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

Defne Saatci [a], Thomas Johnson [b], Madeleine Smee [b], Adrienne van Nieuwenhuizen [c], Lahiru Handunnetthi [b,d,*]

[a] Nuffield Department of Primary Care Health Sciences, Radcliffe Observatory Quarter, Woodstock Road, University of Oxford, OX2 6GG, UK
[b] Wellcome Centre for Human Genetics, University of Oxford, Roosevelt Drive, OX3 9DU, UK
[c] Weill Institute for Neurosciences, School of Medicine, The University of California, San Francisco, 401, Parnassus Ave, San Francisco, CA, 94143, USA
[d] Nuffield Department of Clinical Neurosciences. Level 6, West Wing, John Radcliffe Hospital, University of Oxford, OX3 9DU, UK

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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 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 1.03–1.1)] 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 European and North American countries suggested that latitude is linked to the excess winter births (Davies et al., 2003a; 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., 2019; 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

* Corresponding author. Clinical Lecturer in Neurology Wellcome Centre for Human Genetics University of Oxford, OX3 9DU, UK.
E-mail address: lahiru@well.ox.ac.uk (L. Handunnetthi).

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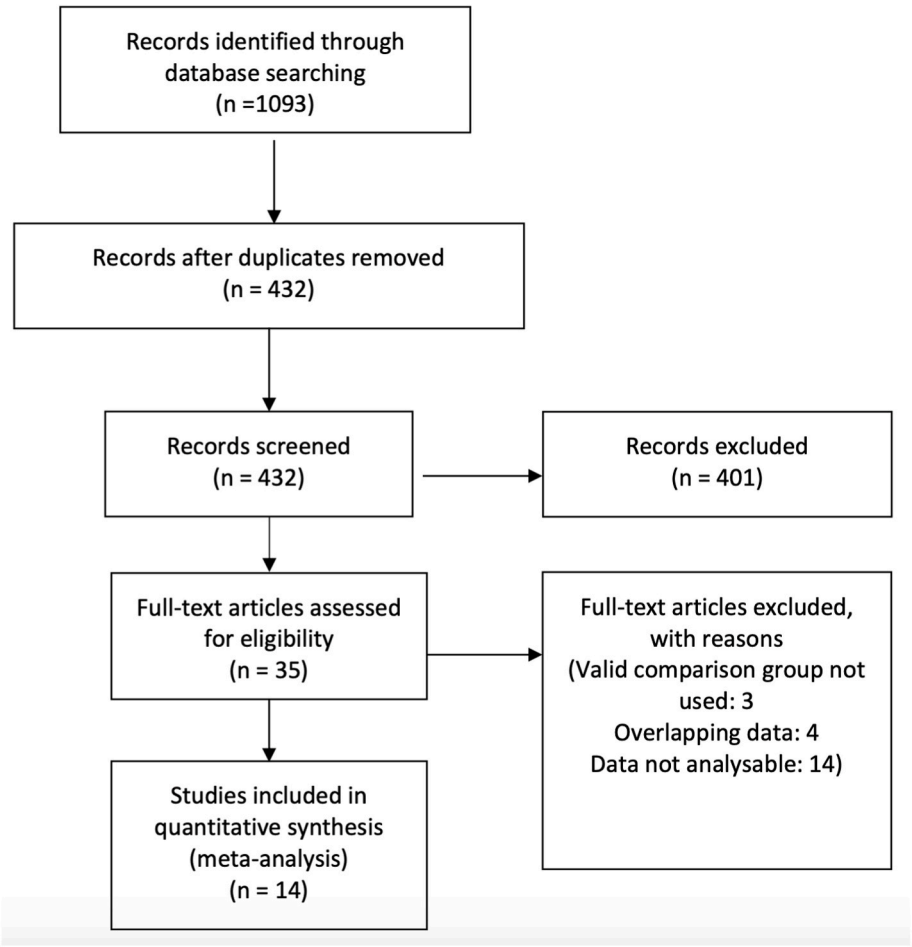

Fig. 1. Study flow diagram.

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

Table 1
Population and study characteristics of included studies within the meta-analysis.

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	Single-centre	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	Population-based	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	Case-Control	Puerto Rico	All births: 1932–1967	710	Schizophrenia	Monthly	7	Higher schizophrenia births seen in February.

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 $\geq$ 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 I^2. An I^2 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.

Table 2
Meta-analysis of risk of schizophrenia by month of birth.

Months	Number of studies	RR (95%CI)	p-value	Heterogeneity (I^2)	Egger's Test (p-value)
January	10	1.06 (1.03–1.1)	<0.001	77%	0.36
February	10	1.03 (1.00–1.05)	0.02	55%	0.67
March	10	1.03 (0.98–1.07)	0.21	89%	0.35
April	10	1.01 (0.99–1.03)	0.32	41%	0.59
May	10	1.01 (0.99–1.03)	0.25	23%	0.23
June	10	0.98 (0.95–1.02)	0.32	78%	0.90
July	10	0.97 (0.94–0.99)	0.01	59%	0.72
August	10	0.96 (0.93–0.98)	0.04	70%	0.54
September	10	0.95 (0.92–0.98)	<0.001	71%	0.86
October	10	0.97 (0.95–0.98)	<0.001	12%	0.33
November	10	0.99 (0.96–1.01)	0.36	58%	0.26
December	10	1.04 (1.00–1.08)	0.04	83%	0.22

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 1.03–1.1)] 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)],

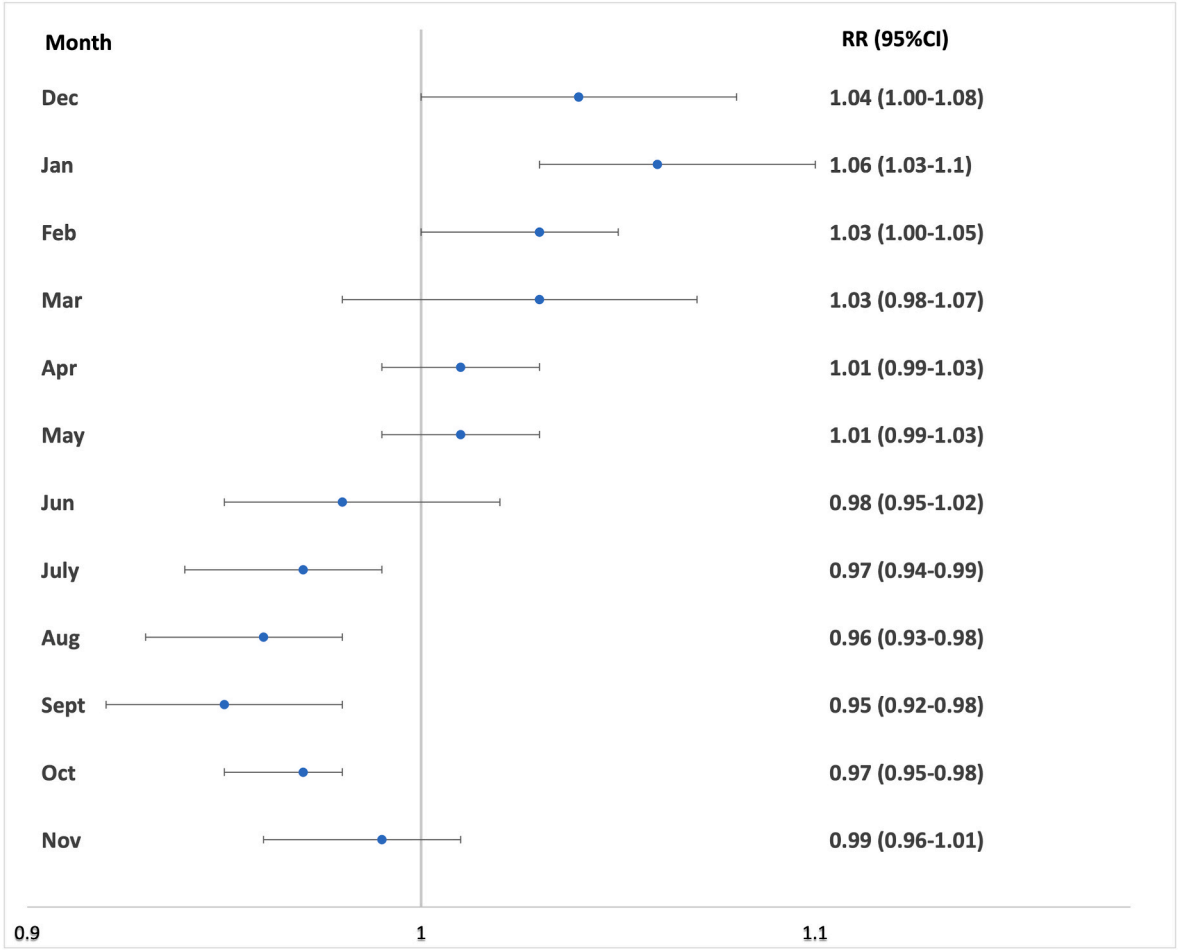

Fig. 2. Meta-analysis of schizophrenia risk by month of birth. Relative risk (RR) and 95% confidence intervals are shown for each month.

Table 3
Meta-regression analysis for latitude, daylight and age of study.

	Latitude Coefficient (95%CI)	p-value	Variance accounted	Daylight Coefficient (95%CI)	p-value	Variance accounted	Age of Study Coefficient (95%CI)	p-value	Variance accounted (%)
January	0.0004 (−0.0014 to 0.0023)	0.65	0%	−0.0002 (−0.0007 to 0.0004)	0.52	0%	−0.0004 [-0.0023 to 0.0016]	0.19	0
February	−0.0007 (−0.0018 to 0.0005)	0.28	41%	0.00 (−0.0004 to 0.0005)	0.38	0%	0.0006 [-0.0009 to 0.0020]	0.84	0
March	0.00 (−0.0023 to 0.0024)	0.97	0%	0.0005 (−0.0003 to 0.0013)	0.49	4%	0.0006 [-0.0018 to 0.0030]	0.87	0
April	0.0011 (−0.0002 to 0.0025)	0.10	0%	0.0003 (−0.0003 to 0.0009)	0.46	7%	0.0015 [0.0004 to 0.0026]	0.006	92
May	−0.0003 (−0.0015 to 0.0009)	0.60	0%	−0.0001 (−0.0005 to 0.0003)	0.58	0%	0.0010 [0.00 to 0.0021]	0.05	96
June	0.0005 (−0.0015 to 0.0025)	0.60	0%	0.0003 (−0.0002 to 0.0009)	0.18	3%	0.0003 [-0.0018 to 0.0024]	0.75	0
July	0.0004 (−0.0012 to 0.0019)	0.65	0%	0.0001 (−0.0004 to 0.0005)	0.68	0%	0.0005 [-0.0011 to 0.0021]	0.54	0
August	0.00 (−0.0018 to 0.0018)	0.90	0%	0.0004 (−0.0003 to 0.0011)	0.09	2%	0.0018 [0.00 to 0.0035]	0.05	18
September	0.0002 (−0.0015 to 0.0020)	0.80	0%	−0.0005 (−0.0011 to 0.0001)	0.13	16%	−0.0012 [-0.0029 to 0.0005]	0.15	21
October	−0.0003 (−0.0013 to 0.0007)	0.53	0%	0.00 (−0.0004 to 0.0003)	0.78	0%	−0.0006 [-0.0016 to 0.0004]	0.26	0
November	0.0013 (−0.0007 to 0.0033)	0.70	0%	−0.0002 (−0.0007 to 0.0003)	0.36	14%	−0.002 [-0.0031 to −0.001]	<0.001	100
December	−0.0013 (−0.0045 to 0.0019)	0.43	0%	0.0006 (−0.0005 to 0.0016)	0.28	0%	−0.0030 [-0.006 to 0.0001]	0.06	15

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

Month-of-Birth Effect	Month	Latitude Coefficient	p-value	Daylight Coefficient	p-value
Peak	December	−0.0019	0.41	0.001	0.22
	January	0.0011	0.25	−0.0003	0.24
	February	−0.00037	0.84	−0.0006	0.17
Trough	July	0.00010	0.23	0.00009	0.72
	August	−0.00023	0.85	0.00007	0.12
	September	−0.00047	0.57	−0.0003	0.31
	October	−0.00047	0.45	−0.0002	0.31

September [0.95 (95%CI 0.92–0.98)]and October [0.97 (95%CI 0.95–0.98)] (Table 2, Fig. 2). Heterogeneity was low for October, moderate for April and May, and high for all other months (Table 2). Meta-regression analyses investigating age of study, latitude and daylight individually did not account for the heterogeneity observed in those months with significantly higher schizophrenia births (Table 3). Furthermore, seasonality was detected for schizophrenic births compared to the general population using the Cosinor test with the peak corresponding to February and the trough corresponding to August ($p < 0.001$, amplitude = 158 births, phase = 2.2, low point = 8.2).

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 schizophrenia	Monthly Influenza cases	Kendal Tau	p-value	Monthly enterovirus cases	Kendal Tau	p-value	Monthly toxoplasma cases	Kendal Tau	p-value	Monthly meningoccocal cases	Kendal 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	0.23
February	513	277			1			2			0.75		
March	425	126			0.3			1.5			1.5		
April	383	50			1.7			0.75			0.25		
May	372	49			3			1			0.25		
June	355	94			3.2			1.5			0		
July	355	124			3.2			1.5			1		
August	355	82			3.7			2.25			0.75		
September	414	69			2.8			0.75			0.75		
October	444	43			2.7			1.25			0.75		
November	438	51			2.2			1.5			0.75		
December	455	81			3			1.5			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 (Eyles 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 counties were available for inclusion in this meta-analysis. Collectively, our results suggests 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 (Nielsen 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.bbih.2022.100486.

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