to a diagnosis of schizophrenia. Parents and siblings were categorised hierarchically with a history of schizophrenia (ICD–8 code 295 or ICD–10 code F20), 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), respectively, if they had been admitted or received out-patient care with one of these diagnoses.

Assessment of urbanicity

Independently of this study, Statistics Denmark (1997*a*) has categorised the 276 municipalities in Denmark in three main groups: (a) municipalities in the capital region; (b) municipalities where the largest city has more than 10 000 inhabitants; or (c) other municipalities. Furthermore, each main group, which holds approximately one-third of the population, was subdivided into four subgroups according to degree of urbanisation (Table 1). Note that the scale for classification of degree of urbanisation in the capital region is a mixture of geographic location and city size, whereas the scale for classification of degree of urbanisation in the remaining municipalities is uniform according to city size. In our previous study (Mortensen *et al*, 1999), this detailed 12-level classification of urbanisation was grouped into five categories: (1) capital; (2) capital suburb; (3) provincial city with more than 100 000 inhabitants; (4) provincial town with more than 10 000 inhabitants; (5) rural areas (see Table 1). By place of birth, we are referring to this five-level classification unless stated otherwise.

Denmark is a small homogeneous country with a population of 5.3 million people and a total area of 43 000 km^2.

Table 1 Distribution of 10 264 cases of schizophrenia, 50.7 million person-years at risk and estimates of relative risks for the total study population according to the detailed classification of degree of urbanisation of place of birth

Detailed degree of urbanisation of place of birth[1]	Cases (*n*)	Person-years	Relative risk (95% CI)[2]	
Municipalities in the capital region				
Capital (1)	3210	8 926 711	2.30	(2.04–2.60)
Capital suburb (2)	958	4 552 162	1.73	(1.51–1.98)
> 10 000 inhabitants in built-up area (4)	462	2 433 877	1.50	(1.29–1.74)
Other (5)	93	605 615	1.33	(1.06–1.69)
Municipalities where the largest city has more than 10 000 inhabitants				
Largest city has more than 100 000 inhabitants (3)	1300	6 429 845	1.58	(1.38–1.79)
Largest city has 40 000–99 999 inhabitants (4)	659	3 691 487	1.39	(1.21–1.60)
Largest city has 20 000–39 999 inhabitants (4)	1102	6 947 291	1.25	(1.10–1.43)
Largest city has 10 000–19 999 inhabitants (4)	688	4 367 539	1.22	(1.06–1.40)
Other municipalities				
50–100% of inhabitants in built-up[3] area (5)	512	3 450 250	1.14	(0.99–1.32)
33.3–50% of inhabitants in built-up area (5)	685	4 823 608	1.09	(0.95–1.25)
<33.3% of inhabitants in built-up area (5)	313	2 351 639	1.00	(0.85–1.17)
Outside built-up area (reference) (5)	282	2 118 632	1.00	

1. Numerals (1)–(5) refer to the 5-level classification of degree of urbanisation: (1) capital; (2) capital suburb; (3) provincial cities with more than 100 000 inhabitants; (4) provincial towns with more than 10 000 inhabitants; (5) rural area.
2. The relative risk was adjusted for age and its interaction with gender, calendar year of diagnosis, ages of the mother and father at the time of child's birth, season of birth and mental illness in a parent or sibling.
3. Built-up areas were defined by cities with more than 2000 inhabitants.

The population densities for the capital, capital suburbs, provincial cities, provincial towns and rural areas respectively are 5220, 845, 470, 180 and 55 people per km^2 (Statistics Denmark, 1997*b*). Distances are small in Denmark – most people live within 25 kilometres of a city with more than 30 000 inhabitants and even closer to a psychiatric hospital.

Statistical analysis

The relative risk of schizophrenia was estimated by log-linear Poisson regression (Breslow & Day, 1987) using the GENMOD procedure in SAS version 6.12 (SAS Institute Inc, 1997). All relative risks were adjusted for age, gender, interaction between age and gender, calendar year of diagnosis, age of the mother and father at the time of the person's birth, place and season of birth, and history of mental illness in parents or siblings. Age, calendar year of diagnosis and history of mental illness in siblings were treated as time-dependent variables (Clayton & Hills, 1993), whereas history of mental illness in a parent was treated as a variable that was independent of time. To obtain complete confounder control (Breslow & Day, 1980), age was categorised with the following cut-off points: 5, 14, 15, 16, 17, 18, 19, 20, 22, 24, 26, 28, 30, 35 or 40 years; calendar year was categorised in 3-year bands in the ICD–8 period and in 1-year bands in the ICD–10 period. Furthermore, maternal and paternal age at the time of the child's birth were categorised with the following cut-off points: 12, 18, 20, 22, 25, 30, 35, 40 or unknown.

To replicate the findings in our previous study (Mortensen *et al*, 1999), the effect of month of birth was modelled as a sine function with a period of 12 months, where both the amplitude and the time of peak risk were estimated. The variance of the time of peak risk and that of the amplitude were calculated by the delta method (Agresti, 1990). *P* values were based on likelihood ratio tests and 95% confidence intervals were calculated by Wald's test (Clayton & Hills, 1993). The adjusted-score test (Breslow, 1996) suggested that the regression models were not subject to overdispersion.

Attributable risk

The population attributable risk is an estimate of the fraction of the total number of cases of schizophrenia in the population that would not have occurred if the effect of a specific risk factor had been eliminated, that is, if the risk could have been reduced to that of the exposure category with the lowest risk. The estimation was carried out as described by Bruzzi *et al* (1985), on the basis of adjusted relative risks and the distribution of exposure in the cases.

Study Populations A–D

In order to compare our results with our previous study (Mortensen *et al*, 1999), to evaluate the effect of the change in the diagnostic criteria and the inclusion of out-patient information and to eliminate potential sources of bias in the selection of the study population used in our previous study, analyses of relative risk were performed separately for four mutually exclusive study populations: Study Populations A and B contained people whose mother was born in Denmark after 1 April 1935, and Study Populations C and D contained people whose mother was either born in Denmark before 1 April 1935 or was born outside Denmark. Incidence of schizophrenia was investigated in Study Populations A and C from 1 April 1970 to 31 December 1993 (ICD–8, in-patients) and in Study Populations B and D from 1 January 1994 to 31 December 1998 (ICD–10, in- and out-patients) (see Table 2).

Study Population A is almost identical to the study population used by Mortensen *et al* (1999). Compared with that study, it excludes persons born in foreign countries (32 062 people, 85 cases) and those with unknown place of birth (1506 people, four cases) and includes diagnoses for persons with schizophrenia admitted to a psychiatric hospital before 1 January 1994, who were diagnosed later than this date (104 cases).

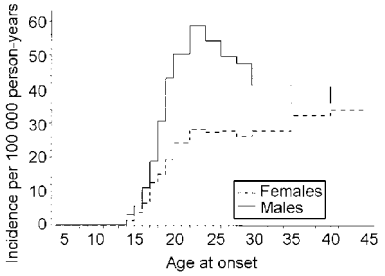

Fig. 1 Incidence of schizophrenia per 100 000 person-years at risk according to age and gender in a Danish population-based cohort of 2.66 million people where 10 264 people developed schizophrenia during 50.7 million person-years of follow-up.

Table 2 Adjusted relative risk of schizophrenia in a population-based cohort of 2.66 million Danish people according to family history of mental illness and place and season of birth

Variable	Relative risk (95% CI)[1]									
	Mother born in Denmark later than 1 April 1935				Mother either born in Denmark before 1 April 1935 or born outside Denmark				No maternal restrictions	
	Study Population A		Study Population B		Study Population C		Study Population D		Total study population	
	Follow-up 1970 to 1993		Follow-up 1994 to 1998		Follow-up 1970 to 1993		Follow-up 1994 to 1998		Follow-up 1970 to 1998	
Maternal history										
Schizophrenia	9.37	(7.67–11.4)	7.31	(5.76–9.27)	6.12	(4.88–7.67)	4.19	(2.65–6.62)	7.10	(6.28–8.01)
Schizophrenia-like psychoses	4.46	(3.61–5.50)	4.20	(3.33–5.31)	3.07	(2.52–3.76)	3.07	(2.15–4.37)	3.68	(3.28–4.13)
Other mental disorders	2.09	(1.89–2.32)	2.34	(2.10–2.60)	1.73	(1.58–1.90)	1.65	(1.39–1.95)	1.95	(1.85–2.06)
Mother not affected (reference)	1.00		1.00		1.00		1.00		1.00	
Paternal history										
Schizophrenia	6.54	(4.84–8.84)	4.74	(3.40–6.61)	4.95	(3.19–7.69)	4.05	(1.92–8.54)	5.39	(4.45–6.53)
Schizophrenia-like psychoses	3.36	(2.43–4.66)	3.43	(2.47–4.78)	2.69	(1.91–3.80)	2.78	(1.57–4.92)	3.11	(2.60–3.74)
Other mental disorders	1.77	(1.57–2.00)	1.77	(1.56–2.00)	1.64	(1.47–1.83)	1.72	(1.42–2.09)	1.73	(1.62–1.84)
Father not affected (reference)	1.00		1.00		1.00		1.00		1.00	
History in siblings										
Schizophrenia	6.12	(4.73–7.90)	5.11	(4.08–6.40)	6.74	(5.60–8.10)	4.45	(3.38–5.85)	5.68	(5.07–6.37)
Schizophrenia-like psychoses	3.82	(2.69–5.42)	2.82	(2.03–3.91)	3.28	(2.33–4.60)	3.77	(2.63–5.39)	3.36	(2.83–3.99)
Other mental disorders	2.16	(1.83–2.54)	1.74	(1.49–2.02)	2.13	(1.84–2.47)	1.75	(1.42–2.16)	1.96	(1.80–2.13)
No affected siblings (reference)	1.00		1.00		1.00		1.00		1.00	
Place of birth										
Capital	2.16	(1.92–2.43)	2.02	(1.77–2.30)	2.10	(1.92–2.30)	2.32	(1.98–2.73)	2.13	(2.01–2.25)
Capital suburb	1.56	(1.33–1.83)	1.54	(1.31–1.81)	1.64	(1.44–1.86)	1.71	(1.37–2.13)	1.60	(1.48–1.73)
Provincial cities	1.54	(1.34–1.77)	1.57	(1.36–1.82)	1.37	(1.22–1.54)	1.30	(1.05–1.61)	1.46	(1.36–1.56)
Provincial towns	1.26	(1.11–1.42)	1.19	(1.05–1.35)	1.25	(1.14–1.37)	1.07	(0.90–1.27)	1.21	(1.14–1.28)
Rural area (reference)	1.00		1.00		1.00		1.00		1.00	
Season of birth										
Amplitude	1.11	(1.05–1.17)	1.01	(0.95–1.07)	1.00	(0.96–1.05)	1.07	(0.99–1.16)	1.02	(1.00–1.05)
Time of peak (day/month)	6/3	(7/2–5/4)	[2]		[2]		24/5	(16/3–1/8)	25/3	(14/1–5/6)

1. The relative risk was adjusted for age and its interaction with gender, calendar year of diagnosis, ages of the mother and father at the time of child's birth, and all variables in the table.
2. A sine function with an amplitude of one has no time of peak.

RESULTS

A total of 10 264 persons (6933 males and 3331 females) developed schizophrenia during the 50.7 million person-years of follow-up. Figure 1 shows the incidence of schizophrenia per 100 000 person-years at risk according to age and gender. The incidence for males peaks at age 22–23 years at 58.8 cases per 100 000 person-years at risk, whereas the incidence for females peaks at ages above 40 years at 33.8 cases per 100 000 person-years at risk. Table 3 shows the distribution of persons who developed schizophrenia and the person-years of follow-up in the total study population, according to risk factors, study sub-population and gender. Among the 10 264 patients, 275 had a mother with schizophrenia, 107 had a father with schizophrenia and 319 had at least one sibling with schizophrenia. Overall, 2684 persons in Study Population A and 3924 people in Study Population C developed schizophrenia according to the ICD–8 criteria (in-patients), while 2452 people in Study Population B and 1204 persons in Study Population D developed schizophrenia according to the ICD–10 criteria (in- and out-patients).

The relative risks associated with the risk factors identified in our study are shown in Table 2 for Study Populations A, B, C, D and for the total study population. In all study populations, history of mental illness in a parent or sibling, referred to as family history of mental illness, increased risk significantly ($P<0.0001$) and the higher the rank of mental illness in family members, the higher the risk of developing schizophrenia.

Table 3 Distribution of 10 264 cases of schizophrenia and 50.7 million person-years at risk in a population-based cohort of 2.66 million Danish people

Variable	Cases (*n*)	Person-years
Gender		
Male	6933	26 878 929
Female	3331	23 819 726
Maternal history		
Schizophrenia	275	158 832
Schizophrenia-like psychoses	298	354 807
Other mental disorders	1606	3 718 334
Mother not affected	8085	46 466 682
Paternal history		
Schizophrenia	107	92 711
Schizophrenia-like psychoses	118	177 980
Other mental disorders	1072	2 880 251
Father not affected	8075	45 858 837
History in siblings		
Schizophrenia	319	129 561
Schizophrenia-like psychoses	134	97 902
Other mental disorders	625	908 315
No affected siblings	9186	49 562 876
Place of birth		
Capital	3210	8 926 711
Capital suburb	958	4 552 162
Provincial cities	1300	6 429 845
Provincial towns	2911	17 440 193
Rural area	1885	13 349 744
Study population		
A: ICD–8, mother born in Denmark 1935 or later	2684	24 551 052
B: ICD–10, mother born in Denmark 1935 or later	2452	8 971 004
C: ICD–8, mother born in Denmark pre-1935 or outside Denmark	3924	14 045 119
D: ICD–10, mother born in Denmark pre-1935 or outside Denmark	1204	3 131 480
Total	10 264	50 698 655

Comparison with previous study

For Study Population A, the addition of the late-diagnosed cases of schizophrenia (104 cases) and the exclusion of persons born abroad (85 cases) and with unknown place of birth (four cases) did not affect estimates of relative risk (Mortensen *et al*, 1999). The effect of place of birth was only slightly reduced when controlling for family history of schizophrenia, schizophrenia-like psychoses or other mental disorders instead of only for family history of schizophrenia. If we had chosen to adjust only for family history of schizophrenia, then for Study Population A the effect of place of birth would have been 2.37 (95% CI 2.11–2.67), 1.65 (95% CI 1.41–1.94), 1.58 (95% CI 1.37–1.82) and 1.29 (95% CI 1.15–1.46) for persons born in the capital, capital suburbs, the provincial cities or provincial towns, respectively, as compared with persons born in rural areas.

Family history

The relative risk associated with maternal history of mental illness differed significantly between study populations ($P<0.0001$) whereas the relative risks associated with history of mental illness in the father or siblings did not differ significantly between study populations ($P=0.65$ and $P=0.05$, respectively). Compared with people whose mother had neither been admitted to a psychiatric hospital nor had been in out-patient care, those with a mother with schizophrenia had a relative risk of 7.10 (95% CI 6.28–8.01), those having a mother with schizophrenia-like psychoses had a relative risk of 3.68 (95% CI 3.28–4.13) and those having a mother with other mental disorders had a relative risk of 1.95 (95% CI 1.85–2.06).

Urbanicity

The relative risk associated with urban birth did not differ significantly between study populations ($P=0.12$), and urban birth had a significant effect ($P<0.0001$) in all study populations. Compared with people born in rural areas, those born in the capital had a relative risk of 2.13 (95% CI 2.01–2.25). Furthermore, stratification by place of birth had no impact on age of onset, and the effect of place of birth was

not modified by gender (P=0.30), nor by year of birth (P=0.27).

The detailed (12-level) classification of urbanisation of place of birth had a significant effect ($P<0.0001$), see Table 1. Compared with those born outside built-up areas, those born in the capital had a relative risk of 2.30 (95% CI 2.04–2.60). In each main group of municipalities, the higher the degree of urbanisation of place of birth, the higher the risk of developing schizophrenia.

Seasonality

The effect of season of birth differed significantly between study populations (P=0.01). For Study Population A there was a significant effect of season of birth (P=0.0005): the amplitude of the sine function was estimated to be 1.11 (95% CI 1.05–1.17) and the time of peak was estimated to be 6 March (95% CI 7 February–April 5), meaning that persons born in early March had a risk 1.11 times that of those born in early June or early December. For Study Populations B, C, D and the total study population there was no significant effect of season of birth ($P>0.25$), and the effect of season of birth for Study Population A differed significantly from that of Study Populations B, C and D (P=0.02). For the total study population, the amplitude and the time of peak was estimated to be 1.02 (95% CI 1.00–1.05) and 25 March (95% CI 14 January to 5 June), respectively. Excluding out-patient information (1054 cases) did not result in any modifications of the effect of season of birth nor of the effect of family history of mental illness or place of birth. There was no interaction between season of birth and age at onset (P=0.85) or gender (P=0.14), and the effect of season of birth was not modified by year of birth (P=0.72).

Attributable risk

The attributable risks associated with the significant risk factors in the total study population are shown in Table 4. A family history of schizophrenia accounted for 5.4% of the cases of schizophrenia, meaning that if those with a mother with schizophrenia had the same risk as those with no maternal history of mental illness, 5.4% of the total number of cases would not have occurred. The 12-level classification of degree of urbanization of place of birth accounted for 34.3% of the cases of schizophrenia in the population, meaning that if those born in built-up areas had the same risk as those born outside built-up areas, 34.3% of the cases would not have occurred. In total, family history of mental illness and the 12-level classification of place of birth accounted for a total of 48.3% of the cases of schizophrenia in the population. The attributable risk associated with the 12-level categorisation of urbanicity is higher than the one associated with the five-level categorisation. This is obvious, since the 12-level categorisation compared with the five-level categorisation indicates a greater reduction in risk for a larger proportion of the population (see Tables 1–3).

DISCUSSION

Urbanicity

The effect of place of birth did not differ significantly between study populations, and it was nearly identical to that in our previous study (Mortensen *et al*, 1999). There was a dose–response relationship between degree of urbanisation of place of birth and subsequent risk of developing schizophrenia for both classification of degree of urbanisation (see Tables 1 and 2). The effect of place of birth in this study was only slightly reduced when adjustment for family history of schizophrenia was extended to adjustment for family history of mental illness. Therefore, the effect of place of birth in this and our previous study (Mortensen *et al*, 1999) cannot be explained by inadequate adjustment for mental illness in family members. Furthermore, the effect of place of birth was identical for Study Populations A, B, C and D, meaning that the effect of place of birth did not depend upon the diagnostic system used, the inclusion of out-patient information, or potential sources of bias in the selection of the study population used by Mortensen *et al* (1999). Furthermore, it is unlikely that differences in the availability of psychiatric services explain the urban–rural differences. In Denmark, services are free, distances are small and there were no urban–rural differences in age at onset, which means that there was no evidence of urban–rural differences in the threshold for psychiatric admission with schizophrenia.

The causes of urban–rural differences are unknown. A number of explanations, including methodological artefacts and differential exposure to specific risk factors, have been considered, for example, obstetric complications, infections, diet, toxic exposures, household crowding, exposure to pets, breast-feeding, or an artefact due to migration (Freeman, 1994; Mortensen, 2000). So far, we have evidence that differences are not due to selective migration (Mortensen, 2000), obstetric complications (Eaton *et al*, 2000; Kendell *et al*, 2000), socio-economic differences (Mortensen *et al*, 2000), or prenatal exposure to the influenza virus (Selten & Slaets, 1994; Westergaard *et al*, 1999). Obviously, our results above also show that the difference cannot be ascribed to differences in family history of mental illness, but neither we nor other groups have any positive evidence of factors that do explain it.

Table 4 Population attributable risk according to family history of mental illness and place of birth

Variable	Population attributable risk (%)
Mental illness in a parent or sibling	21.9
Schizophrenia in a parent or sibling	5.4
Schizophrenia-like psychoses in a parent or sibling	3.7
Other mental disorders in a parent or sibling	14.0
Place of birth, 5-level classification	28.9
Place of birth, 12-level classification	34.3
Mental illness in a parent or sibling and 5-level classification of place of birth	44.1
Mental illness in a parent or sibling and 12-level classification of place of birth	48.3

Seasonality

As seen in Fig. 1, the incidence of schizophrenia varies greatly within 5-year age bands. This was particularly evident in the age band from 15–19 years. To reduce the risk of introducing methodological artefacts described as residual confounding (Breslow & Day, 1980) or age-incidence (Lewis, 1989), we used a more detailed adjustment for age and calendar year of diagnosis than was used in our previous study (Mortensen *et al*, 1999). However, this had no influence on the estimates of relative risk.

Furthermore, using a Cox regression model (Andersen *et al*, 1997), entering age as a continuous variable gave estimates of relative risk identical to those presented in Table 2 for Study Population A. This approach excludes the possibility that age-incidence could generate an artificial season of birth effect. Therefore, we conclude that the effect of season of birth found for Study Population A and in the study reported by Mortensen *et al* (1999) was not due to residual confounding by age or calendar year of diagnosis.

The distribution of age, calendar year of diagnosis, year of birth, maternal and paternal age at time of person's birth, age gap to older siblings and birth order differed between Study Populations A, B, C and D. Therefore, we expected that the finding of an effect of season of birth in Study Population A and not in Study Populations B, C and D implied that the effect of season of birth was modified by one of these variables. Additional analyses were performed, but none of these potential effect modifiers revealed any consistent pattern among the study populations. We conclude that season of birth may be an effect of an unknown factor or factors more common in Study Population A than in Study Populations B, C and D, and that this sub-population cannot be identified by any one of the variables mentioned above. In contrast to a Finnish study by Suvisaari *et al* (2000), we have no evidence that the season of birth effect has changed over time or between birth cohorts. In conclusion, the previous findings of an effect of season of birth could not be generalised to this larger study population, and we have not been able to identify the reason for these differences between the study populations.

CLINICAL IMPLICATIONS

- Factors related to urban births may be major determinants of schizophrenia occurrence at the population level.
- Family history of schizophrenia is the strongest determinant of schizophrenia risk at the individual level.
- These results are invariant with regard to diagnostic system, inclusion of out-patient information and bias in selecting the study population.

LIMITATIONS

- Use of clinical diagnoses, not research diagnoses.
- Factors underlying the effect of birth are not identified.
- We only had data on a limited number of risk factors.

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Mental illness in family members

During the change of diagnostic system from the ICD–8 (1970–1993) to the ICD–10 (1994–1998), the incidence of being diagnosed with schizophrenia increased by 28%. As family members of patients with schizophrenia in the ICD–10 period had typically been diagnosed during the ICD–8 period, estimates of history of mental illness based on the ICD–10 period were attenuated slightly compared with estimates based on the ICD–8 period. Furthermore, family history of mental illness had a slightly higher effect for people with mothers born in Denmark later than 1935 compared with people with mothers either born in Denmark before 1935 or born outside Denmark. The earlier the mother's year of birth, the greater the probability that information on psychiatric diagnoses in parents were not included in the Danish Psychiatric Central Register, and the greater the probability of incomplete information on all siblings. However, these differences in relative risk were only minor and history of schizophrenia in family members was still the strongest individual risk factor.

It is highly plausible that both the effect of schizophrenia in family members and the effect of schizophrenia-like psychoses were due to genetic factors. However, it is less clear whether the relatively highly increased risk associated with a family history of other mental disorders was also due to genetic factors or if it was due to other mechanisms, for example, socio-economic differences.

Attributable risk

A relative risk measures an individual's own risk of acquiring a disease, whereas an attributable risk measures the impact this relative risk has on the population occurrence of the disease, that is, the attributable risk has two determinants, the relative risk and the frequency of exposure in the population. Even though the relative risk associated with urban birth is low, the very high frequency of urban births in the population results in a high attributable risk. Conversely, the very high relative risk associated with schizophrenia in a mother and the very low frequency of children having a mother with schizophrenia results in a moderate attributable risk. Therefore, to measure the impact of an exposure at the individual level, the relative risk should be used, whereas the attributable risk measures the impact of an exposure at the population level.

Of course, the attributable risk associated with a family history of mental illness should not be taken as an indicator of the potential theoretical impact of eliminating genetic factors, factors that probably would not often be expressed as schizophrenia. That impact may well be 100% for one or several genetic factors if all are necessary causes. In other words, genetic factors may largely determine how many individuals might develop schizophrenia, but relatively common factors, some linked

to urbanicity, may strongly influence how many individuals do develop the disease.

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