Is the season of birth association with psychosis due to seasonal variations in foetal growth or other related exposures? A cohort study


**Objective:** To investigate the association between season of birth and psychosis, and to assess whether any association is caused by seasonal fluctuations in foetal growth or other related exposures.

**Method:** Cohort of 747,432 Swedish males and females born between 1973 and 1980 and followed up from 16 years of age to 31 December 1999. Psychiatric admissions were identified using the Swedish Inpatient Discharge Register. The analysis is based on the 696,025 subjects with complete data.

**Results:** A total of 506 (0.07%) subjects developed schizophrenia and 879 (0.13%) non-affective non-schizophrenic psychoses. There was a moderate increased risk of schizophrenia amongst winter births, hazard ratio 1.23 (95% confidence interval 0.96–1.59), but this did not reach conventional levels of statistical significance. There was no association with non-affective psychoses. We found no evidence that associations were confounded by measures of foetal growth or maternal socioeconomic position. There was no evidence that seasonal effects on schizophrenia differed in men and women.

**Conclusion:** Season of birth associations with schizophrenia do not appear to be confounded by birth-related exposures.

Introduction

There is a well-recognized association between season of birth and schizophrenia risk. Risk is greatest amongst those born in the spring and winter months, with around 5–8% of cases born during this period (1). Variations in incidence in relation to season of birth account for an estimated 10% of cases (2). A recent study, however, indicates that the strength of seasonal variation in risk has diminished in more recent birth cohorts (3).

Two principle explanations have been offered for the associations observed with season of birth. First, they may reflect exposure in utero or early infancy to infections whose incidence varies seasonally. Evidence to support this explanation is mixed (4–7). Some studies report that the season of birth effect is stronger in urban areas (8, 9) and this may reflect the ease of transmission of infectious agents in more crowded areas, but this finding has not been consistent (3). Secondly, it has been suggested that the season of birth effect reflects seasonal patterns of procreation in those with a genetic predisposition to psychosis. However, evidence for this hypothesis is mixed with some positive (10) and some negative studies (2). A third possible explanation lies in the seasonal variations in birth weight and subsequent growth (11, 12). Babies born in the winter months tend to be of lower weight and of shorter stature in adulthood. Impaired neurodevelopment as a result of seasonal perturbations to foetal and childhood growth may underlie the observed patterns. This view is supported by the relatively consistent findings that low birth weight is associated with an increased risk of psychosis (13, 14).
The specificity of the association of season of birth with schizophrenia rather than with other non-affective psychoses has been the subject of less research. Furthermore, few studies have assessed the extent to which seasonal associations are confounded by seasonal fluctuations in growth. The relatively few studies that have assessed the extent to which seasonal associations vary with gender or socioeconomic position report that associations are similar in males and females. Studies of social class differences in seasonal associations have produced conflicting findings (1).

Aims of the study
To examine the association of season of birth with early onset adult psychosis in a cohort of Swedish males and females. We assessed (i) the specificity of any association with schizophrenia, (ii) whether it is confounded by measures of foetal growth and (iii) whether associations differ by gender or socioeconomic position.

Material and methods
A cohort of 747 432 males and females, born in Sweden between 1973 and 1980 were followed up from 16 years of age to 31 December 1999 with respect to in-patient hospital care for psychosis. Information on hospital care was obtained from the Swedish Inpatient Discharge Register. Birth data were extracted from the Swedish Medical Birth Registry (MBR) and information on maternal education was obtained from the Population and Housing Census of 1990. We studied admissions to hospital for schizophrenia (ICD-9 295; ICD-10: F20) and other non-affective psychosis (ICD-9: 297-8; ICD-10: F21-29). We examined associations with season of birth by categorizing subjects into the following four groups: winter births (December to February), spring (March to May), summer (June to August) and autumn (September to November). We examined associations of schizophrenia and other non-affective psychoses with season of birth before and after controlling for (i) maternal characteristics: age (five categories – ≤20, 20–25, 25–30, 30–35 and 35+ years), parity (three categories – 1, 2 or 3+) and rural/urban residence at birth (three categories: main cities, other urban areas, rural and other areas (9); (ii) birth complications: the two variables which were most completely recorded – Caesarean section, Apgar score at 1 min (≤6 or 7+); (iii) measures of foetal growth: birth weight (as five categories: <2.5, 2.5–2.9, 3–3.4, 3.5–3.9, 4+ kg); birth length (as a continuous variable); gestational age (<36, 37–40 and 41+ weeks) and (iv) childhood socioeconomic position as indexed by the level of maternal education (four categories: <9 years, 9–10 years, full secondary education, higher education).

We excluded all subjects diagnosed with schizophrenia or other non-affective psychosis before 16 years of age. Overall, 51 407 subjects (7%) were excluded from the main analysis on account of missing data for one or more of the factors investigated. Our main analyses are therefore based on 696 025 subjects.

Data analysis
Our analysis is based on hospital admissions for non-affective psychosis between 1989 and 1999. Subjects were followed up for a mean of 7.28 years (range 1 day to 11.0 years) after 16 years of age.

All analyses were carried out in STATA. We used Cox’s proportional hazards models to assess the influence of season of birth on the risk of schizophrenia and on other non-affective psychosis. We examined associations with season of birth as a four-level categorical variable and across all 12 months of birth (regardless of year of birth) by fitting a sine function. This enabled us to estimate both the month of greatest risk and the level of increased risk. Subjects were censored at the time of first admission for schizophrenia or non-schizophrenic, non-affective psychosis, death (full data available until 31 December 1999) or emigration (data on emigration were available up until 31 December 1998). All analyses were controlled for sex and age. We then assessed the effects on hazard ratios of controlling for obstetric complications and measures of foetal growth as defined above. Lastly we assessed the additional effect of controlling for maternal education (full model). Tests for interaction were based on likelihood ratio tests comparing models with and without the relevant explanatory variables.

Results
A total of 506 subjects (0.07%) were admitted to hospital with a diagnosis of schizophrenia at least once in the period of follow-up and 879 (0.13%) were admitted with a diagnosis of non-affective, non-schizophrenic psychosis. The mean time between the 16 years of age and hospital admission for schizophrenia was 4.63 (range 0.04–10.36 years) and for other non-affective psychoses 4.69 (range 0.01–10.58 years). The incidence rate for schizophrenia was 0.10 per 1000 person-years and for non-schizophrenic, non-affective psychosis was...
0.18 per 1000 person-years. There were modest, but statistically significant ($P < 0.001$), seasonal differences in the birth weight of babies born at different times of the year – those born in the winter had the lowest birth weight. The mean birth weights were: winter births: 3498 g; spring: 3523 g; summer: 3508 g and autumn: 3511 g.

Study subjects 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 (7.7% vs. 4.0%), were more likely to have been born in the winter (December to February: 26.2% vs. 23.5%), to be male (52.0% vs. 51.3%) and to have a lower level of maternal education (<9 years: 19.7% vs. 13.0%). All these differences were statistically significant because of the large sample size.

Table 1 shows the associations of schizophrenia and non-affective non-schizophrenic psychoses with season of birth. We present results after controlling (i) for age and sex, (ii) age, sex and birth-related factors and (iii) all previous factors and maternal education. There is only weak evidence of a season of birth effect for schizophrenia and the seasonal differences were not statistically significant ($P = 0.39$). The patterns of risk are, however, in keeping with those observed in previous studies with a 23% (95% CI –4% to +58%) increased risk amongst winter births and 8% increase (–15% to +39%) for spring birth compared with summer births. Controlling for measures of foetal growth, obstetric complications and measures of socioeconomic position did not attenuate the associations. There is little association with other non-affective psychoses. Hazard ratios by month are shown in Fig. 1. No striking seasonal effects are apparent. We repeated the analyses in the full data set without excluding the 51 407 subjects with missing data on one or more of the possible confounding factors. The results were essentially the same: hazard ratios for schizophrenia associated with birth in winter: 1.23 (0.98–1.56); spring: 1.04 (0.83–1.31); summer (reference category); autumn: 1.07 (0.83–1.37) ($P = 0.24$).

We also modelled season of birth effects as a sine function – there was no statistically significant evidence of cyclical effects in relation to schizophrenia ($P = 0.33$) or other non-affective psychoses ($P = 0.67$). For both schizophrenic and non-schizophrenic psychoses the peak of the sine function (the birth months associated with greatest risk) was in January/December.

There was no evidence that effects of season of birth differed in men and women for schizophrenia [$P$ (interaction) = 0.45] or non-affective psychosis [$P$ (interaction) = 0.53]. Likewise the effects of season of birth were similar in the offspring of well and less well-educated mothers.

**Discussion**

We have found only modest evidence of an association between season of birth and early onset schizophrenia, and this association was not statistically significant. We found little evidence for an association with other non-affective psychoses. However our study lacked statistical power to detect the 5–8% increases in risk amongst winter and spring births reported in a recent review of the literature (1), and our hazard ratios and their 95% confidence intervals are consistent with such increases. The weak associations we did find appeared to be specific for schizophrenia. We found no evidence that seasonal patterns varied with gender – a finding in keeping with that of a recent analysis of data from Finland (3). Associations were not confounded by measures of foetal growth or obstetric complications.
There are two main strengths of our study. First, it is based on a defined birth cohort followed up into early adulthood. Secondly, the detailed birth and socioeconomic data enabled us to assess the possible confounding effect of these factors. We found no evidence of such confounding. There are several limitations to our analysis. First, we lacked the statistical power to detect the effects reported in other studies (1). Secondly, case ascertainment was based on hospital admitted cases only and used diagnoses recorded on an administrative database. Analyses of diagnoses recorded on the Swedish inpatient discharge register, however, indicate that schizophrenia is diagnosed with reasonable accuracy (15, 16).

Lastly, as family history of psychotic disorder was not available, we were unable to control for its possible confounding effects in this analysis. A recent analysis of schizophrenia in Denmark, however, indicates that family history is not an important confounder (2).

A better understanding of the biological mechanisms underpinning season of birth effects on schizophrenia will provide important clues concerning the aetiology and prevention of schizophrenia. Our findings suggest that such mechanisms are likely to be specific to patients with a diagnosis of schizophrenia. Long-term follow-up of this Swedish cohort will give us increased power to investigate these issues in more detail.

Fig. 1. Age and sex adjusted hazard ratios (95% CI) of schizophrenia and non-affective non-schizophrenic psychosis in relation to month of birth (1 = January...12 = December; reference category is January).
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References