Association between psychotic disorder and urban place of birth is not mediated by obstetric complications or childhood socio-economic position: a cohort study

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ABSTRACT

Background. Although urban place of birth has been identified as a risk factor for schizophrenia, the extent to which this association is mediated by socially patterned risk factors such as obstetric complications and childhood socio-economic position is unclear. The diagnostic specificity of the association within the clinical psychotic syndromes is also unclear.

Method. A population cohort of 696 025 males and females, born in Sweden between 1973 and 1980 and with linked birth and socio-economic data was followed up from age 16 for up to 9·8 years. Hospitalized cases of schizophrenia and other non-affective psychosis were identified from the Swedish Inpatient Discharge Register. We examined associations of these disorders with a three-level measure of urbanicity of birthplace before and after controlling for measures of foetal nutrition, obstetric complications and level of maternal education.

Results. Urban compared to rural birthplace was associated both with increased risk of adult onset schizophrenia (hazard ratio 1·34, CI 0·91–1·96) and other non-affective psychoses (hazard ratio 1·63, CI 1·18–2·26). None of these associations was greatly affected by adjustment for obstetric complications or maternal educational level. In the group of other non-affective psychoses urban–rural differences in disease risk were strongest among those born in the winter months.

Conclusion. Urbanization of birthplace is associated with increased risk of non-affective psychosis but this is not confined to narrowly defined cases. The magnitude of the association in Sweden is lower than that reported in other studies. Causal factors underlying this association appear to operate independently of risks associated with obstetric complications and parental educational status.

INTRODUCTION

Population-based studies indicate that people born in urban areas are at increased risk of schizophrenia and that the increased risk is independent of family history of psychosis. Studies in Denmark, a small homogeneous country with a population of 5·3 million, report relative risks (RR) of between 2·13 and 2·40 (Mortensen et al. 1999; Pedersen & Mortensen, 2001 a, b). The strength of associations seen in studies carried out in other social and cultural settings are generally lower. In the Netherlands, Marcelis et al. (1998) reported a RR of 1·84 and in the USA (Torrey et al. 1997), analyses based upon 1980 Census data reported a RR of 1·66. In the Untied Kingdom, Takei et al. (1995) showed a
marginal risk of schizophrenia (odds ratio (OR) 1.12, 95% CI 1.06–1.19) for persons born in city areas compared with non-city areas, although they used non-schizophrenic psychiatric admissions as their control population. A Finnish study of four birth cohorts spanning the period 1950–1969 (Haukka et al. 2001) found that urban place of birth marginally increased the risk of schizophrenia in all cohorts, except for those born after 1965, when incidence was increased by about 25% in relation to urban residency. In Sweden, Lewis et al. (1992) reported a relative risk of 1.65 (CI 1.19–2.28) for those brought up in cities compared with rural areas, but their study was carried out on males only.

The biological and social mechanisms that could mediate this association are unclear. The association reported by Lewis et al. (1992) remained after adjusting for several possible confounding factors known to be connected with urban residence, including family history, cannabis use and parental divorce. Machon et al. (1983) and Takei et al. (1995), report an interaction with season of birth (place of residence associations were stronger among cases who were born in winter) but this was not replicated by Mortensen et al. (1999) or by Pedersen et al. (2001a, b). Obstetric complications are known to be socially patterned (Jonas et al. 1992; Wilcox et al. 1995; Gudmundsson et al. 1997) but the potential role of obstetric complications and childhood socio-economic position as possible mediating variables in relatively unexplored. Eaton et al. (2000) investigated obstetric complications (but not socio-economic position) in a record-linkage study involving a small sample of early onset cases of schizophrenia, and cases of other non-affective and affective psychoses. After controlling for maternal parity, the OR for those born in Copenhagen compared with rural areas was 4.34 (95% CI 2.45–7.69). The association was little different after controlling for other obstetric factors including birth weight and mode of delivery. In addition, the association with non-affective psychosis was stronger than that with schizophrenia (OR 5.72, 95% CI 3.74–8.73) suggesting that urbanization of birthplace may not be specific to schizophrenia.

To investigate these questions further, we assembled a cohort based upon linked birth, socio-economic and psychiatric admission data from Sweden. We examined the association between urbanization of birthplace and the risk of adult onset (>16 years) schizophrenia and other non-affective psychoses. We then investigated the distribution of the potentially confounding risk factors of obstetric complications and childhood socio-economic position across a three-level measure of urbanicity. Finally, we examined the extent to which urban–rural birthplace differences in schizophrenia are due to the social patterning of obstetric complications and childhood socio-economic position in urban areas.

METHOD
Population
The risk set was based upon 747,432 males and females, born in Sweden between 1973 and 1980, and still alive and resident in Sweden at the age of 16. We excluded all subjects diagnosed with schizophrenia or other non-affective psychosis before the age of 16. Overall, 51,407 (6.9%) subjects were excluded from the main analysis on account of missing data for one or more of the factors investigated.

Our main analyses were therefore based on 696,025 subjects. Information on the study sample was obtained from a linkage between the Swedish Medical Birth Registry (MBR), the Population and Housing Censuses of 1970 and 1990, and the Swedish Inpatient Discharge Register (up to December 1997).

Our analysis was based on hospital admissions between 1989 and 1997. Admissions were coded using the International Classification of Diseases (ICD-9) (WHO, 1978) was used in Sweden from 1987 to 1996 and ICD-10 (WHO, 1993) has been used since 1997. We examined associations with all non-affective, non-drug related psychoses (ICD-9 295, 297–298; ICD-10 F20–29), categorizing these disorders into two groups: (1) people admitted with a diagnosis of schizophrenia (ICD-9 295; ICD-10 F20) at any point in the period of follow-up; (2) all remaining non-schizophrenic non-affective psychoses (ICD-9 297–298, ICD-10 F21–29). Many subjects had more than one hospital admission, with different diagnoses. We therefore carried out an additional analysis based upon a more restrictive definition for schizophrenia: if...
subjects were admitted on more than one occasion, we used the latest diagnosis as we assumed this to be the most accurate. Using this method of case definition, the number of cases of schizophrenia fell from 363 to 303.

Subjects were followed up for a mean of 5.1 years (range: 1 day to 9.8 years) after the age of 16.

**Risk factors**

**Place of birth**

Place of birth was coded using a nine-category classification: (1) main cities (Stockholm, Gothenburg, and Malmo); (2) suburbs to main cities; (3) large cities (population 50–200,000); (4) medium size cities (population 20–50,000); (5) industrial municipalities (where > 40% of the population is employed in the industrial sector regardless of city size); (6) other larger municipalities (population 15–50,000); (7) municipalities in rural areas; (8) sparsely populated areas; (9) other smaller municipalities (population < 15,000). We classified place of birth according to the degree of urbanization based upon this nine-point classification. To reduce the number of categories, we grouped these nine categories (on the basis of a division decided *a priori*) into a three level measure (coded 1 to 3 in the following order): main cities and their suburbs (categories 1 and 2); large and medium size cities (categories 3, 4, 5 and 6) and rural areas (categories 7, 8 and 9).

**Obstetric complications and measures of foetal nutrition**

We extracted data on the following indicators: birth weight; birth length; gestational age; season of birth; age of mother (at childbirth); Caesarean section; APGAR score at 1 min; and parity.

**Childhood socio-economic position**

We used maternal education as an indicator of childhood socio-economic position. We had information on paternal education, but as this was missing for 10% of subjects this variable was not included in our main analysis. Education was categorized into four groups: < 9 years; 9–10 years; full secondary education; higher education.

**Statistical methods**

All analyses were carried out in STATA (Stata-Corp, 2001). We used ANOVA and chi-square statistics as appropriate to test for association of potentially confounding factors with urbanicity. We used Cox’s proportional hazards models to assess the influence of degree of urbanization on the risk of schizophrenia and other non-affective psychosis. We tested the validity of the proportional hazards assumption graphically with log–log plots. We also compared hazard ratios for incidence of schizophrenia for each half of the time period and found these to be comparable. All analyses were controlled for age (by using it as the time axis in the Cox model) and for sex. We assessed the effects on hazard ratios of controlling for our specified obstetric complications, entering the following obstetric explanatory variables separately: birth weight (as five categories: < 2500 g, 2501–3000 g, 3001–3500 g, 3501–4000 g, and > 4000 g); birth length (as a continuous term); gestational age (≤ 36, 37–41 and ≥ 41 weeks); season of birth (spring, summer, autumn, winter (defined as December, January and February)); APGAR score at 1 min (≤ 6 or > 7); maternal parity (1, 2 or ≥ 3); Caesarean section birth; maternal age (≤ 20, 20–24, 25–29, 30–34, ≥ 35). Lastly, we assessed the effect of controlling for maternal education (a four level variable, full model). Tests for interaction were based on likelihood ratio tests comparing models with and without the relevant explanatory variables. Subjects were censored at the time of first admission for non-affective, non-drug-related psychotic illness, death or emigration.

**RESULTS**

Three hundred and sixty-three (0.05%) subjects were admitted to hospital with a diagnosis of schizophrenia at least once in the period of follow-up and 590 (0.08%) were admitted with a diagnosis of non-affective, non-schizophrenic psychosis. The time between the age of 16 and hospital admission for schizophrenia ranged from 0.04 to 8.32 years and for non-affective, non-schizophrenic psychoses from 0.01 to 8.82 years. The annual incidence rate for schizophrenia was 0.10 per 1000 person years and for non-schizophrenic, non-affective psychosis was 0.17 per 1000 person years.
Those with missing data tended to be of lower birth weight (101 g lighter); shorter at birth (0.4 cm shorter), were more likely to be born before 36 weeks gestation (7.69% vs. 3.97%); were more likely to have been born in the winter (December–February: 26.15% vs. 23.54%); to be male (52.02% vs. 51.32%); and to have a lower level of maternal education (<9 years, 19.70% vs. 13.00%). All these differences were statistically significant because of the large sample size.

There was no evidence of interaction between sex and place of birth with respect to their effects on schizophrenia ($P=0.55$) or...
non-schizophrenic, non-affective psychosis ($P = 0.54$). Our analyses were therefore based on the dataset combining male and female subjects.

**Table 1. Characteristics of subjects with schizophrenia and other non-affective psychoses**

<table>
<thead>
<tr>
<th>Municipality</th>
<th>Cases (N)</th>
<th>Person-years</th>
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<th>Schizophrenia (N = 363)</th>
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**Table 2. Age and sex adjusted hazard ratios of schizophrenia and non-affective non-schizophrenic psychosis for all nine categories of municipality of birth place**

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**Characteristics of subjects with schizophrenia and other non-affective psychoses**

Table 1 shows the distribution of the variables used in the analysis for cases of schizophrenia, non-affective non-schizophrenic psychoses and for our reference population of non-cases (controls). Of the non-cases, 10-9% were born in rural areas (categories 7, 8, 9). The figure was slightly lower for schizophrenia (9-4%), and lower again (7-7%) for non-affective, non-schizophrenic psychoses. Of our control population 13-5% were born in the main cities compared to 18-5% in the schizophrenia group and 16-3% of the cases of other non-affective psychoses. Those with schizophrenia were more often born in the winter months and had a larger proportion of mothers of low educational status.

**Age and sex adjusted models for association between psychotic disorders and urbanicity**

Table 2 shows age and sex adjusted hazard ratios for schizophrenia and non-affective psychoses for all nine categories of municipality. Subjects born in main cities had the highest risk of both schizophrenia and non-affective non-schizophrenic psychosis. There were fewer cases in categories 7, 8 and 9, and the hazard ratios for ‘sparsely populated areas’ were high compared with the other two rural municipalities.

**Urban patterning of obstetric complications and maternal education**

Table 3 shows the associations between our potentially confounding factors and the aggregated 3-level measure of urbanization. Babies born in main cities and suburbs were more likely to have lower birth weight, shorter birth length, lower APGAR scores and increased risk of birth by Caesarean section. Mother’s education was clearly patterned with better educated mothers tending to live in urban areas.

**Multivariable models for associations between psychotic disorders and urbanicity**

In Table 4 we report analyses based upon the three-level measure of the degree of urbanization of place of birth. There are associations between place of birth and schizophrenia and other non-affective non-schizophrenic psychoses, but the effect size is larger for other non-affective psychoses. Controlling first for obstetric complications, and subsequently for maternal education had little effect on the strength of these associations. We found no evidence that the effects of place of birth on risk schizophrenia differed with respect to season of birth ($P_{interaction} = 0.61$). However, for other
non-affective psychoses we found some evidence for such an interaction ($P_{interaction} = 0.046$): the association with urban birth was stronger in those born in winter (HR for birth in main cities, 2.74 (1.24–6.04)) compared with summer (HR for birth in main cities, 1.29 (0.72–2.29)).

**DISCUSSION**

**Main findings**

These data confirm previous studies reporting an association between urban place of birth and risk of schizophrenia. We show however that the association is not specific to narrowly defined schizophrenia and, indeed, may be stronger for other non-affective, non-schizophrenic psychoses. There is also an interaction with season of birth in non-schizophrenic non-affective psychoses, the greatest risk being in winter born.

Our analyses show significant associations between urban birthplace and indicators
foetal under-nutrition, such as birth weight and length. In addition, high APGAR score, maternal parity and incidence of caesarean sections also varied in relation to place of birth. Although previous studies have reported associations between these indicators and increased lifetime risk of adult onset schizophrenia (e.g. Wahlbeck et al. 2001) our data show that the risk factors associated with urbanization operate independently. Further, the association with urbanization appears not to be mediated through childhood socio-economic position despite reports of an association between higher parental social class and schizophrenia (Jones et al. 1994; Makikyro et al. 1997). These findings apply to non-affective psychoses and to schizophrenia, whether based upon broad or narrowly defined cases.

Study strengths and limitations
This study has a number of strengths, including the prospective cohort design and the independent nature of the assessments carried out for obstetric complications, place of birth and diagnosis. There are several limitations however. First, our period of follow-up was short and our findings apply only to cases of early age of onset. We may therefore have overestimated, or underestimated, the effects of urbanization on the incidence of schizophrenia across the life course. These findings require replication in samples containing individuals in the entire age of risk. Secondly, case detection was based on hospital admitted cases where diagnoses were recorded in an administrative database. Urbanization may be associated with factors connected with the risk of admission, rather than risk of disease, and our observed association could be accounted for by differences in the availability of psychiatric services in urban and rural areas. Mortensen et al. (1999) discount this possibility on the basis of small distances in Denmark, but we cannot eliminate this is an explanatory factor for our findings. Thirdly, it is also possible that clinicians in rural areas may be more conservative with regard to the diagnosis of schizophrenia than those in urban areas. This point would have some validity if our effect was confined to schizophrenia but in our study urban birthplace was associated with the broad range of non-affective psychoses. It is possible that there could be systematic differences in clinicians’ diagnostic habits within the board group of non-affective psychoses, but we think it is unlikely that there would be significant differences at the boundaries of psychosis itself.

Fourthly, missing data might have introduced selection bias. We investigated this further by assessing the effect of urban place of birth using the complete dataset adjusted only for age and sex. Hazard ratios were only marginally different in the full dataset (HR 1.26, CI 0.89–1.79 for schizophrenia and HR 1.73, CI 1.26–2.37 for non-affective psychoses for main cities/suburbs compared to rural areas). Therefore, restricting the analyses to subjects with complete data probably did not have bias our main results. Controlling for paternal education in the more limited dataset (due to missing values) had no effect on the strength of the associations, so we think it highly unlikely that confounding due to socio-economic status lies behind the urban effect. Finally, we do not have data for family history of schizophrenia, although Mortensen et al. (1999) found that family history of schizophrenia did not explain or affect the urban–rural differences observed in their study.

Findings compared with other studies of urban–rural differences
The strength of the association between urban place of birth and non-affective psychoses in this Swedish population is similar to that reported by Lewis et al. (1992) for schizophrenia among male Swedish conscripts. For narrowly-defined schizophrenia, the hazard ratios were somewhat smaller in our study. If our findings are considered with Lewis et al. (1992), Torrey et al. (1997) and Marcelis et al. (1998) the range of values lies between 1.20 and 1.84. The findings of Haukka et al. (2001), in Finland, also lie at the lower end of this range. Although Haukka et al. did not report a point estimate for the relative risk for urban versus rural birth, their Poisson regression model showed an increased incidence of about 25% (their Fig. 1) for the cohort ascertained in 1965–1969. Furthermore, they found that two previous birth cohorts (1955–1959 and 1960–1964) showed only marginal increases for urban born, and the oldest cohort (1950–1954) had a slightly higher incidence among rural born, leading the authors to conclude that urban birth has emerged as a risk
factor for schizophrenia in Finland only in cases born after 1955.

The range of values from these different European studies suggests that the magnitude of the risk associated with place of birth is smaller in most countries compared with that reported in Denmark. This may be explained by secular trends in urbanization and by differences in definitions of ‘urban’ and ‘rural’. For example, Haukka et al. (2001) classified municipalities as ‘urban’ if at least 95% of its inhabitants lived in settlements where the distance between neighbouring houses was < 200 m and the population in these settlements exceeded 200. This is a very different ‘urban’ environment from downtown New York or even the metropolitan areas of Copenhagen and Gothenburg. It is likely that the risk attributable to ‘urban birth’ varies significantly in different sociocultural settings. This appears to be the case for other risk factors: Pedersen & Mortensen (2001a) showed that the risk associated with season of birth varied markedly between subpopulations, even within one country (Denmark). Factors associated with urban place of birth may behave in similar fashion. We should therefore be cautious in generalizing the population attributable risk (PAR) for ‘urban’ place of birth from estimates determined in studies carried out in one country.

Our data suggest that urban birthplace is a general risk factor for broadly defined clinical psychotic syndromes similar to the finding of Eaton et al. (2000). There is no indication in our analysis that associations with schizophrenia increase with greater diagnostic precision; indeed the trend was in the opposite direction. The small reduction in the point estimate of the hazard ratio is not of great consequence, but these data do not suggest that associations are likely to increase with greater diagnostic precision. In a community survey of psychotic symptoms, Van Os et al. (2001) showed that level of urbanicity was associated not only with psychotic disorders defined in terms of DSM-III-R but also, independently, with any rating of delusion and/or hallucination, and with any rating of psychosis-like symptoms. While their study was based upon residence of adults at the time of the survey rather than at birth, the progressive association between level of urbanization and the prevalence of the broad range of clinical psychotic syndromes, as well as prevalence of lesser psychotic states, is consistent with our data.

Our findings cast new light upon the possible interaction effects between season and place of birth. Machon et al. (1983), O’Callaghan et al. (1991) and Takei et al. (1995) found that place of residence associations were stronger among winter born cases but this was not replicated by Mortensen et al. (1999) or by Pedersen & Mortensen (2001a). We found the interaction only in non-schizophrenic non-affective psychoses, which may partly account for conflicting findings in studies based upon schizophrenia alone. This finding requires replication, but seasonal differences may reflect seasonally varying exposures such as infection. These would be more likely to affect those born in cities because person to person transmission is more likely in densely populated areas.

In conclusion, we find that the association between urban place of birth and schizophrenia is unlikely to be due to rural–urban differences in obstetric complications or childhood socio-economic position. Studies are required to further open up the ‘black box’ of urban-birth risk, focusing on risk factors operating in childhood and through early adolescence. These have been reviewed by Eaton et al. (2000) and should include nutritional factors, infectious agents and psychosocial risk factors resulting from social adversity. Studies should include all non-affective psychoses, however, and investigate associations with different models of case definition over the life course of the illness.

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