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Regional variation in the incidence of schizophrenia in Finland: a study of birth cohorts born from 1950 to 1969

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ABSTRACT

Background. We investigated whether there is regional variation in the incidence of schizophrenia and if so, whether it is caused by urban–rural differences, larger spatial clustering, or both. To control for the effect of migration, we examined regional variation in the incidence according to place of birth.

Methods. Finnish birth cohorts born from 1950 to 1969 were followed in the National Hospital Discharge Register from 1969 until 1991, and all cases of schizophrenia (ICD-8 or ICD-9 295) were identified ($N = 14828$). Forty-eight of the 559 municipalities were classified as urban and 25% of the Finnish population lived in these municipalities in 1960. For the analysis of spatial clustering, municipalities were grouped into 57 functional small-areas. We used Poisson regression model with the number of births of individuals who later developed schizophrenia as a response variable, and place of birth (urban/rural), birth cohort (1950–54, 1955–9, 1960–64, and 1965–9), functional small-area units, and sex as response variables.

Results. The incidence was slightly higher among the rural-born in the oldest birth cohort. In the other cohorts, it was higher among the urban-born, and the difference between urban and rural born increased in the youngest cohorts. Significant spatial clustering of schizophrenia was observed in eastern Finland.

Conclusions. Urban birth is a risk factor for schizophrenia in Finland in cohorts born since 1955. However, genuine spatial clustering of schizophrenia in eastern Finland was also observed, possibly caused by genetic isolation.

INTRODUCTION

Schizophrenia occurs worldwide, but reported prevalences vary widely, the range exceeding 50-fold from the lowest (0·3 per 1000) to the highest 22 per 1000) (Torrey, 1987; Hovatta *et al.* 1997)). Both the highest (Hovatta *et al.* 1997) and the lowest (Torrey, 1987) prevalences have been observed in isolated populations. Significant regional variation is also seen in the incidence of broadly defined schizophrenia, but the range is much narrower than the prevalence (Jablensky *et al.* 1992). However, subpopulations with exceptionally high incidence have been identified (Harrison *et al.* 1997).

Besides variations between countries, significant differences in the occurrence of schizophrenia within countries have been detected. Differences between urban and rural areas have been reported on the one hand, and differences between larger regional units such as states, counties, or municipalities on the other. A higher incidence or prevalence of schizophrenia has been reported among those born (Marcelis *et al.* 1998; Mortensen *et al.* 1999), brought up

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(Lewis *et al*. 1992), or living (Freeman, 1994; Widerlöv & Lindström, 1997; Schelin *et al*. 2000) in urban areas, although living in urban areas seems to be associated with increased risk of later development of schizophrenia simply because it correlates with urban birth (Marcelis *et al*. 1999). Finland is an exception in this regard in that both prevalence and incidence have been higher than urban areas (Suominen, 1975; Lehtinen *et al*. 1990). However, worldwide the highest morbid risks of schizophrenia have been observed in isolated rural areas (Böök *et al*. 1978; Hovatta *et al*. 1997).

Differences in the occurrence of schizophrenia between larger regional areas have been observed in several countries. In the United States, the rates of hospital-treated mental illnesses and schizophrenia, measured in 9 separate years between 1880 and 1963, were consistently higher in Northeastern and Pacific Coast States compared with the rest of the country (Torrey, 1990). In Croatia, the cumulative incidence of schizophrenia among the population born in 1953 was highest in southern, coastal parts of the country and lowest in eastern, inland parts of the country (Folnegovic & Folnegovic-Smalc, 1992). An Irish study conducted in an isolated rural county found evidence of geographic variation (Youssef *et al*. 1991) that was more prominent among females than males (Youssef *et al*. 1993). In Finland, prevalence and incidence are highest in eastern and northern Finland and lowest in southwestern Finland (Salokangas *et al*. 1987; Lehtinen *et al*. 1990; Hovatta *et al*. 1997; Korkeila *et al*. 1998) and pockets of exceptionally high prevalence have been observed in eastern and northeastern Finland (Hovatta *et al*. 1997).

If these differences are caused by an uneven distribution of risk factors for schizophrenia, they are of considerable significance to aetiological research. However, the observed differences may also have resulted from variations in diagnostic practice (Leff, 1977), problems in defining the population denominators for subgroups (Mortensen *et al*. 1997), or by selective migration (Folnegovic & Folnegovic-Smalc, 1992; Freeman, 1994). In fact, the opinion that the incidence of schizophrenia is uniform across cultures is widely held (Jablensky *et al*. 1992; McGlashan & Hoffman, 2000).

In Finland, excellent health-care and population registers ensure that information on both schizophrenia patients and general population is accurate throughout the country, and the validity of register diagnosis of schizophrenia is acceptable throughout the country, with a higher tendency toward false-negative than false-positive schizophrenia diagnosis (Pakaslahti, 1987; Mäkikyrö *et al*. 1998; Isohanni *et al*. 1997). However, extensive internal migration and rapid urbanization occurred in Finland after World War II. In the 1960s considerable migration to Sweden also took place. Thus, selective migration might explain the high incidence and prevalence of schizophrenia in eastern and northeastern Finland, which is economically disadvantaged compared with the rest of the country. To control for the effect of migration, we investigated regional differences in the incidence of schizophrenia according to place of birth instead of current residence.

The aim of this study was to investigate urban–rural differences and larger regional variation in the incidence of schizophrenia in Finland when calculated according to the place of birth. A historical cohort design involving birth cohorts born in Finland from 1950 to 1969 was applied in the study.

METHOD

Register data

The study population consisted of birth cohorts born in Finland from 1950 to 1969 and was almost identical to that used in our previous study (Suvisaari *et al*. 2000). Birth cohorts were identified from the Population Register Center, which provided sex-specific, monthly numbers of births in each Finnish municipality. ($N = 559$ from 1950 to 1969) as multi-dimensional tables with sex and year, month and place of birth as marginals. From each of the cohorts thus formed we obtained the number of deaths up to 1969 and the number of deaths from 1970 to 1991. Persons born outside Finland or of unknown birthplace were excluded.

The National Hospital Discharge Register was used to identify all persons who had been hospitalized because of schizophrenia before 1 January 1992. Background demographic variables for each affected individual were obtained from the Population Register Center.

Table 1. *Schizophrenia incidence per* 1000 *person-years in Finland for cohorts born* 1950–1969. *Confidence limits for relative risk* (*RR*) *are based on a Poisson regression model with one variable at a time in the model. Significances of univarite models with sex, birth year, or age were* $P < 0{\cdot}001$, *and for urbanization* $P = 0{\cdot}1520$

	Cases	Person years	Incidence	RR
Sex				
Female	6388	13055	0·4893	Reference
Male	8440	13434	0·6283	1·2840 (1·2429, 1·3264)
Birth year				
1950–54	6301	9760	0·6456	Reference
1955–9	4467	7858	0·5685	0·8806 (0·8475, 0·9150)
1960–64	2712	5559	0·4879	0·7557 (0·7225, 0·7905)
1965–9	1348	3313	0·4069	0·6304 (0·5944, 0·6685)
Age				
15–18	1335	4069	0·3281	Reference
19–20	2208	3159	0·6989	2·1302 (1·9902, 2·2800)
21–22	2499	3247	0·7696	2·3455 (2·1947, 2·5066)
23–24	2126	3038	0·6998	2·1329 (1·9918, 2·2840)
25–26	1818	2736	0·6646	2·0254 (1·8873, 2·1737)
27–28	1478	2425	0·6095	1·8576 (1·7250, 2·0002)
29–30	1135	2104	0·5394	1·6439 (1·5188, 1·7793)
31–35	1655	3858	0·4290	1·3073 (1·2164, 1·4051)
36–41	574	1853	0·3097	0·9440 (0·8561, 1·0411)
Urbanization				
Non-urban	11006	19797	0·5559	Reference

Annual data were obtained for 1969–91 from each of the registers and linked using personal identification numbers, which code the date of birth and sex and are unique for each person.

Age at onset was defined as age at the beginning of first hospitalization for any psychotic disorder (ICD-8 and ICD-9 codes 295–299), which is a closer approximation of the true age at onset than the age of first hospitalization for schizophrenia.

Each of the 559 municipalities was categorized as urban or rural based on the information of census 1960. A municipality was classified as urban if at least 95% of its inhabitants lived in settlements where the distance between neighbouring houses was less than 200 metres and the population in these settlements exceeded 200. Forty-eight of the 559 municipalities were classified as urban and 25% of the Finnish population lived in these municipalities in 1960.

For the analysis of spatial clustering, municipalities were grouped into 57 functional small-area units (Löytönen & Maasilta, 1997). Each functional area comprises a central nodal region within which regional interactions take place, and a subordinated surrounding area.

Statistical methods

An ordinary Poisson regression model was used to analyse incidence rates in the functional small-area units (Breslow & Day, 1987; McCullagh & Nelder, 1994). In this model the variables were, age (15–18, 19–20, 21–22, 23–24, 25–26, 27–28, 29–30, 31–35, 35–41), sex (female, male), birth year (1950–54, 1955–9, 1960–64, 1965–9) and degree of urbanization (rural, urban). Also the 57 small-areas were used as categorical explanatory variables producing one parameter estimate for each small-area unit. The response variable was the frequency of schizophrenia cases in the life-table cell, the number of person-years in the cell being used as an offset term.

RESULTS

Males had a 28% higher incidence of schizophrenia than females, and the age-specific incidence was highest in the 21–22 year age group (Table 1). The incidence declined between birth cohorts born in the 1950s and 1960s, as reported earlier (Suvisaari *et al.* 1999). The

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Table 2. *Poisson regression model for incidence of schizophrenia in Finland for cohorts born* 1950–1969. *Terms added sequentially into the model*

	df	Deviance	*P*
Sex	1	229	< 0·0001
Birth cohort	3	331	< 0·0001
Age	8	1662	< 0·0001
Urbanization	1	6	0·0113
Region	56	786	0·0000
Age–sex interaction	8	47	< 0·0001
Urbanization–birth cohort interaction	3	17	0·0006
Age–birth cohort interaction	19	43	0·0012

relative risk for birth cohort 1965–9 was 27% lower compared with the 1950–54 cohort. In the univarite analyses the difference between rural and urban place of birth was not significant.

The Poisson regression model detected significant interactions between sex and age, urban/rural birthplace and birth cohort, and age and birth cohort (Table 2). The interaction between sex and age showed that the peak of incidence in respect to age was sharper among males than females. This accords with our earlier results, which showed bimodality in the age at onset among females (Suvisaari *et al*. 1998). The interaction between urbanization and birth cohort was caused by significant change in the effect of urban environment between the older and younger cohorts (Fig. 1). In the oldest cohort (1950–54) the risk was higher in rural environment, but in the youngest cohort (1964–9) the risk was higher in the urban settlements.

The map of relative risks for functional small-areas was created by using Helsinki area as reference and calculating relative risks for other areas using parameter estimates from Poisson regression model, where small-areas were used as categorical explanatory variables. The map of relative risks for small-areas demonstrates clustering of high incidence in eastern parts of

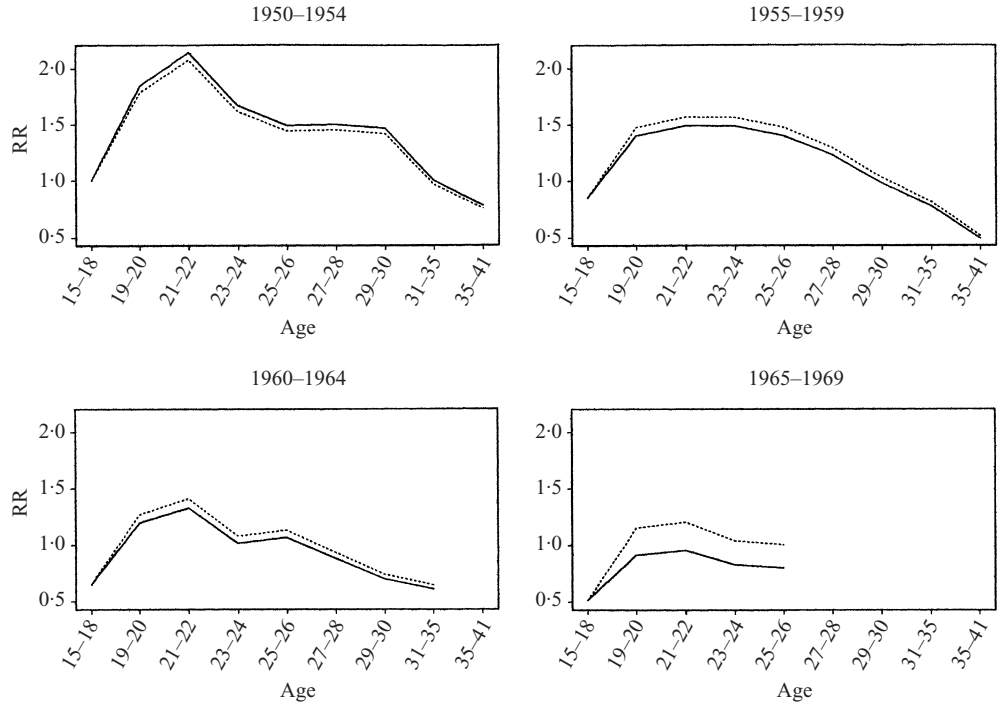

FIG. 1. The relative risk of schizophrenia in Finland for cohorts 1950–1969 in respect to age, birth cohort and degree of urbanization. Estimated with Poisson regression model with age, birth cohort, sex, degree of urbanization, region and their significant interactions as covariates (—, rural; ---, urban).

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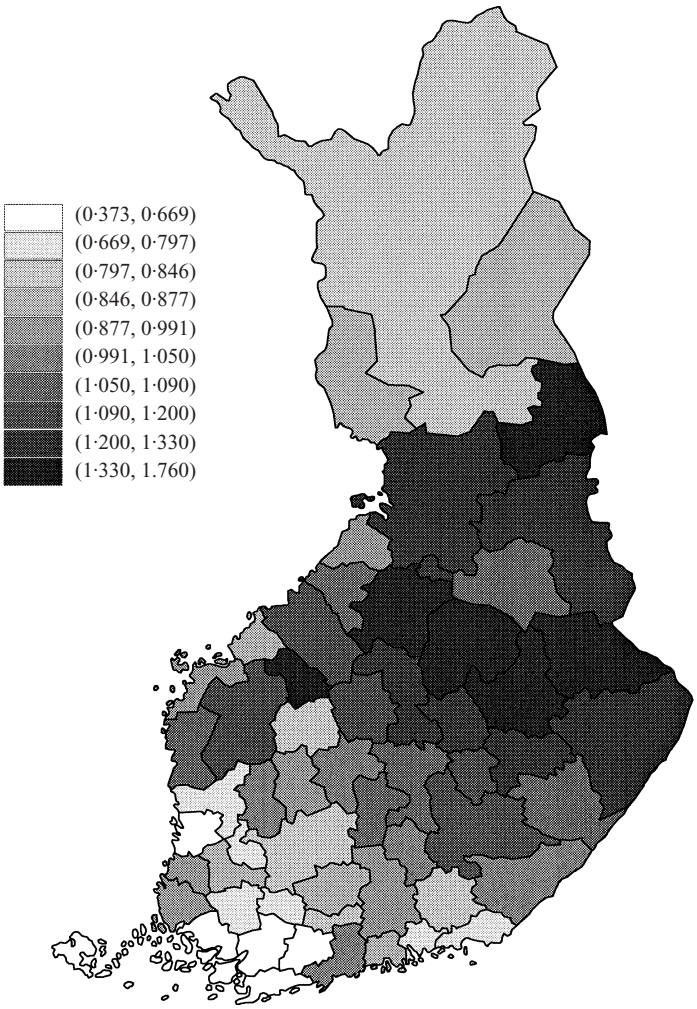

FIG. 2. The relative risk of schizophrenia in Finland for cohorts 1950–1969 in respect to region, Helsinki region used as reference. Estimated with Poisson regression model with age, birth cohort, sex, degree of urbanization, region and their significant interactions as covariates.

Finland (Fig. 2). These relative risks are adjusted for age, birth cohort, sex, urbanization, and their significant interactions. Thus, the observed variation in the relative risks are due to other, unmeasured factors, that are connected to the regions.

DISCUSSION

In our previous studies on the incidence of schizophrenia, we found a significant decline in the incidence of schizophrenia between cohorts born in the 1950s and 1960s (Suvisaari *et al.* 1999). The incidence declined more rapidly among the rural-born than among the urban-born (Suvisaari *et al.* 2000). We also found a prominent seasonal variation of births among patients born from 1955 to 1959, which declined considerably among those born in the 1960s (Suvisaari *et al.* 2000). Seasonal variation of births among unaffected siblings was otherwise similar to that observed among patients, but the increase in the magnitude of seasonal variation among those born from 1955 to 1959 was

limited to patients (Suvisaari *et al*. 2001). Our current study complements these findings in providing information on the regional variation in the incidence. Our results suggest that the clustering of schizophrenia in eastern Finland is not caused by selective migration and that in Finland also urban birth has emerged as a risk factor for schizophrenia.

Urban–rural differences in the incidence of schizophrenia

The emergence of urban birth as a risk factor of schizophrenia in Finland suggests that the factors in urban living that confer increased risk of developing schizophrenia may not have existed in Finland until the 1960s, or that the intensity of the factors is increasing. Alternatively, the same factors may have been more prevalent in rural areas before the 1960s. Cooper & Sartorius (1977) have suggested that the rapid increase in size of towns caused by industrialization in the 19th century caused cultural and environmental changes, which increased the risk of poor outcome among patients with schizophrenia and possibly also increased the incidence of schizophrenia during the 19th century (Hare, 1983). In Finland, urbanization occurred much later than in other European countries (Korkiasaari & Söderling, 1994). Large scale migration from rural to urban communities started after World War II and was most extensive in the early 1960s (Korkiasaari & Söderling, 1994). The economical structure has changed exceptionally rapidly in Finland: only in Greece has the proportion of rural population decreased as rapidly since 1960, and unlike in other Western countries, the proportion of population working in industry continued to increase until the early 1970s (Korkiasaari & Söderling, 1994). Thus, it seems possible that the factors associated with urban birth that increase the risk of schizophrenia may not previously have existed in Finland.

In other countries, the highest incidences of schizophrenia have been found in central city areas, which usually are socially deprived (Freeman, 1994). A study examining geographic patterns of development in Finland during the 1950s found that none of the 219 least developed municipalities were urban (Palmgren, 1964). These differences between Finland and other Western countries may explain why rural birth used to be a risk factor of schizophrenia. The increase in the effect of urban birth is consistent with a recent Dutch study (Marcelis *et al*. 1998).

Regional clustering of schizophrenia

The observed clustering of schizophrenia in eastern Finland accords with previous findings of higher incidence (Salokangas *et al*. 1987; Korkeila *et al*. 1998) and prevalence (Lehtinen *et al*. 1990; Hovatta *et al*. 1997) among those who live there. The high incidence among persons who have been born in these areas suggests that early risk factors of schizophrenia, either genetic, environmental, or both, have accumulated there.

Genetic isolation and enrichment of genes predisposing to schizophrenia may be the best explanation of the observed eastern Finland cluster. The settlement of eastern and northern Finland by small founder populations began only in the 1500s, and regional isolates formed at that time have remained surprisingly stable. The routes of this internal movement are seen in the regional distribution of many simple Mendelian single gene mutations of the Finnish disease heritage (Norio, 1981; De la Chapelle & Wright, 1998; Peltonen *et al*. 1999), and the observed regional clustering of schizophrenia coincides with the borders of this late settlement area. It is also noteworthy that in Sweden, on the border with Finnish Lapland, one of the world's highest prevalences of schizophrenia has been reported in a Finnish-speaking isolate founded by the same migration movement (Böök *et al*. 1978).

However, the high incidence in eastern and northeastern Finland may also have been caused by clustering of environmental risk factors. Almost the entire northern and eastern Finland areas belonged to the least developed regions in Finland in the 1950s (Palmgren, 1964). Infant mortality was severalfold higher, duration of pregnancies shorter and newborns significantly more often underweight in eastern and northern Finland than in southern and western Finland (Timonen *et al*. 1966). Thus, pre- and perinatal adverse events could be one factor involved in the clustering of schizophrenia there. The low standard of living may also increase the risk of prenatal and childhood infections, which have

long been suspected as risk factors for schizophrenia (Yolken & Torrey, 1995), or cause poor nutrition during pregnancy, another factor known to be associated with increased risk for later development of schizophrenia (Susser *et al*. 1996).

Limitations

The validity of our findings depends on the accuracy of Finnish registers and on the reliability of clinical diagnosis of schizophrenia. The accuracy of data on psychiatric diagnoses in the Finnish Hospital Discharge Register was studied in 1986 and found to be excellent (Keskimäki & Aro, 1991). The primary diagnosis in the register and in the hospital case notes was identical in 99% for schizophrenia and 98% for all mental disorders, and the dates of admission and discharge were identical in 96% of the cases. The information in the Pension and Free Medicine Registers is accurate, because the payment of these benefits is based on the registers. Internal migration from eastern and northern Finland and emigration to Sweden started in the later 1950s. This could have caused changes in the regional incidence patterns if the mobility of parents of future schizophrenia patients somehow differed from that of the general population. However, a similar regional pattern was observed among the birth cohorts born in the 1940s, which proves that the regional pattern was already present in this period (data not shown). However, we chose to exclude these cohorts from the final analysis because of the missing follow-up information from the 1960s and because of the special characteristics of wartime internal migration.

Because of the definition of urban residence, there is large variation in the degree of urbanization in non-urban settlements. On the other hand, urban areas are quite uniformly urban. The information of urbanization was based on the 1960 census, which is in the middle of our birth cohorts. Because large changes took place in the population structure in Finland from 1950 to 1969, using the 1960 census data seemed reasonable. In a previous publication, we regarded only the three largest towns, Helsinki, Tampere and Turku, as urban (Suvisaari *et al*. 2000). In 1960, 16% of the population lived in these towns. The definition used in this study added 45 municipalities as urban. Nine per cent of the population lived in these 45 municipalities, which mainly consisted of old Finnish towns that tended to be rather small but had high population density. Because the factors related to urban birth that confer increased risk of developing schizophrenia are unknown, there is no correct definition of 'urban birth'. A definition based on population density seemed reasonable and has been used before (Verdoux *et al*. 1997; Marcelis *et al*. 1998).

Clinical diagnosis of schizophrenia is less reliable than a research diagnosis. However, studied that compare research diagnoses based on structured clinical interviews (Kuusi, 1986; Pakaslahti, 1987; Salokangas *et al*. 1987; Cannon *et al*. 1998*a*) or all available case note information (Isohanni *et al*. 1997; Mäkikyrö *et al*. 1998) have observed that Finnish psychiatrists tend to apply a narrow definition of schizophrenia in their clinical practice, with more tendency toward false-negative than false-positive diagnoses. This applies to all studies, regardless of whether they were conducted in southern (Kuusi, 1986; Pakaslahti, 1987; Cannon *et al*. 1998*b*) or northern (Isohanni et al. 1997; Mäkikyrö *et al*. 1998) Finland. Also, the rate of both psychotic and non-psychotic affective disorders has been highest in eastern Finland in previous studies (Suominen, 1975; Korkeila *et al*. 1998), suggesting that diagnostic shifts do not account for the high rate of schizophrenia in this area.

Conclusions

We observed two types of regional variation in the incidence of schizophrenia according to place of birth in Finland. Urban birth emerged as a risk factor of schizophrenia in Finland among birth cohorts born in the 1960s, suggesting either that the factors in urban living that confer increased risk of developing schizophrenia compared with living that confer increased risk of developing schizophrenia compared with living in rural areas may not have existed in Finland before, or that their intensity is increasing. We also observed significant clustering of schizophrenia in eastern Finland suggesting that risk factors that operate early in life, either genetic, environmental, or both have accumulated there. Our results indicate that the

analysis of regional distribution of a disease may provide valuable information for aetiological research.

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