A Systematic Review and Meta-analysis of Northern Hemisphere Season of Birth Studies in Schizophrenia

by Geoffrey Davies, Joy Welham, David Chant, E. Fuller Torrey, and John McGrath

Abstract

Based on the epidemiological finding that individuals with schizophrenia tend to be born in winter/spring when compared to the general population, we examined (1) the strength and timing of this effect in Northern Hemisphere sites, and (2) the correlation between the season of birth effect size and latitude. Studies were located via electronic data sources, published citations, and letters to authors. Inclusion criteria were that studies specify the diagnostic criteria used, that studies specify the counts of schizophrenia and general population births for each month, and that subjects and the general population be drawn from the same birth years and catchment area. We extracted data from eight studies based on 126,196 patients with schizophrenia and 86,605,807 general population births and drawn from 27 Northern Hemisphere sites. Comparing winter/spring versus summer/autumn births, we found a significant excess for winter/spring births (pooled odds ratio = 1.07; 95% confidence interval 1.05, 1.08; population attributable risk = 3.3%). There was a small but significant positive correlation between the odds ratios for the season of birth comparison and latitude ($r = 0.271, p < 0.005$). Furthermore, the shape of the seasonality in schizophrenia births varied by latitude band. These variations may encourage researchers to generate candidate seasonally fluctuating exposures.

Keywords: Schizophrenia, epidemiology, season of birth, latitude.

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The season of birth effect in schizophrenia is one of the most replicated features in schizophrenia epidemiology, with most Northern Hemisphere studies finding a 5 to 15 percent excess in the winter and early spring (Torrey et al. 1996). A recent meta-analysis of seasonality findings from the Southern Hemisphere, however, failed to detect this effect (McGrath and Welham 1999). One possible explanation may relate to the latitude, with greater size of effect at high latitudes (reviewed by Torrey et al. 1997). The countries included in the Southern Hemisphere meta-analysis (Australia, New Zealand, Reunion Island, and South Africa) are closer to the equator than the Northern European, Scandinavian, and North American sites that have contributed most season of birth studies. Given that a meta-analysis has not been conducted on Northern Hemisphere studies to date, the aim of this study was to undertake such a systematic review while examining the potential effect of latitude.

Methods

Electronic data bases (Medline, PsychLIT, Embase, LILACS) were searched for relevant articles using the search string "(schizophrenia or psychosis) and (season*)." The electronic search was completed on all available years until the end of 2000. Citations in review articles and other relevant publications were checked. Letters were sent to authors of studies that met the inclusion criteria in order to access data suitable for this study.

Based on expert commentaries (Bradbury and Miller 1985; Torrey et al. 1997), we selected four readily operationalized quality criteria, each of which was required for inclusion in the meta-analysis. We required that the publications (1) state the diagnostic criteria used (any explicit criteria were sufficient); (2) state the counts of schizophrenia and general population births for each month; (3) specify and match the years of birth of the subjects and of the general population (e.g., both cases and general population births based on those born between 1920 and 1950); and (4) draw the patient group and the general population from the identical catchment area (e.g., city, state, nation).

From each publication, we attempted to extract the observed and expected births for each month, or, if monthly data were not available, for each season. If these

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data were not available from the publications, we wrote to the senior authors to obtain them.

For each study site, we allocated the latitude as defined in the Getty *Thesaurus of Geographical Names* (Getty Research Institute). Ideally, the latitude for large areas should be based on population-based spatial distributions averaged over the years during which the births occurred. However, such data were not available.

The meta-analysis was conducted using Arcus Biomedical Statistics Software (Arcus 1997). The data were analyzed using the Mantel-Haenzel odds ratio and a fixed effect model. We used the SAS statistical software to conduct the subsequent regression with latitude (SAS Institute 1998).

Results

Of the 88 studies identified from the search, only 8 studies met all inclusion criteria; they are described in table 1. Full details are available on request.

From these studies, data for 126,196 individuals with schizophrenia and 86,605,807 general population births from 27 different sites (including 21 U.S. States from Torrey et al. 1977) were extracted. These countries covered latitudes from 1.4° to 64.0° North. Singapore (at latitude 1.4°) was the only study between 0° and 30° North.

As figure 1 indicates, there was a small but significant risk of schizophrenia in offspring born in winter/spring in the Northern Hemisphere, with a pooled odds ratio of 1.07 (95% confidence interval 1.05, 1.08). The population attributable risk for this exposure (i.e., being born in winter or early spring) was only 3.3 percent.

Figure 2 shows the linear regression of these odds ratios by latitude. The correlation gave a significant slope estimate of $r = 0.271$ ($p < 0.005$), corresponding to a nearly 0.02 percent increase in odds per 10 degrees increase in latitude. When Singapore was removed from the analysis, the slope became attenuated with a trend association evident ($r = 0.261$; $p < 0.085$).

In figure 3, for various latitude bands, the within-year fluctuations are shown as the ratio of observed counts of schizophrenia births to the counts one would expect if the proportion followed that of the general population births. Between these bands, the amplitude of these fluctuations ranged from a minimum of 0.87 to a maximum of 1.03 and demonstrated identifiable troughs during different consecutive months.

Discussion

The overall excess of winter/spring schizophrenia births was confirmed in this meta-analysis of selected Northern Hemisphere studies. This is important because meta-analyses combine data from small and large studies, thus allowing greater precision in the estimate of the effect size. However, while the regression analysis suggested a small but significant increase in the magnitude of the seasonal effect with increasing latitude, these data should be interpreted with caution because of the fewer studies at low latitudes able to be included in this analysis. The data also suggest that the size of the effect may be smaller in countries above 50° (see Finland, Denmark, Germany, and the Netherlands). Thus, the relationship between latitude and the size of the season of birth effect may be nonlinear (an inverted U shape). Some possible explanations are that factors related to diagnostic stringency (e.g., the standard in Scandinavia compared with other countries) or the distribution of potential exposures (e.g., viruses or vitamin D) are not linear across the latitudes. There were also some differences in methods in the included studies. For example, there were differences in the birth years covered and the diagnostic system used, which led to the possibility of birth cohort effects (e.g., where the magnitude of the season of birth effect changes over time and older cohorts include a greater number of affective patients).

Comparing the shape of the monthly rates by latitude band provides insight into how aggregating data into half-years or seasons (as in our meta-analysis) can result in the loss of information (Torrey et al. 1997). For example, the data from Singapore suggest a brief trough from March to April. This trough appears to gradually shift toward autumn in data collected farther away from the equator. The nadir of the trough becomes most clear in September in the most northern latitude band (a band that includes the large populations from the Netherlands, Denmark, and Finland). Whereas the magnitude of peaks and troughs does not change dramatically across the latitudes, the timing of the trough more clearly changes relative to any peak. This finding lends weight to the point made by Bradbury and Miller (1985) and Torrey et al. (1997): when studying seasonality, troughs may be just as illuminating as peaks. It also underscores the point that seasons defined for temperate regions with four relatively discrete seasons may not define well seasons in the extreme latitudes, for example the wet/dry seasons characteristic of the tropics (de Messias et al. 2001) or the light/dark cycle of the arctic north. Categorizing the data into standard defined seasons may obscure these subtle variations.

The meta-analysis found that the population attributable risk for birth during winter or spring was small: 3.3 percent. In contrast, Mortensen et al. (1999) found that while the seasonal excess of schizophrenia births in Denmark was small (relative risk = 1.11), this factor was associated with a population attributable risk of 10.5 percent. However, as season of birth is a risk indicator, it can serve

Table 1. Studies included in the review

Band	Latitude	Origin of data	Author	Count	Birth years	Diagnostic system
< 10°	1.4°	Singapore	Parker et al. (2000)	9,655	1930–1984	ICD 295.0–4, 9
10–19°			None			
20–29°			None			
30–39°		United States				
	30°	Texas	Torrey et al. (1977)	3,159	1933–1955	*DSM–II* 295.0–99
	32°	Mississippi	Torrey et al. (1977)	831	1921–1955	*DSM–II* 295.0–99
	32°	Georgia	Torrey et al. (1977)	389	1927–1955	*DSM–II* 295.0–99
	33°	Alabama	Torrey et al. (1977)	886	1920–1924; 1928–1955	*DSM–II* 295.0–99
	34°	South Carolina	Torrey et al. (1977)	753	1928–1955	*DSM–II* 295.0–99
	35°	Arkansas	Torrey et al. (1977)	393	1927–1955	*DSM–II* 295.0–99
	35.3°	North Carolina	Torrey et al. (1977)	4,442	1920–1955	*DSM–II* 295.0–99
	37°	Virginia	Torrey et al. (1977)	2,520	1920–1955	*DSM–II* 295.0–99
	37°	Kentucky	Torrey et al. (1977)	1,853	1920–1955	*DSM–II* 295.0–99
	38°	Missouri	Torrey et al. (1977)	14,964	1927–1955	*DSM–II* 295.0–99
	39°	West Virginia	Torrey et al. (1977)	652	1925–1955	*DSM–II* 295.0–99
40–49°		United States				
	40°	Illinois	Torrey et al. (1977)	7,852	1922–1955	*DSM–II* 295.0–99
	40°	Ohio	Torrey et al. (1996)	17,733	1925–1975	*DSM–II–R* 295.1–3,7,9
	40.8°	Pennsylvania	Torrey et al. (1996)	18,334	1925–1975	*DSM–II–R* 295.1–3,7,9
	41.7°	Rhode Island	Torrey et al. (1977)	1,339	1920–1955	*DSM–II* 295.0–99
	41.8°	Connecticut	Torrey et al. (1977)	2,519	1920–1955	*DSM–II* 295.0–99
	42.2°	Massachusetts	Torrey et al. (1977)	5,007	1920–1955	*DSM–II* 295.0–99
	44°	New Hampshire	Torrey et al. (1977)	281	1920–1955	*DSM–II* 295.0–99
	45°	Wisconsin	Torrey et al. (1977)	1,152	1920–1955	*DSM–II* 295.0–99
	45°	Maine	Torrey et al. (1977)	3,600	1920–1955	*DSM–II* 295.0–99
	46°	Minnesota	Torrey et al. (1977)	992	1920–1955	*DSM–II* 295.0–99
	49.5°	Germany (Mannheim)	Häfner et al. (1987)	2,020	*ns*	ICD 295.0–9
50+°	52.25°	The Netherlands	Selten et al. (2000)	29,891	1926–1970	ICD–295
	52.5°	Germany (Berlin)	Franzek and Beckmann (1992)	1,299	1896–1965	*DSM–III–R*
	56.5°	Denmark	Mortensen et al. (1999)	2,669	1968–1993	ICD
	64°	Finland	Suvisaari et al. (2000)	15,892	1950–1969	*DSM–III–R*

Note.—*ns* = nonsignificant.

Figure 1. Cochrane plot for the winter/spring and summer/autumn comparison (rank ordered by latitude)

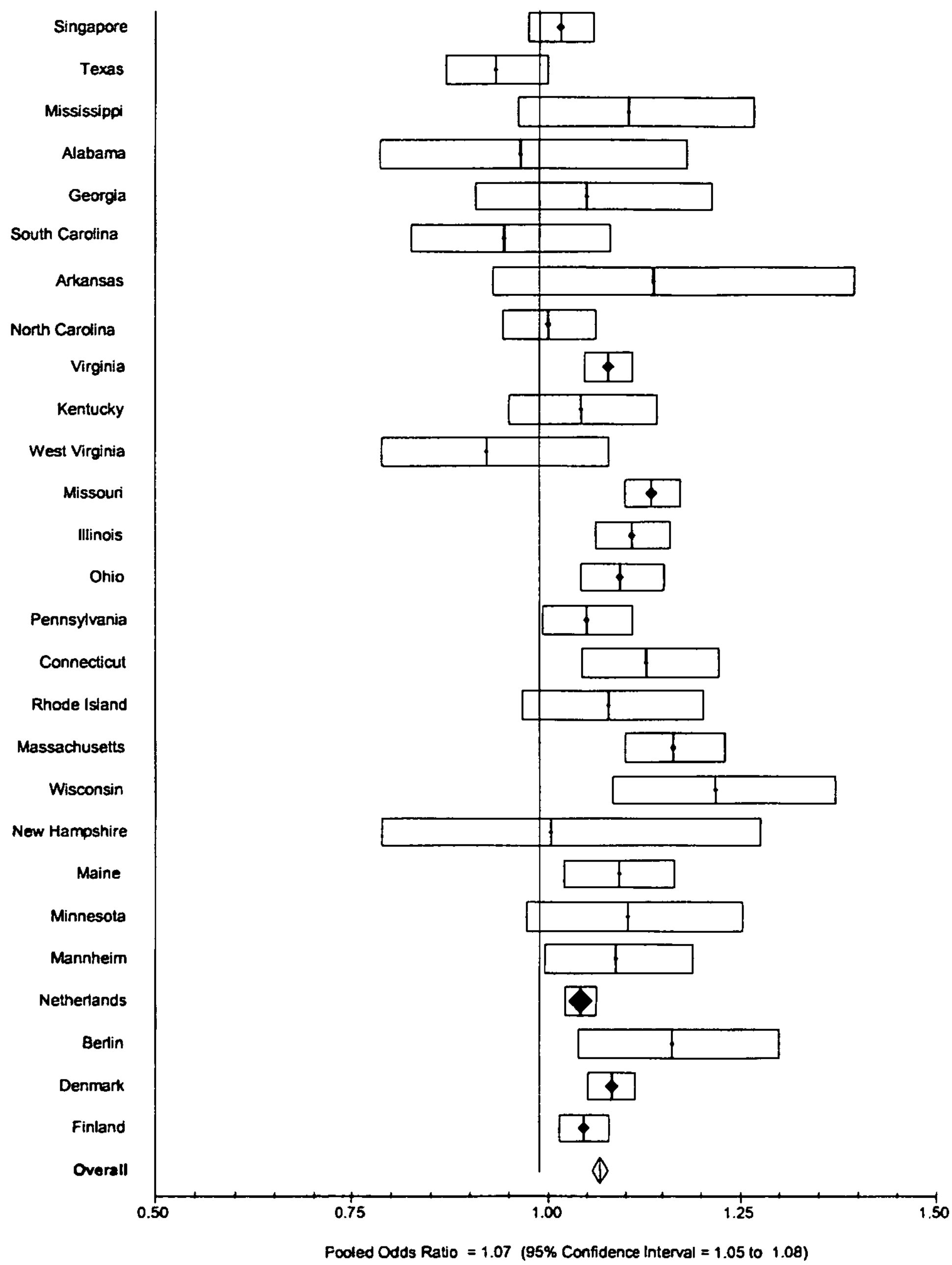
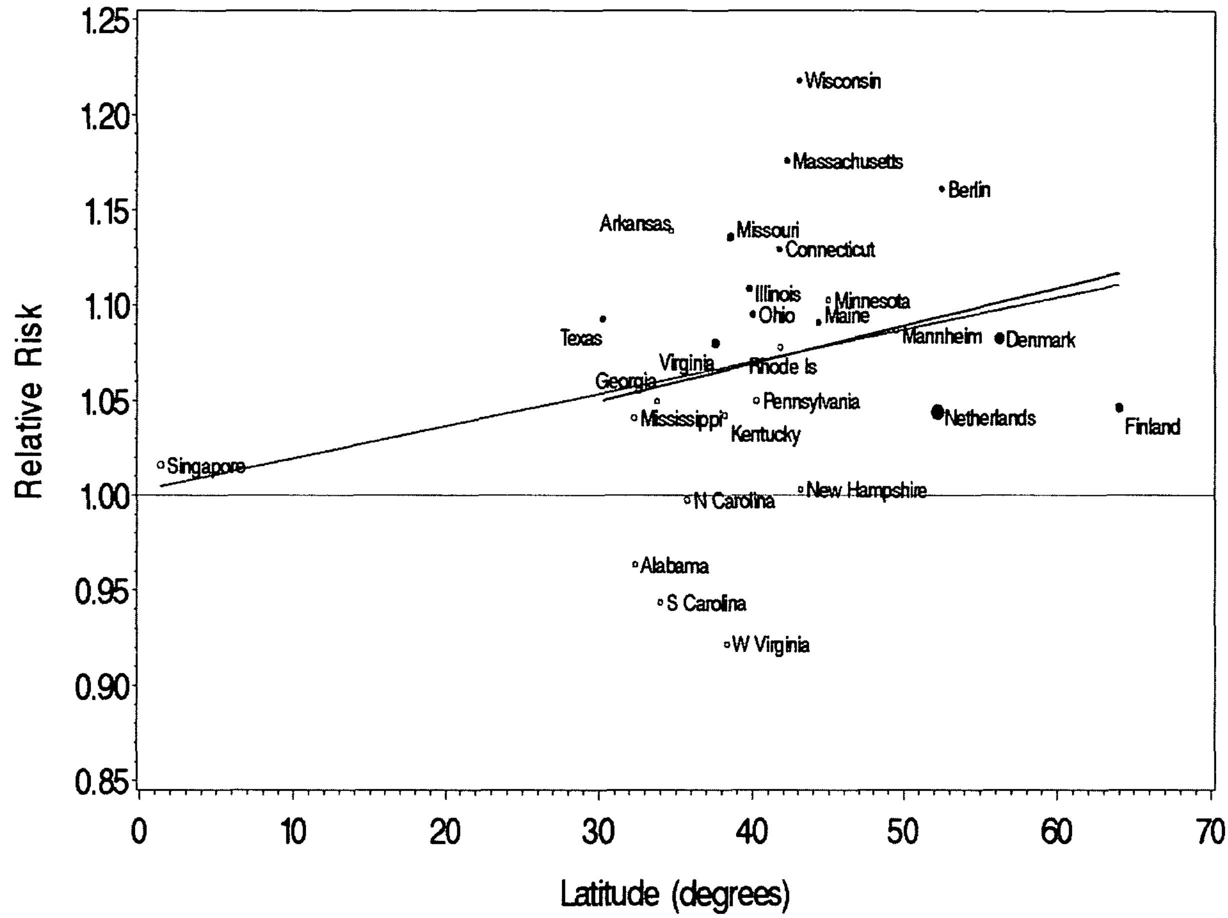


Figure 2. Relationship between relative risk and latitude[1]



[1] The lighter line indicates the regression for all studies; the shorter, darker line excludes Singapore.

only to generate potential risk-modifying variables: current candidates include perinatal viral exposures (Torrey et al. 1997) and low prenatal vitamin D (McGrath 1999). If we can identify these underlying risks, this may have important implications for the primary prevention of schizophrenia (McGrath 2000). Thus, further good-quality studies, especially from nontemperate regions, may provide a clearer understanding of the roles of latitude and seasonality in schizophrenia births and assist in the generation of new candidate exposures (Welham et al. 2000).

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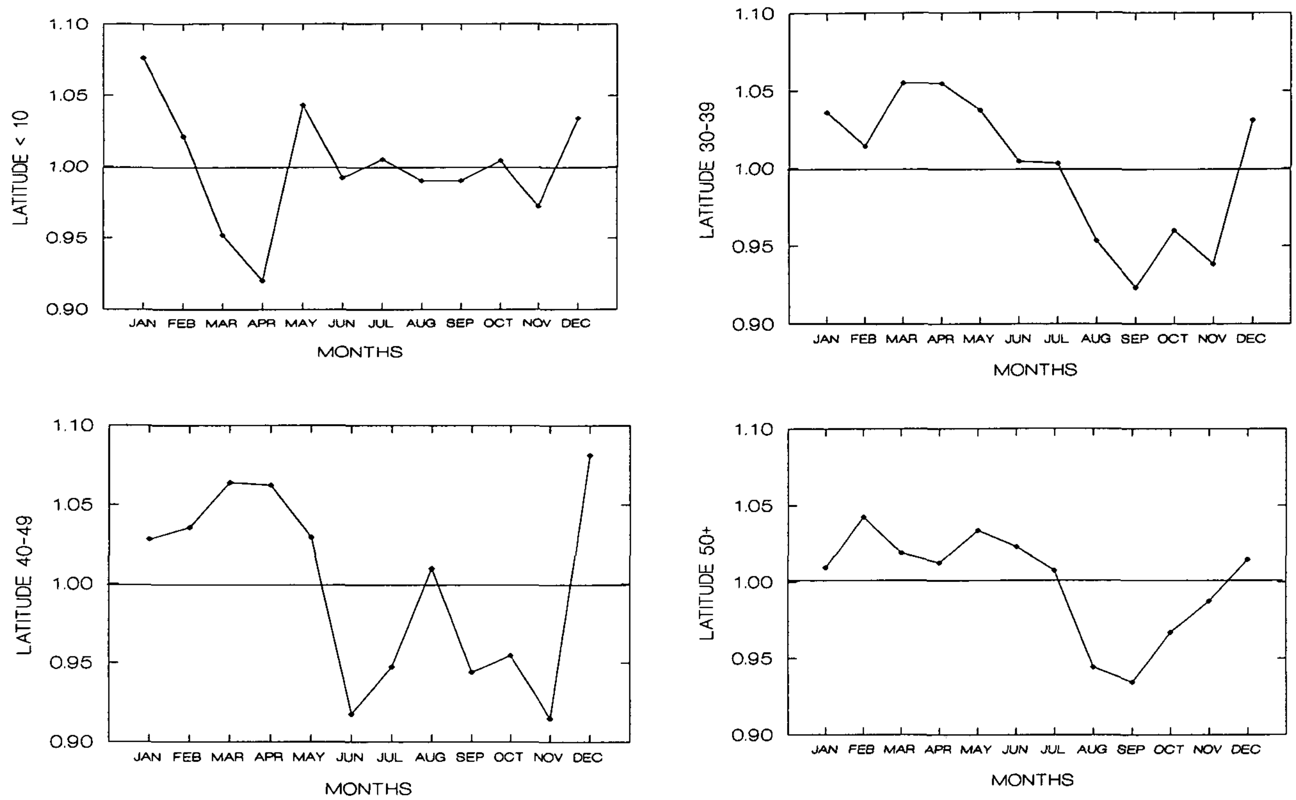
Figure 3. Observed/expected ratios per month for each latitude band



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