The role of latitude and infections in the month-of-birth effect linked to schizophrenia

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ABSTRACT

There is an intriguing association between winter births and subsequent increased risk of schizophrenia. However, little is known about the environmental risk factors that contribute this month-of-birth effect. The aims of this study were to carry out a systematic review and meta-analysis of studies investigating the month-of-birth effect in schizophrenia and to explore possible factors such as latitude, daylight and infections that could explain this epidemiological observation. Medline, Embase and the Cochrane Library were searched for articles published up to December 23, 2021. Study selection, data extraction and analysis were undertaken according to Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines. Generic inverse-variance with random effects models were used to determine the risk ratios (RR) and 95% confidence intervals (CI) for each month-of-birth. Associations between variables latitude and daylight were investigated using linear regression and Kendall’s rank correlation coefficients were calculated to assess the relationship between monthly infections rates schizophrenia births. Ten studies were included in the meta-analysis encompassing 262,188 schizophrenia patients. We identified significantly higher number of schizophrenia births in December [1.04 (95%CI 1.00–1.08)], January [1.06 (95%CI 1.03–1.10)] and February [1.03 (95%CI 1.00–1.05)]. We did not find any association between latitude and the magnitude of the month-of-birth effect. On the other hand, we found a significant negative correlation between monthly severe enterovirus cases and schizophrenia births (tau = 0.57, p = 0.0099) using data from Taiwan. This highlights a role for enterovirus infections in mediating the month-of-birth effect in schizophrenia and these results carry implications for disease prevention strategies.

1. Introduction

The association between winter births and subsequent increased risk of schizophrenia is an intriguing and well-studied area of research (Mortensen et al., 1999; O’Hare et al., 1980). This points towards a seasonally fluctuating risk factor in early life. However, the factors that mediate this effect have remained elusive and little progress has been made in this area of research. In 2003, a meta-analysis of studies from Northern Europe and North American countries suggested that latitude is linked to the excess winter births (Davies et al., 2003; Parker et al., 2000; Selten et al., 2000; Suvisaari et al., 2001; Torrey et al., 1977). Accordingly, it was hypothesised that sunlight and more specifically vitamin D levels could play an important role in the disease, but subsequent genetic epidemiology studies have not supported this theory (Taylor et al., 2016). Since then, several new studies investigating the month-of-birth effect in schizophrenia have emerged (Carrion-Baralt et al., 2004; Disanto et al., 2012; Cheng et al., 2013; Karlsson et al., 2017; Munoz-Delgado et al., 2003; Mino and Oshima, 2006). Some of these studies were carried out in low latitude countries where sunlight does not vary substantially throughout the year but the link between winter birth and risk of schizophrenia has persisted in these countries (Carrion-Baralt et al., 2004; Munoz-Delgado et al., 2003). This in turn has brought doubt to the relevance of latitude to the month-of-birth effect in schizophrenia.

The developing brain is particularly susceptible to environmental factors that can influence genetically determined neurodevelopmental

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processes. Several observational studies have identified an association between maternal infection during pregnancy and subsequent increased risk of schizophrenia in their offspring (Buka et al., 2001, 2008; Babulas et al., 2006; Saatci et al., 2021). Timing of infection is important, and although not comprehensive, infections in the second trimester seem to mediate this increased risk (Saatci et al., 2021). This is further supported by evidence from mouse models of maternal immune activation, in which pregnant mice are challenged with immune insults and their adult offspring show disease relevant behavioural, pathological, and neurochemical changes (Gumusoglu and Stevens, 2019). Interestingly, many infections show fluctuations throughout the year including neurotropic enteroviruses (Pons-Salort et al., 2018), but little has been done to investigate their role in mediating the month-of-birth effect in schizophrenia.

Understanding the factors that contribute to the month-of-birth effect in schizophrenia is an important area of research because it could, not only shed light on the underlying disease mechanisms but also help to identify modifiable risk factors in early life. Accordingly, in this study we 1. carried out an updated systematic review and meta-analysis of population-based studies investigating the link between month of birth and schizophrenia in line with the MOOSE guidelines (Stroup et al., 2000), and 2. explored whether latitude, daylight and infective agents could explain the month-of-birth-effect in schizophrenia.

2. Methods

2.1. Search strategy

Medline, EMBASE and the Cochrane Library were searched from inception to December 23, 2021, using the search terms, “month of birth”, “season of birth”, “schizophrenia” and “non-affective psychosis” (full search strategies available in Supplementary Table 1). Reference lists were hand-searched. There were no language restrictions.

2.2. Study selection

We included any comparative cohort study investigating the association between month or season of birth and the outcome of subsequent schizophrenia or non-affective psychotic disorders in the Northern Hemisphere. We excluded unpublished studies, any study without a valid population-control group and outcomes that included affective psychotic disorders or other neurodevelopmental disorders. Two reviewers (LH and DS) independently assessed the eligibility of each title and abstract identified from the search strategy. Full-text articles were retrieved for further assessment of inclusion. Authors were contacted if full text articles were unavailable.

2.3. Data extraction

Data was extracted by two reviewers (LH and DS) using a standardised form (Supplementary Table 2), detailing year of publication, study design, exposures/outcomes of interest, and study-specific summary statistics (i.e., odds ratios (ORs) and relative risks (RRs) with 95% confidence intervals). If summary statistics were unavailable, these were estimated using total number of schizophrenia births and general population births available in each study. Any missing data was addressed by contacting authors. For publications that had overlapping datasets, the ones chosen for inclusion were those with the highest quality studies.

Fig. 1. Study flow diagram.
and the largest datasets.

### 2.4. Quality assessment

Both reviewers (LH and DS) used the validated Newcastle-Ottawa Scale for observational studies to assess risk of bias in each research study extracted (Wells et al., Tugwell). A score of ≥ 7 was deemed a high-quality study with low risk of bias.

### 2.5. Outcome assessment and exploratory variables

The outcome of interest was the month of birth for schizophrenia patients and healthy controls. The following exploratory variables were defined a priori: age of study (defined as the time from the median of the study period), latitude, daylight, and infections previously implicated in schizophrenia pathogenesis (including influenza, meningococcal disease, enterovirus and toxoplasmosis) as detailed in our protocol published on PROSPERO, ID: CRD42022299737. These variables were selected because of existing evidence of their role in contributing to the underlying seasonal variation of schizophrenia births (Davies et al., 2003a; Parker et al., 2000; Selten et al., 2000; Suvisaari et al., 2001; Torrey et al., 1977; Saatci et al., 2021; Khandaker et al., 2012).

### 2.6. Statistical analysis

For our outcome of interest (month-of-schizophrenia births), we used random-effects meta-analyses using the generic inverse variance method were carried out to calculate summary estimates. Heterogeneity, a measure of the percentage of the total observed variance and between-study variation, was calculated using I². An I² greater than 50% was considered as high heterogeneity. A priori selected factors (latitude, daylight and infection) that contributed to the heterogeneity were explored using random-effects meta-regression model (mixed-effects model), using the Restricted Maximum Likelihood (REML) estimator. Furthermore, Egger’s test were used to evaluate any publication bias. All analyses were carried out using the ‘dmetar’ package in R.

We assessed seasonal variation of schizophrenic births compared to the general population using the Cosinor regression model, using month of birth from each study to represent the time. This generalized linear model fits a linear regression under the Poisson distribution using cosine and sine terms that describe the sinusoid and provides information on the mean, amplitude (distance from mean to the peak) and the phase (the peak month) (Barnett, 2010). We used month of birth from each study to represent time. Analyses were carried out using the ‘season’ package in R.

To further explore the association between schizophrenia seasonality and our selected exploratory variables (latitude, daylight and infection), we carried out two separate statistical analyses. For latitude and daylight, data were publicly available for all study regions through Google Maps and the World Meteorological Organization (Organization), respectively. We employed linear regression to investigate the relationship between latitude/daylight and schizophrenia seasonality.

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### Table 1

| Study Author, Year | Study Design | Country | Study Time Period | Number of included schizophrenia patients | Outcome of Interest | Division of year for analysis | Newcastle Ottawa Score | Findings |
|--------------------|-------------|---------|-------------------|------------------------------------------|---------------------|-----------------------------|---------------------|---------|
| Mino et al., 2006  | Population-based | Japan   | Schizophrenia births: 1910–1996 General Population Births: 1940–1996 | 88778 | Schizophrenia | Monthly | 6 | Excess births seen in Winter/Spring for both females and males. |
| Cheng et al., 2013 | Population-based | Taiwan  | All births: 1950–1989 | 5047 | Schizophrenia | Monthly | 7 | Excess births seen in Winter/Spring compared to Autumn/Summer. Seen in females. |
| Parker et al., 2000 | Population-based | Singapore | Schizophrenia births: 1930–1984 General Population Births: 1960–1984 | 9141 | Schizophrenia | Monthly | 6 | No seasonal excess births for schizophrenia patients. Identified. Trough months include March–April. |
| Selten et al., 2000 | Population-based | Netherlands | All births: 1926–1970 | 29891 | Schizophrenia | Monthly | 8 | Excess late spring/early summer births and deficit in late summer/early autumn in schizophrenia patients. |
| Suvisaari et al., 2001 | Population-based | Finland  | All births: 1950–1969 | 15389 | Schizophrenia | Monthly | 8 | Excess winter/spring births in schizophrenia patients. |
| Disanto et al., 2012 | Population-based | UK      | Schizophrenia diagnosis: 2003–2011 General Population Births: 1950–1990 | 26676 | Schizophrenia | Monthly | 6 | Excess schizophrenia births in winter (January) and deficit in summer (July). |
| Karlsson et al., 2019 | Population-based | Sweden   | All births: 1940–1997 | 30684 | Schizophrenia | Monthly | 8 | Excess winter (December) schizophrenia births. |
| Munoz-Delgado et al., 2003 | Population-based | Mexico  | Schizophrenia diagnosis: 1913–1989 General Population Births: 1991–2001 | 2288 | Schizophrenia | Monthly | 5 | Non-significant increment in Autumn/Winter months. |
| Torrey et al., 1977 | Case-Control | USA     | All births: 1920–1955 | 53584 | Schizophrenia | Monthly | 7 | Higher schizophrenia births seen from December to May (peak March/April). |
| Carrion-Baralt et al., 2004 | Population-based | Puerto Rico | All births: 1932–1967 | 710 | Schizophrenia | Monthly | 7 | Higher schizophrenia births seen in February. |

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For infective agents, complete monthly infection rates were publicly available for only one country, Taiwan, through their Centres for Disease Control publications (https://www.cdc.gov.tw/En). To explore the strength and direction of association between infection rates and schizophrenia seasonality we used Kendall’s rank correlation, as the data is ordinal and non-parametric. We included average rates of infection over 4 years for enterovirus (Suvisaari et al., 1999), influenza (Brown et al., 2004), toxoplasmosis (Brown et al., 2005) and meningococcal disease (Abrahao et al., 2005).

3. Results

A total of 1093 publications were screened to assess their eligibility for inclusion. 35 articles were eligible for full-text review and 10 publications met the inclusion criteria (Fig. 1). The included studies and their population characteristics are presented in Table 1. Quality assessment found that 6 out of 10 studies were of a high quality with low risk of bias. Furthermore, Egger’s test did not identify any publication bias (Table 2). The excluded studies and the reasons their exclusion are detailed in Supplementary Table 3.

3.1. Month of birth and schizophrenia

There were 262,188 schizophrenic births in total. We identified significantly higher schizophrenia births in December [1.04 (95%CI 1.00–1.08)], January [1.06 (95%CI 1.03–1.11)] and February [1.03 (95% CI 1.00–1.05)]. There were significantly lower schizophrenia births in July [0.97 (95% CI 0.94–0.99)], August [0.96 (95% CI 0.93–0.98)],

| Month  | Number of studies | RR (95%CI) | p-value | Heterogeneity (I²) | Egger’s Test (p-value) |
|--------|-------------------|------------|---------|--------------------|-----------------------|
| January | 10                | 1.06       | <0.001  | 77%                | 0.36                  |
| February| 10                | 1.03       | 0.02    | 55%                | 0.67                  |
| March  | 10                | 1.03       | 0.21    | 89%                | 0.35                  |
| April  | 10                | 1.01       | 0.32    | 41%                | 0.59                  |
| May    | 10                | 1.01       | 0.25    | 23%                | 0.23                  |
| June   | 10                | 0.98       | 0.32    | 78%                | 0.90                  |
| July   | 10                | 0.97       | 0.01    | 59%                | 0.72                  |
| August | 10                | 0.96       | 0.04    | 70%                | 0.54                  |
| September | 10           | 0.95      | <0.001  | 71%                | 0.86                  |
| October | 10               | 0.97      | <0.001  | 12%                | 0.33                  |
| November | 10            | 0.99      | 0.36    | 58%                | 0.26                  |
| December | 10              | 1.04      | 0.04    | 83%                | 0.22                  |

Fig. 2. Meta-analysis of schizophrenia risk by month of birth. Relative risk (RR) and 95% confidence intervals are shown for each month.
October

| Month          | Month of Birth Effect | Latitude Coefficient | p-value | Daylight Coefficient | p-value |
|----------------|-----------------------|----------------------|---------|----------------------|---------|
| December       | 0.00014               | 0.65                 | 0%      | 0.0002               | 0.0004  |
| January        | 0.0004 (0.0004 to 0.0023) | 0.65                 | 0%      | 0.0002 (0.00007 to 0.0004) | 0.0016 |
| February       | 0.0007 (0.0018)       | 0.65                 | 0%      | 0.0010 (0.0004 to 0.0005) | 0.0004  |
| March          | 0.0005 (0.00023 to 0.0024) | 0.65                 | 0%      | 0.0008 (0.00035 to 0.0006) | 0.0006  |
| April          | 0.0011 (0.0002 to 0.0025) | 0.65                 | 0%      | 0.0008 (0.0003 to 0.0009) | 0.0006  |
| May            | 0.0003 (0.00015 to 0.0009) | 0.65                 | 0%      | 0.0005 (0.00005 to 0.0005) | 0.0006  |
| June           | 0.0005 (0.00015 to 0.0025) | 0.65                 | 0%      | 0.0006 (0.0002 to 0.0005) | 0.0006  |
| July           | 0.0004 (0.00012 to 0.0005) | 0.65                 | 0%      | 0.0006 (0.0004 to 0.0007) | 0.0007  |
| August         | 0.00 (0.0018 to 0.0018) | 0.65                 | 0%      | 0.0006 (0.0003 to 0.0005) | 0.0006  |
| September      | 0.0002 (0.0015 to 0.0020) | 0.65                 | 0%      | 0.0006 (0.00011 to 0.0001) | 0.0006  |
| October        | 0.0003 (0.00013 to 0.0007) | 0.65                 | 0%      | 0.0005 (0.0004 to 0.0006) | 0.0006  |
| November       | 0.0013 (0.00007 to 0.0003) | 0.65                 | 0%      | 0.0006 (0.00005 to 0.0005) | 0.0006  |
| December       | 0.0013 (0.00005 to 0.0019) | 0.65                 | 0%      | 0.0006 (0.00005 to 0.0005) | 0.0006  |

### Table 4
Linear regression analysis for latitude and daylight in Northern Hemisphere studies.

#### 3.2. Candidates that can explain the month-of-birth effect

#### 3.2.1. Latitude

Latitude was reported for all study regions. We did not identify any association between the relative risk of schizophrenia and latitude (Table 4). Further, grouping studies into latitude bands (<20°, 20°–39°, 40°–60°, and >60°) did not reveal any differences in the within-year fluctuations of schizophrenia births (Supplementary Fig. 1).

#### 3.2.2. Daylight

Daylight was reported for 8 out of 10 study regions. We did not identify any association between the relative risk of schizophrenia and daylight levels reported for the country of study origin (Table 4).

#### 3.2.3. Infections

We found a significant negative correlation between monthly severe enterovirus cases (peak summer, August) and schizophrenia births (peak winter, January–February) (tau = −0.57, p = 0.0099) using data from Taiwan. This corresponds to enterovirus infection during the second trimester of pregnancy. We did not observe any correlation between other monthly infections of severe influenza, toxoplasmosis and meningococcal disease and schizophrenia births (Table 5).

### Table 5
Association between month of birth and monthly infection rates in Taiwan.

| Month of Birth | Month of Influenza cases | Kendall Tau | p-value | Month of enterovirus cases | Kendall Tau | p-value | Month of toxoplasma cases | Kendall Tau | p-value | Month of meningococcal cases | Kendall Tau | p-value |
|----------------|--------------------------|-------------|---------|---------------------------|-------------|---------|---------------------------|-------------|---------|-------------------------------|-------------|---------|
| January        | 486                      | 189         | 0.17    | 0.45                      | 1.3         | −0.57   | 0.0099                    | 0.5         | −0.12  | 0.61                          | 1           | 0.29    |
| February       | 513                      | 277         | 1       | 2                         | 1           | 0.15    | 0.75                       | 1           | 0.75    | 0.75                          | 1           | 0.75    |
| March          | 425                      | 126         | 0.3     | 1.5                       | 1           | 0.75    | 0.75                       | 1           | 0.75    | 0.75                          | 1           | 0.75    |
| April          | 383                      | 50          | 1.7     | 0.75                      | 0.75        | 0.75    | 0.75                       | 0.75        | 0.75    | 0.75                          | 0.75        | 0.75    |
| May            | 372                      | 49          | 3       | 1                         | 1           | 0.75    | 0.75                       | 0.75        | 0.75    | 0.75                          | 0.75        | 0.75    |
| June           | 355                      | 94          | 3.2     | 1.5                       | 1           | 0.75    | 0.75                       | 0.75        | 0.75    | 0.75                          | 0.75        | 0.75    |
| July           | 355                      | 124         | 3.2     | 1.5                       | 1           | 0.75    | 0.75                       | 0.75        | 0.75    | 0.75                          | 0.75        | 0.75    |
| August         | 355                      | 82          | 3.2     | 1.5                       | 1           | 0.75    | 0.75                       | 0.75        | 0.75    | 0.75                          | 0.75        | 0.75    |
| September      | 414                      | 69          | 2.8     | 1.5                       | 1           | 0.75    | 0.75                       | 0.75        | 0.75    | 0.75                          | 0.75        | 0.75    |
| October        | 444                      | 43          | 2.7     | 1.5                       | 1           | 0.75    | 0.75                       | 0.75        | 0.75    | 0.75                          | 0.75        | 0.75    |
| November       | 438                      | 51          | 2.2     | 1.5                       | 1           | 0.75    | 0.75                       | 0.75        | 0.75    | 0.75                          | 0.75        | 0.75    |
| December       | 455                      | 81          | 3       | 1.5                       | 1           | 0.75    | 0.75                       | 0.75        | 0.75    | 0.75                          | 0.75        | 0.75    |
4. Discussion

In this systematic review and meta-analysis, we report an excess of schizophrenia births in December, January and February. We included 262,188 individuals with schizophrenia from 10 studies encompassing a range of regions and latitudes making this the largest study to date. Overall, our findings broadly support the previous work by Davies and colleagues (Davies et al., 2003b) who found an excess of winter–spring births compared to summer–autumn births. However, we were able to expand our analyses to provide more precise risk estimates by month of birth. This is particularly relevant because the four discrete seasons in temperate regions are not well defined in the extremes of latitude, but the month of birth effect has been reported in low latitude counties such as Puerto Rico (Carrion-Baralt et al., 2004) and Mexico (Munoz-Delgado et al., 2003).

The underlying mechanisms mediating the month-of-birth effect in schizophrenia births is not well understood. Previous studies have postulated that latitude and vitamin D levels could play a role in schizophrenia (Byles et al., 2018; McGrath et al., 2010). In line with this, Davies and colleagues showed that higher latitude countries had more schizophrenia births in the winter months as well as longer periods of risk within the year (Davies et al., 2003a). However, we did not find any association between latitude and the magnitude of the month-of-birth effect or the length of risk period. Furthermore, we found no association between daylight and the magnitude of the month-of-birth effect. Our analyses were better equipped to address this question because more studies from low latitude countries were available for inclusion in this meta-analysis. Collectively, our results suggest that latitude and daylight are unlikely to contribute to the month-of-birth effect in schizophrenia. Thus, further work exploring other candidate environmental risk factors is warranted. It is however important to recognise that our results do not rule out the importance of these factors in the pathogenesis of schizophrenia altogether.

Epidemiological studies have identified maternal infections during pregnancy as an important environmental risk factor in schizophrenia (Buka et al., 2001, 2008; Babulas et al., 2006; Saatci et al., 2021). In particular, infections during the second trimester seem to mediate this increased risk in schizophrenia (Saatci et al., 2021). This is supported by observations that maternal immune activation in mice at a time point analogous to the second trimester leads to downregulation of schizophrenia associated genes in the foetal mouse brain (Handunnetthi et al., 2021) and behavioural deficits in adult offspring (Meyer et al., 2008). This window of vulnerability corresponds to disease relevant neurodevelopmental processes such neurogenesis, neuronal cell migration and synaptogenesis (Gumusoglu and Stevens, 2019). Therefore, we explored the relationship between several infections implicated in schizophrenia and the month-of-birth effect using data from Taiwan. Intriguingly, we identified a strong negative correlation between monthly enterovirus cases and schizophrenia births, with the peaks of enterovirus infection in August and schizophrenia births in January–February. Furthermore, the seasonality of non-polio enterovirus infections appears to be similar across different regions with a peak in the summer months (van der Sanden et al., 2009; Bubba et al., 2020; Kadambari et al., 2014) and have consistently shown this seasonal variation over the last five decades (van der Sanden et al., 2009). Central nervous system involvement in enterovirus infections during childhood is well established, with polio causing long-term neuropsychiatric complications (Wiestler et al., 2007) and non-polio enteroviruses resulting in meningitis and subsequent neurodevelopmental complications (Chang et al., 2007; de Ceano-Vivas et al., 2021). Our findings for the first time connect this neurotropic enterovirus infection to the window of vulnerability in the second trimester, bringing together two independent lines of research in schizophrenia pathogenesis.

There were several limitations to this study. Firstly, despite efforts to account for between-study variance, there remained a high level of heterogeneity in our meta-analysis. We were unable to fully explain this heterogeneity in meta-regression analyses through age of study, latitude and daylight, indicating unidentified study-level factors are likely to contribute to the heterogeneity. Further, the limited number of available studies meant that some of our meta-regression analyses may have been subject to overfitting. Secondly, as this is meta-analysis based on observational studies, there remains the possibility of bias introduced from studies of varying quality. Thirdly, our analyses examining the factors that contribute to the month-of-birth effect were exploratory and we were limited by the completeness and quality of available data on these risk factors. Specifically, we only had infection data from one country and our finding will need further exploration and replication. We acknowledge that several environmental risk factors, including many other neurotropic infections that were not explored in this study, could play a role in mediating the month-of-birth effect and that further studies are needed.

5. Conclusion

Overall, we carried out an updated meta-analysis of studies investigating the month-of-birth effect and schizophrenia to highlight increased schizophrenia births in December, January and February. We subsequently explored factors that could explain this month-of-birth effect and provided novel insight into the role of enteroviruses in mediating this long held observation in schizophrenia. Further research is warranted to expand these exploratory findings and to understand how enterovirus infections could exert deleterious effects on neurodevelopmental processes. It would also be interesting investigate if infections can interact with other factors such as latitude to mediate the month-of-birth effect. Importantly, treatment and prevention of maternal infection during pregnancy are tractable health goals and thus these findings carry clear implications for future prevention strategies in schizophrenia.

Author contributions

DS: Methodology, Data curation, Formal analysis, Writing – original draft; Writing – review & editing; TJ: Methodology, Writing – original draft; Writing – review & editing; MS: Methodology, Writing – original draft; Writing – review & editing; AVN: Methodology, Writing – original draft; Writing – review & editing; LH: Conceptualization, Funding acquisition, Methodology, Writing – original draft; Writing – review & editing.

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Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jbiib.2022.100486.

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