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Birth month and later diagnosis of schizophrenia. A population-based cohort study in Sweden

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ABSTRACT

The objective of the present study was to examine if the monthly variation in births of individuals diagnosed with schizophrenia currently differs from that of unaffected individuals in Sweden. In an extensive linkage of Swedish national and regional population registers we here investigate the birth pattern of the population born 1940–97 (5,995,499 individuals) which included 30,684 individuals diagnosed with schizophrenia in the National Patient Register by December 31, 2016. Among 2,409,862 individuals born since 1973 we investigated potential confounding by co-variates associated with pregnancy and birth. We also compared the monthly birth pattern of 22,570 affected individuals to that of their 41,528 unaffected full siblings. We observe a significant birth excess of individuals with schizophrenia in December, HR 1.07 95%CI (1.01–1.13). Patients born in December received a registered diagnosis of schizophrenia at a slightly younger age than those born during other months. A number of co-variates were associated not only with schizophrenia but also varied across birth months. Inclusion of these in the models however had virtually no influence on the risk for schizophrenia associated with December birth. In comparisons between full siblings, the association between December birth and later diagnosis of schizophrenia remained, albeit slightly attenuated, HR 1.06 (0.99–1.12). Risk for schizophrenia associated with birth in December in Sweden during the study period does not appear to be fully explained by our investigated co-variates or factors shared between family members and may thus represent monthly/seasonal variation in environmental factors involved in the etiology of schizophrenia.

1. Introduction

An excess of winter-spring births among individuals diagnosed with schizophrenia is among the most replicated findings in schizophrenia research (Torrey et al., 1997). Studies using large population-based data from Nordic countries (Hultman et al., 1999; Mortensen et al., 1999; Suvisaari et al., 1999) have reported an excess in schizophrenia births during winter-spring months among individuals born between the 1930's and the 1980's but follow-up studies on later cohorts with extensive data on potentially important co-variates are lacking. The largest study to date included more than 26,000 patients and reported a 13% birth excess of individuals with schizophrenia in January as compared to the general population born in England between 1950 and 1990 (Disanto et al., 2012).

Albeit a consistent observation, the causes of the seasonal variation remain elusive. Popular hypotheses regarding environmental causes include variations in exposures to sunlight (McGrath et al., 2002), vitamin D (McGrath et al., 2010) or infections (Torrey and Peterson, 1976) during pregnancy or early life. Indeed, these are all factors that are known to vary across seasons, e.g. (Fisman, 2007), but are not necessarily constant over time. A population-based study from Finland reported a strong seasonal effect during the second half of the 1950's, coinciding with epidemics of poliomyelitis, that were attenuated during the 1960's and 70's (Suvisaari et al., 2000).

Hypotheses regarding familial causes, potentially involving parental selection into different birth months are supported by some (Hare, 1976; McNeil et al., 1976) but not all (Buck and Simpson, 1978; Pulver et al., 1992) studies that investigated the birth patterns among schizophrenia patients and their unaffected siblings. The largest sibling study to date included a population-based sample of 15,389 Finnish patients and their 37,819 unaffected siblings and reported a seasonal birth pattern of healthy siblings somewhere in between that of their affected sibling and that observed in the general population (Suvisaari et al., 2001).

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No interaction between season of birth and familial risk for schizophrenia has been reported (Mortensen et al., 1999), suggesting that the seasonality factor(s) affects individuals to the same degree regardless of their level of genetic risk. Moreover, large population-based studies of sibling recurrence risk suggest that schizophrenia among cases born during high-risk periods is neither more nor less heritable than among cases born at other times of the year (Suvisaari et al., 2004; Svensson et al., 2012).

Seasonal variation in birth weight (Chodick et al., 2009) and gestational age at birth (Lee et al., 2006) have been reported in both developed and developing countries. While selection into conception and birth month based on parental behavior and socioeconomic position has been suggested to explain a substantial part of this variation (Darrow et al., 2009), a recent sibling study indicate that both birth weight and gestational age at birth are subject to influences by factors not shared between siblings (Currie and Schwandt, 2013). While both birth weight and gestational age at birth have been associated with the later development of schizophrenia, Fouskakis *el al* (Fouskakis et al., 2004)., found no evidence that seasonal variations in these confound the association between winter birth and schizophrenia in Sweden (Fouskakis et al., 2004).

The following study was conducted to investigate if a birth month effect was observed in schizophrenia among almost 6 million individuals born in Sweden between the years 1940–1997 and followed in Swedish registers from 1973 through 2016. We considered a number of co-variates including, sex, birth decade, geographic region, maternal schizophrenia and age. Moreover, in populations nested within this cohort, we further considered potential confounding by birth weight, gestational length, birth order and maternal educational attainment. Finally, we attempted to address potential confounding by factors shared between family members, due to a non-random distribution of parents into different birth months, by using matched sibling comparisons.

2. Material and methods

2.1. General setting

This study is based on a linkage of several health and population registers, specifically created to perform studies of the etiology of psychiatric disorders, called Psychiatry Sweden (PS). Approval was granted by the Regional Ethical Committee of Stockholm. No informed consent was required for the analysis of anonymized register data.

2.2. Study populations

Population 1; All persons born in Sweden between 1940 and 1997 who were alive (65,217 were deceased) and living in Sweden (144,071 had emigrated) on their 13th birthday were identified in the total population register, leaving a total number of 6,113,155 persons. Of these, data on one or more co-variate was missing for 117,656 individuals (2%) leaving a total of 5,995,499 individuals included in the current study, see Tables 1 and S1.

Population 2; In order to study the effects of co-variates associated with pregnancy and birth, some of the analyses were restricted to persons born between 1973 and 1997 during which data from the Medical Birth Register (MBR) was available. Of these, 22,002 were deceased and 96,720 had emigrated before age 13 leaving a total of 2,561,139 persons included in this study population. Among these, data on one or several of the co-variates was missing for 151,277 individuals (6%) leaving a total of 2,409,862 individuals included in the study, see Tables 2 and S2.

Population 3; To investigate the role of parental selection into birth months we identified a subset of nuclear families with at least two full siblings (a total of 4,735,358 individuals) where at least one was diagnosed with schizophrenia resulting in a total of 22,570 affected individuals and their 41,528 unaffected full siblings.

2.3. Schizophrenia

Individuals diagnosed with schizophrenia (ICD10: F20, ICD8, 9: 295, excluding 295.50 and 295.70) were extracted from the National Patient Register (NPR). The NPR includes virtually all inpatient care in Sweden since 1973, and psychiatric outpatient visits since 2001.

2.4. Co-variates

Data on socio-economic status in terms of highest education level among parents were obtained from the Longitudinal Integration Database for Health Insurance and Labor market studies, updated annually since 1990 and integrates data from the labor market, educational and social sectors. The Total Population Register was initiated 1968. This basic register includes the entire Swedish population with variables like sex, birthdate and place of residence. Information on first relatives was collected from the Multigenerational Register. Date of death was retrieved from the National Cause of Death Register. Data on gestational age at birth (weeks) and birth weight (grams) were obtained from the MBR, initiated in 1973.

2.5. Statistical methods

We analyzed birth month as a categorical variable using Cox proportional hazards regression to calculate hazard ratios (HRs) and 95% confidence intervals (CI) for schizophrenia. Individuals were followed up from 13 years of age until the diagnosis of schizophrenia, emigration, death, or December 31, 2016, whichever came first. Matched-sibling analyses comparing affected individuals with their unaffected full siblings were performed to investigate whether the observed association between December birth and offspring schizophrenia could be the result of confounding by shared familial factors. There may be clustering where some families for any reason, even unmeasured, give birth in certain months. Cox proportional hazards regression, stratified by family identity, was performed for matched full siblings, discordant on outcome, adjusted for birth order and sex, factors that can/will vary between pregnancies of the same mother. Throughout, we used two-sided 5% level of significance corresponding to a Wald two-sided 95% confidence interval. No corrections for multiple comparisons were performed. Statistical analyses were made using SPSS statistics version 21 or STATA version 15.

3. Results

In population 1, consisting of individuals born 1940–97, we identified 30,684 individuals diagnosed with schizophrenia resulting in a prevalence of 0.51%. As can be seen from Table S1, these patients were more likely to be male, born during the 1950's and 60's, in the middle and northern parts of Sweden, to have a mother diagnosed with schizophrenia and to have a mother who was 35 or older at the time of birth.

3.1. Birth month

We calculated the proportion of births during the period 1940–1997 during each month of the year. As can be seen from Table 1, a strong monthly variation in over-all births in Sweden is observed with peaks in the spring months (March–May) and troughs in late fall and winter (Nov–Feb). Since we expected an excess of schizophrenia births during the winter months, we calculated crude hazard ratios (HR) for schizophrenia for each month of the year using June as reference. The only birth month statistically significantly associated with schizophrenia was December, crude HR 1.07, 95%CI (1.01–1.13). Many of the included co-variates were not only associated with schizophrenia but also with

Table 1
Risk for schizophrenia by birth month among individuals born in Sweden during the period 1940–1997 followed in national health care registers until December 31st, 2016.

Birth month	Schizophrenia	Controls	Risk for schizophrenia				
	n = 30,684	n = 5,964,815	Crude		Adjusted[a]		
	%	%	HR[b]	95% CI[c]	HR	95%CI	p-value
January	8.30	8.17	1.02	0.97–1.08	1.02	0.97–1.08	0.476
February	7.94	8.02	1.00	0.95–1.06	1.00	0.95–1.06	0.936
March	9.43	9.51	0.99	0.94–1.05	0.99	0.94–1.05	0.814
April	9.42	9.45	1.00	0.95–1.05	1.00	0.95–1.05	0.978
May	9.16	9.22	0.99	0.94–1.05	0.99	0.94–1.05	0.770
June	8.44	8.49	Ref	–	Ref	–	–
July	8.25	8.43	0.99	0.94–1.05	0.99	0.94–1.05	0.750
August	7.90	8.12	0.99	0.94–1.05	1.00	0.94–1.05	0.804
September	8.20	8.15	1.01	0.97–1.07	1.01	0.96–1.07	0.650
October	7.61	7.79	0.99	0.93–1.04	0.98	0.93–1.04	0.517
November	7.40	7.22	1.03	0.97–1.09	1.03	0.97–1.09	0.359
December	7.95	7.43	1.07	1.01–1.13	1.06	1.01–1.13	0.027

[a] Adjusted for sex, birth decade, region of birth, maternal schizophrenia and maternal age.
[b] Hazard ratio (HR).
[c] Confidence interval.

Table 2
Risk for schizophrenia by birth month among individuals born in Sweden during the period 1973–1997 followed in national health care registers until December 31st, 2016.

Birth month	Schizophrenia	Controls	Risk for schizophrenia				
	n = 5119	n = 2,404,743	Crude		Adjusted[a]		
	%	%	HR[b]	95% CI[c]	HR	95%CI	p-value
January	9.01	8.34	1.03	0.90–1.17	1.03	0.90–1.17	0.69
February	8.17	8.22	0.95	0.83–1.09	0.95	0.83–1.09	0.45
March	9.38	9.59	0.94	0.82–1.06	0.94	0.82–1.07	0.32
April	9.22	9.47	0.94	0.82–1.07	0.94	0.82–1.07	0.34
May	8.73	9.14	0.92	0.81–1.05	0.92	0.81–1.05	0.24
June	8.69	8.56	Ref	–	Ref	–	–
July	8.26	8.55	0,96	0.84–1.10	0.96	0.84–1.10	0.55
August	8.09	8.32	0.97	0.85–1.11	0.97	0.85–1.11	0.66
September	8.40	8.11	1.03	0.90–1.17	1.03	0.90–1.17	0.68
October	7.11	7.65	0.93	0.81–1.06	0.92	0.81–1.06	0.27
November	6.99	7.00	1.00	0.87–1.15	1.00	0.87–1.14	0.95
December	7.95	7.05	1.14	0.99–1.30	1.13	0.99–1.29	0.08

[a] Adjusted for gestational age at birth, birthweight, birth order and maternal educational attainment.
[b] Hazard ratio (HR).
[c] Confidence interval.

Table 3
Risk for schizophrenia by birth period among individuals born in Sweden during the period 1940–1997 followed in national health care registers until December 31st, 2016.

Birth period	General population				p-value	Sibling comparison				p-value
	HR crude[a]	95% CI	HR adjusted[b]	95% CI		HR crude[c]	95% CI	HR adjusted[d]	95% CI	
May–Jul	Ref	–	Ref	–	–	Ref	–	Ref	–	–
Aug–Oct	1.00	0.97–1.04	1.00	0.97–1.03	0.916	1	0.96–1.05	1	0.96–1.05	0.830
Nov–Jan	1.05	1.01–1.08	1.04	1.01–1.08	0.010	1.05	1.00–1.10	1.05	1.00–1.10	0.080
Feb–Apr	1.00	0.97–1.03	1.00	0.97–1.04	0.807	1.04	1.00–1.09	1.04	1.00–1.09	0.124

[a] Unadjusted hazard ratios for schizophrenia associated with different birth periods using May–July as reference.
[b] Hazard ratios for schizophrenia associated with different birth periods, adjusted for all co-variates in Table 1.
[c] Unadjusted hazard ratios for schizophrenia among matched siblings associated with different birth periods.
[d] Hazard ratios for schizophrenia among matched siblings associated with different birth periods adjusted for sex and parity.

December births (Table S1). For example, a decreasing trend in December births from the 1940's to the 1990's is observed in the comparison population. This trend appears to be less pronounced among individuals later diagnosed with schizophrenia. Women diagnosed with schizophrenia appeared slightly more likely to give birth to a child in December than comparison women. Adjustments for the co-variates included here, however, had a minimal effect on the association between December birth and later diagnosis of schizophrenia, Table 1. From Table 1 it can also be seen that the flanking months of November and January are associated with some excess risk whereas no other

month do. Comparing the risk associated with birth during the period Nov–Jan to that of the period May–July suggests an average 4% increased risk for schizophrenia among those born Nov–Jan (p = 0.010) in the fully adjusted model, see Table 3.

3.2. Increasing risk associated with December birth over time

Analyses across each of the decades studied indicated a stable association between December birth (vs. those born during Jan–Nov) and schizophrenia from the 1940's through the 1960's, ranging between 1.03 (0.94–1.12) and 1.06 (0.98–1.15), increasing to 1.12 (1.00–1.26) during the 1970's, 1.10 (0.95–1.28) during the 1980's and 1.28 (0.96–1.70) among those born during 1990–97. The trend in the association between December birth and schizophrenia to become progressively stronger in the more recent birth cohorts can potentially be explained by a younger age at first diagnosis among those born in December as compared to those born January–November. Indeed, the mean age (± SD) at first diagnosis among those born in December during the years 1960–97 (n = 1,081, with a potential registered diagnosis from age 13 in the NPR initiated in 1973) was lower than among those born during January–November (n = 10,834), 28.9 ± 8.4 vs 29.7 ± 8.5, p = 0.005. The association between December birth (vs birth during other months of the year) and a later diagnosis of schizophrenia was also stronger among those diagnosed with schizophrenia before their 26th birthday (HR 1.18, 95% CI 1.09–1.28) than among those diagnosed later in life (HR 1.03, 95% CI 0.98–1.08).

3.3. Pre- and perinatal factors

In study population 2, consisting of individuals born during the period 1973–1997, December birth was more strongly, albeit not significantly, associated with schizophrenia, crude HR 1.14, 95%CI (0.99–1.30), see Table 2 as compared to the observed association in the larger population 1, see Table 1. Individuals who were later diagnosed with schizophrenia were more likely to be pre-term (born before gestational week 37), of low birth weight (< 3500 g), to have three or more older siblings (birth order ≥ 4) and to have a mother with lower educational attainment (≤ 9 years), see Table S2. From Table S2, it is also evident that these co-variates are not equally distributed across birth months. Inclusion of these co-variates into the model, however, had a minimal influence on the association between December birth and schizophrenia, HR 1.13, 95%CI (0.99–1.29), see Table 2.

3.4. Shared familial factors associated with December births

We next explored if the risk for schizophrenia associated with December births is independent of factors shared by family members (Darrow et al., 2009). To this end, we identified families with at least two full biological siblings. In this population consisting of 4,735,358 individuals, 7.33% and 7.96% of unaffected and affected individuals, respectively, were born in December resulting in a crude HR for schizophrenia associated with December birth vs all other months of the year of 1.08 (1.03–1.23) in an un-matched comparison which was not affected by inclusion of sex and parity in the model. In other words, December birth was associated with schizophrenia-risk also in the source population for the sibling comparison. Among matched sib-ships with at least one affected individual, 7.72% and 7.97% of unaffected and affected individuals were born in December resulting in a crude HR of 1.06 (0.99–1.13) which was minimally affected by inclusion of birth order and sex into the model, HR 1.05 (0.98–1.12). As for the entire population born 1940–97, we analyzed the matched sibling population by the birth periods, Nov–Jan, Feb–April, May–July and Aug–Oct. Results are presented in Table 3 and suggests excess risk, associated with birth during Nov–Jan as compared to May–July (p = 0.08), possibly including also Feb–April, after taking shared familial factors into account.

4. Discussion

We here report a small, but statistically significant, 6% excess of births of individuals with schizophrenia in the month of December among individuals born in Sweden between 1940 and 1997 after adjusting for potential confounders. Our observation of a difference in the birth pattern between individuals diagnosed with schizophrenia and the rest of the population is in agreement with a very large literature based on both clinical and epidemiological studies in many different regions and during different time-periods, see (Torrey et al., 1997). While most studies report a winter-spring excess (Torrey et al., 1997), our results indicate a peak risk for schizophrenia in December with no statistically significant excess or deficit during other individual months. The period November through January was however also associated with a statistically significantly elevated risk for schizophrenia. The seasonal/monthly birth pattern observed here may thus differ slightly from that reported from neighboring Nordic countries where peak risk for schizophrenia births have been reported in March among Danes born 1968–93 (Mortensen et al., 1999) and in January among Finns born 1950–69 (Suvisaari et al., 2001). Using data that partly overlap with our current study, Hultman and coworkers (Hultman et al., 1999) reported a fairly large excess risk for schizophrenia (1.4-fold) among those born January–April but that study followed births during the period 1973–79 with follow-up only to age 15–21. In close agreement with our observations, Bembenek and coworkers (Bembenek and Kociuba, 2005) reported an 8% excess in schizophrenia births in December in Poland during the years 1964–74. Thus, in agreement with most previous register-based studies, this study of a large Swedish population find a significant excess of schizophrenia births in December. In his study from 1968, Per Dalén (Dalen, 1968) reported on the birth months of patients with schizophrenia treated in Swedish hospitals during the period 1962 through 1964 and who were born 1900–1940 (n = 16,238). Dalén reported a significant deviation in the monthly birth pattern of the patients as compared to that of the entire Swedish population born during these same years. From the figures in his paper, January–March had the most pronounced birth excess of patients indicating that the birth months associated with schizophrenia risk may have shifted slightly in Sweden over the last 100 years.

4.1. Age at diagnosis

We observed an increasing risk of schizophrenia associated with December births in the younger population. This observation appeared to be explained by a younger age at diagnosis among those born in December as compared to those born during other months. While an early age at onset of schizophrenia is associated with poor long-term outcome (Rabinowitz et al., 2006), it is not clear if early and late onset cases differ in terms of the causes of their illness (Kendler et al., 1987). Using the proband's age at register-based diagnosis of schizophrenia (i.e. similar to us), Svensson and coworkers (Svensson et al., 2012) reported that a younger age (< 25) of the proband at diagnosis conferred higher risk for a sibling than an older age (≥ 25) suggesting that young age at diagnosis is related to a larger familial risk, e.g. higher shared genetic or environmental load. With regard to the relative roles of genes and environment in determining age at onset, a recent twin study from Denmark also used age at registered diagnosis, and linked an early age at diagnosis with a more severe genetic predisposition (Hilker et al., 2017). Stepaniak and coworkers (Stepniak et al., 2014), on the other hand reported little support for genetic differences between individuals with early and late onset schizophrenia but a larger role for accumulated environmental risk factors, such as perinatal complications, in determining an early age at onset in a data-rich clinical sample.

4.2. Influence of co-variates assessed at birth and childhood

In our data, November–January births were more common among those born pre-term or with low birth weight as compared to births within the normal ranges of these parameters. Indeed, birth month variations in these parameters have previously been reported from different countries, reviewed in (Lee et al., 2006). Similarly to the monthly variations in schizophrenia births, these variations can also be explained by environmental factors or from selection of parents with different characteristics into different birth months (Darrow et al., 2009). Interestingly, Currie and Schwandt (2013) reported monthly variations in both gestational age and birthweight using within-mother, i.e. sibling, analyses on U.S. register data. Their observations, based on 1.4 million births during the period 1994–2010 in the north-eastern U.S. suggest that factors, not shared between biological siblings, influence these birth outcomes leaving the field open to a wide range of environmental factors, including maternal infections, as suggested by the authors (Currie and Schwandt, 2013). Birth month related differences in gestational age, birth weight, parity or maternal educational attainment do, however, not appear to confound the risk for schizophrenia associated with December birth in our population of individuals born 1973–1997. A similar lack of confounding by fetal growth and maternal education was previously made in Swedish register data by Fouskakis et al. (2004) but that study was restricted to births during 1973–80 and follow-up only until 1999.

4.3. Shared familial factors

Finally, we considered the possibility that the risk associated with December birth is explained by factors unmeasured in our previous analyses. Our major concern was that December birth is not random, leading to selection of individuals into different birth months. Indeed, December births was slightly more common among unaffected siblings of affected individuals (7.72%) than among unaffected individuals in the general population (7.43%) or among unaffected individuals with at least one sibling (7.33%), suggesting that parental selection can potentially explain some of the risk associated with December birth. Nevertheless, our sibling comparison suggest that shared familial factors, which include parental genes, do not fully explain the risk associated with December birth. Although the small risk for schizophrenia associated with December birth observed in the general population and in the population of siblings was no longer statistically significant in our matched analyses of discordant siblings, the risk-estimate remained at 1.05 (0.98–1.12) in our fully adjusted model.

Many of the previous studies of the birth pattern of sibling to patients diagnosed with schizophrenia have investigated relatively few sib-pairs and may therefore have been underpowered (Buck and Simpson, 1978; Hare, 1976; McNeil et al., 1976; Pulver et al., 1992). Based on their observations on large numbers of cases of schizophrenia and their healthy siblings in the Finnish population born 1950–69, Suvisaari and coworkers (Suvisaari et al., 2001) suggested that the seasonal effect consists of both differences in procreational habits of parents to cases and the influence of environmental factors that cause accumulation of schizophrenia births during the winter months. Indeed, these observations are similar to our current observations in Sweden. Two other register studies using Finnish (Suvisaari et al., 2004) and Swedish (Svensson et al., 2012) data, respectively, reported no influence of the season of birth of schizophrenia probands on the risk for schizophrenia in their siblings. Taken together, these studies suggest that patients born during the high risk season do not differ in terms of familial risk-load from those born during other times of the year. While these results collectively argue against genetic confounding in the association between schizophrenia and birth-month/season in Sweden, large-scale studies can determine if individuals born during periods associated with a high-risk for schizophrenia, are genetically different (e.g. have a higher polygenic risk score for schizophrenia) from individuals born during other periods of the year. This was recently investigated in a well-powered study performed in the UK biobank (Escott-Price et al., 2018). Escott-Price et al., found no evidence that genetic risk for schizophrenia, in the form of polygenetic risk score or rare copy-number variants, was associated with month or season of birth in the UK (Escott-Price et al., 2018). In fact, these investigators found no support for the notion that common genetic variation is associated with birth-month.

4.4. Limitations

The current study relies heavily on the reliability of the information in Swedish Medical and population registers in terms of exposures and outcomes as well as in correctly capturing familial relations and birth dates. Dating of the gestational age of fetuses were up until the mid 1980's based on last menstruation and has subsequently been replaced by ultrasound and it is therefore plausible that the dating was less accurate for the first ten years of births. We do however not find any reason to believe that there would be any particular bias in this, or any other, prospectively collected data in the Medical Birth Register with regard to the association between birth month and psychiatric outcomes several decades later. Registered psychiatric diagnoses have been validated and found to be of high quality (Dalman et al., 2002). It is however inevitable that this type of study is sensitive to changes in care and practice over the time-period studied which may have introduced biases. Our data will contain individuals from the same family which may have introduced correlations not explicitly accounted for which may have slightly biased the confidence intervals. Still, these individuals are not very many compared to the number of clusters (families) and should only have very minor influences.

5. Conclusion

In this, one of the largest studies to date using population based registers in a country with fairly equal access to healthcare, we find a significant 6% excess of births in December of individuals who will later be diagnosed with schizophrenia during the years 1940–97. We identified several pregnancy and birth outcomes that also exhibited variation by birth month but did not explain the risk for schizophrenia associated with December birth. In matched sibling analyses, a 5% increased risk for schizophrenia remained associated with December birth although the effect was not significant due to the far smaller sample available for this analysis. Thus, the excess in winter births appear to be related to factors not shared by full biological siblings. The current study is thus one of many studies verifying seasonal or monthly variation in schizophrenia births. We propose that this reflects seasonal variation in one or several environmental factors causally involved in the later development of schizophrenia. Future large scale population-based studies with detailed individual information on environmental exposures occurring during pregnancy or early postnatal life are necessary to identify such factors.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.05.025.

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