TECHNICAL COMMENTARY

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High latitude and winter birth

Introduction

Researchers have observed the existence of high and low prevalence (total number of cases) and incidence (number of new cases during a specified time frame) pockets for schizophrenia, with rates varying depending on time and place of birth. In a given population, the prevalence of schizophrenia may vary depending on latitude, with latitude being related to variances in temperature, precipitation, sun exposure, socio-economic and genetic factors, as well as age and sex structures. This summary table assesses the available evidence pertaining to the prevalence and incidence of schizophrenia and the relationship with latitude, climate, and season of birth.

Method

We have included only systematic reviews with detailed literature search, methodology, and inclusion/exclusion criteria that were published in full text, in English, from the year 2000. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Reviews with pooled data are prioritized for inclusion. Reviews reporting fewer than 50% of items on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA[1]) checklist have been excluded from the library. The evidence was graded guided by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found seven systematic reviews that met our inclusion criteria[3, 4 5, 6 7-9].

- Moderate quality evidence suggests a small effect of increased prevalence of schizophrenia with increased latitude and decreased annual mean daily temperature in the Northern Hemisphere. Incidence rates are increased only for males.
- Moderate to low quality evidence suggests this association may be greatest for those with older fathers at birth (over 45 years old) and particularly for disadvantaged ethnic minority groups.
- Moderate to high quality evidence suggests a small relationship between winter/spring births and increased risk for schizophrenia in the Northern Hemisphere, and high quality evidence suggests a small relationship between winter/spring births and subclinical psychotic symptoms in children in Japan and the U.K.
- Moderate to high quality evidence suggests a small effect of increased rates of deficit schizophrenia (negative symptoms) in offspring born in the summer months of June and July in the Northern Hemisphere.

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Cheng JY, Ko JS, Chen RY, Ng EM

Meta-regression analysis using latitude as moderator of paternal age related schizophrenia risk: high ambient temperature induced de novo mutations or is it related to the cold?

Schizophrenia Research 2008; 99(1-3): 71-6

View review abstract online

Comparison	**Regional prevalence of schizophrenia, latitude of study site and mean daily temperature 25 years prior to year studies were conducted. Analysis includes paternal age at birth as primary predictor.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, precise, indirect) suggests an increased risk for schizophrenia with increased latitude and decreased annual mean daily temperature in the Northern Hemisphere only. Risk is highest with increased paternal age.**

Paternal age, latitude, and ambient temperature

Meta-regressions show no moderating effects of latitude or annual mean daily temperature on the relationship between advanced paternal age and prevalence of schizophrenia from studies in the Northern and Southern hemispheres;

N = 210,652, 4 case-control studies

Latitude: B = 0.01, 95%CI -0.01 to 0.02, p = 0.36

Annual mean daily temperature; B = -0.02, 95%CI -0.05 to 0.01, p = 0.29

N = 3,155,007, 5 cohort studies

Latitude: B = -0.01, 95%CI -0.01 to 0.01, p = 0.71

Annual mean daily temperature: B = 0.01, 95%CI -0.02 to 0.04, p = 0.59

All studies controlled for maternal age.

Removing one Australian case-control study (authors state season of birth effect has not been observed in the Southern hemisphere) showed that increased latitude and decreased annual mean daily temperature is associated with increased paternal age-related risk for schizophrenia;

N = 210,392, 3 case-control studies

Latitude: B = 0.083, 95%CI -0.001 to 0.167, p = 0.051

Annual mean daily temperature: B = -0.171, 95%CI -0.319 to -0.023, p = 0.023

No effect was observed in the cohort study results.

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Consistency in results‡	Inconsistent
Precision in results§	Precise
Directness of results‖	Indirect; estimated variables for temperature and latitude

Davies C, Segre G, Estrade A, Radua J, De Micheli A, Provenzani U, Oliver D, Salazar de Pablo G, Ramella-Cravaro V, Besozzi M, Dazzan P, Miele M, Caputo G, Spallarossa C, Crossland G, Ilyas A, Spada G, Politi P, Murray RM, McGuire P, Fusar-Poli P

Prenatal and perinatal risk and protective factors for psychosis: a systematic review and meta-analysis

The Lancet Psychiatry 2020; 7: 399-410

View review abstract online

Comparison	**Risk of psychotic disorders (mostly schizophrenia spectrum or non-affective psychosis) in adulthood in people who were exposed to winter/spring births in the Northern hemisphere.**
Summary of evidence	**Moderate quality evidence (unclear sample size, inconsistent, precise, direct) suggests a small increased risk of psychotic disorders (mostly schizophrenia spectrum or non-affective psychosis) following exposure to winter or winter/spring birth.**
Winter/spring birth	
Small effects of increased risk of psychotic disorders following exposure to; Winter/spring birth: 8 studies, N not reported, OR = 1.05, 95%CI 1.03 to 1.08, $p < 0.0001$, $I^2 = 77\%$ Winter birth: 11 studies, N not reported, OR = 1.05, 95%CI 1.03 to 1.08, $p < 0.0001$, $I^2 = 55\%$	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Córdova-Palomera A, Calati R, Arias B, Ibáñez M, Moya J, Ortet G, Crespo-Facorro B, Fañanás L

High latitude and winter birth

Season of birth and subclinical psychosis: Systematic review and meta-analysis of new and existing data **Psychiatry Research 2015; 225: 227-235** View review abstract online	
Comparison	**Risk of subclinical psychosis in the Northern Hemisphere and relationship to season of birth.**
Summary of evidence	**High quality evidence (large samples, precise, direct, consistent) suggests a small effect of increased odds of subclinical psychotic symptoms in children aged around 12 years who were born in winter or spring in Japan or the U.K.**
Season of birth	
Data from children (mean age 12 years) showed a significant, small association between increased odds of subclinical psychotic symptoms and winter/spring birth in Japan and the UK; 2 studies, N = 19,829, OR = 1.12, 95%CI 1.03 to 1.21, p = 0.009, I^2 = 0%, p = 0.469 *No significant association was observed for adults in Japan, USA or Spain;* 5 studies, N = 5,033, OR = 1.22, 95%CI 0.87 to 1.70, p = 0.256, I^2 = 66.44%, p = 0.018	
Consistency in results	Consistent for children, inconsistent for adults
Precision in results	Precise
Directness of results	Direct

Davies G, Welham J, Chant D, Torrey EF, McGrath J **A systematic review and meta-analysis of Northern Hemisphere season of birth studies in schizophrenia** **Schizophrenia Bulletin 2003; 29(3): 587-593** View review abstract online	
Comparison	**Risk of schizophrenia in the Northern Hemisphere and relationship to latitude and season of birth.**
Summary of evidence	**Moderate to high quality evidence (large sample, unable to assess consistency, precise, direct) suggests a relationship between winter/spring births and increased risk for schizophrenia in the**

	Northern Hemisphere. **Moderate to low quality evidence (indirect) suggests this risk may increase with latitude within the Northern Hemisphere.**
Latitude and season of birth	
Small, significant increased odds of schizophrenia in offspring born in the Northern Hemisphere in winter/spring compared to summer/autumn; 8 case-control studies from 27 sites, N = 86,732,003, OR = 1.07, 95%CI 1.05 to 1.08, $p < 0.05$ *This risk increased significantly as latitude increased;* $r = 0.271$, $p < 0.005$ This corresponds to a 0.02% increase in odds for every 10º increase in latitude. Latitude varied between 1.4º (Singapore) and 64.0º (Finland). Removing Singapore resulted in decreased strength of association ($r = 0.261$, $p < 0.085$). The data also suggests that the size of the effect may be smaller in countries above 50°.	
Consistency in results	Unable to assess; no measure of heterogeneity reported.
Precision in results	Precise for winter/spring birth, unable to assess latitude (CIs not reported).
Directness of results	Direct for season of birth, indirect for latitude (estimated).

Kinney DK, Teixeira P, Hsu D, Napoleon SC, Crowley DJ, Miller A, Hyman W, Huang E

Relation of Schizophrenia Prevalence to Latitude, Climate, Fish Consumption, Infant Mortality, and Skin Color: A Role for Prenatal Vitamin D Deficiency and Infections?

Schizophrenia Bulletin 2009; 35(3): 582-595

View review abstract online

Comparison	**Regional prevalence of schizophrenia, latitude of study site and daily average minimum temperature in the coldest month of the year at the study site or nearest geographic site 25 years prior to prevalence estimates (authors state that the average age of onset for schizophrenia is early to mid 20's).**
Summary of evidence	**Moderate to low quality evidence (large samples, unable to assess consistency or precision, indirect) suggests a medium-sized relationship between increased latitude, colder climate and increased risk of schizophrenia. Risk is greatest for**

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	disadvantaged ethnic minority groups.
Latitude and climate	
Significant relationship between both latitude and climate and regional prevalence for schizophrenia; Worldwide; 49 prevalence studies (no control groups), N = 2,392,539 Latitude correlation with schizophrenia prevalence; $r = 0.46$, $p < 0.001$ Climate correlation with schizophrenia prevalence; $r = -0.60$, $p < 0.001$ *Similar correlations were observed within each major continental region with a minimum of 3 studies;* Latitude correlation range; $r = 0.51$ to 0.94 Climate correlation range; $r = -0.51$ to -0.99 Major continental regions; *Africa;* Ethiopia, Botswana, and Ghana *East Asia;* South Korea (rural and Seoul), China, Japan (Nagasaki), Taiwan (Taipei) and Hong Kong *South Asia;* India (New Delhi, Chandigarh rural and urban, West Bengal, Tamil Nadu, Vellore, Madras, Punjab, Lucknow slum) and Indonesia (Jakarta slum) *Europe;* Finland, Germany (Munich, Upper Bavaria), The Netherlands (Nijmegen), UK (Camden, Nottingham, and Hampstead), Russia (Moscow), Iceland, Norway (fishing village), Denmark (Bornholm Island, Aarhus), Ireland (Dublin) *North America*; Canada (Oxford Bay, Alberta, Edmonton). US (Los Angeles, Baltimore, New Haven, Honolulu, subgroups of ethnic communities)	
Relationship between disadvantaged ethnic minority groups, latitude, and relative risk for schizophrenia	
Significant large relationship between greater relative risk for schizophrenia in disadvantaged ethnic minority groups from high latitude regions compared to disadvantaged ethnic minority groups from low latitude regions; 5 prevalence studies, N = 342,612, $r = 0.98$, $p = 0.01$ Regions included in analysis were Canada, USA, India, and Taiwan	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Indirect – regional latitude and climate

Messias E, Kirkpatrick B, Bromet E, Ross D, Buchanan RW, Carpenter WTJr, Tek C, Kendler KS, Walsh D, Dollfus S

Summer birth and deficit schizophrenia: a pooled analysis from 6 countries

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Archives of General Psychiatry 2004; 61(10): 985-989 View review abstract online	
Comparison	**Regional prevalence and approximated incidence for deficit schizophrenia (chronic negative symptoms as measured by the SDS) vs. non-deficit schizophrenia and season of birth in the Northern Hemisphere.**
Summary of evidence	**Moderate to high quality evidence (large sample, imprecise, consistent, direct) suggests increased prevalence of deficit schizophrenia in offspring born in June/July in the Northern Hemisphere.** **Moderate quality evidence (indirect) suggests increased incidence of deficit schizophrenia in offspring born in June/July in the Northern Hemisphere.**
Prevalence and incidence of deficit vs. non-deficit schizophrenia and summer birth	
Significant small increased odds of deficit vs. non-deficit schizophrenia in offspring born in June/July in the Northern Hemisphere; Overall: 9 samples, N = 1,594, OR = 1.93, 95%CI 1.46 to 2.55, $p < 0.05$ Prevalence samples: OR = 1.64, 95%CI 1.04 to 2.59, $p < 0.05$, Qp = 0.63 Incidence samples: OR = 1.95, 95%CI 1.31 to 2.91, $p < 0.05$, Qp = 0.84 Convenience samples: OR = 1.59, 95%CI 0.93 to 2.74, $p > 0.05$, Qp = 0.06	
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct for prevalence (regional), indirect for incidence (approximated)

Saha S, Chant DC, Welham JL, McGrath JJ **The incidence and prevalence of schizophrenia varies with latitude** **Acta Psychiatrica Scandinavica 2006; 114(1): 36-39** View review abstract online	
Comparison	**Association of the incidence and prevalence of schizophrenia by latitude. Based on absolute latitude; low = 0 to 30°, medium = 30 to 60° and high = > 60°.**
Summary of evidence	**Moderate to low quality evidence (large samples, unable to assess consistency or precision, indirect) suggests increased prevalence**

	of schizophrenia with higher latitudes, and increased incidence only for males.
Relationship between latitude and incidence and prevalence of schizophrenia	
68 incidence studies, 27 countries worldwide; Low latitude countries = Barbados, Brazil, India, Pakistan, Singapore, Trinidad & Tobago Medium latitude countries = Canada, China, Croatia, Denmark, France, Germany, Ireland, Italy, Jamaica, Japan, New Zealand, Spain, Sweden, the Netherlands, UK &, USA High latitude countries = Canada, Finland, Greenland, Iceland, Norway, Russia & Sweden *For all persons, incidence rates per 100,000 (adjusted for normality and within study clustering);* 8 low latitude studies adjusted harmonic mean; 13.6, 95%CI 8.0 to 22.9 36 medium latitude studies adjusted harmonic mean; 15.1, 95%CI 11.4 to19.9 10 high adjusted harmonic mean; 18.8, 95%CI 10.9 to 32.4 No significant difference between log-transformed harmonic means: $F_{2,79} = 0.37$, $p = 0.69$ *For males, incidence rates (adjusted for normality and within study clustering);* 3 low latitude countries adjusted harmonic mean; 11.9, 95%CI 7.7 to18.4 22 medium latitude countries adjusted harmonic mean; 17.6 95%CI 13.0 to 23.9 7 high latitude countries adjusted harmonic mean; 27.6 95%CI 15.9 to 47.7 Significantly higher incidence rates (log-transformed harmonic means) for males in higher latitudes: $F_{2,55} = 3.56$, $p = 0.04$ *For females, incidence rates (adjusted for normality and within study clustering);* 3 Low latitude countries adjusted harmonic mean; 8.4, 95%CI 4.8 to 14.8 19 medium latitude countries adjusted harmonic mean;12.8, 95%CI 9.1 to 17.8 7 high latitude countries adjusted harmonic mean; 22.6, 95%CI 12.8 to 39.8 No difference between in incidence rates (log-transformed harmonic means) for females: $F_{2,48} = 2.92$, $p = 0.06$	

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94 prevalence studies, 35 countries worldwide; Low latitude countries = Botswana, China, Ethiopia, India, Iran, Micronesia, Puerto Rico, Taiwan, Tanzania, & USA (Hawaii) Medium latitude countries = Argentina, Bulgaria, Canada, Croatia, Denmark, France, Germany, Ghana, Greece, Ireland, Italy, Japan, New Zealand, Reunion Island, Russia, S. Africa, S. Korea, Sri Lanka, Sweden, the Netherlands, UK, USA & Yugoslavia High latitude countries = Canada, Finland, Iceland, Norway & Sweden *For all persons, prevalence rates per 1,000 (adjusted for normality and within study clustering);* 28 low latitude studies adjusted harmonic mean; 3.4, 95%CI 2.5 to 4.5 46 medium latitude countries adjusted harmonic mean; 3.2, 95%CI 2.5 to 4.0 10 high latitude countries adjusted harmonic mean; 8.2, 95%CI 4.9 to13.5 Significantly higher prevalence rates (log-transformed harmonic means) for all persons in higher latitudes: $F_{2,81} = 5.76$, $p = 0.005$ *For males, prevalence rates (adjusted for normality and within study clustering);* 12 low latitude studies adjusted harmonic mean; 2.9, 95%CI 1.9 to 4.3 26 medium latitude countries adjusted harmonic mean; 4.0, 95%CI 3.0 to 5.3 6 high latitude countries adjusted harmonic mean; 8.2, 95%CI 4.5 to14.7 Significantly higher prevalence rates (log-transformed harmonic means) for males in higher latitudes: $F_{2,43} = 4.08$, $p = 0.02$ *For females, prevalence rates (adjusted for normality and within study clustering);* 13 low latitude studies adjusted harmonic mean; 2.9, 95%CI 1.9 to 4.3 25 medium latitude countries adjusted harmonic mean; 3.2, 95%CI 2.4 to 4.2 7 high latitude countries adjusted harmonic mean; 10.0, 95%CI 5.5 to18.2 Significantly higher prevalence rates (log-transformed harmonic means) for females in higher latitudes: $F_{2,42} = 6.72$, $p = 0.003$	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Indirect (latitude estimated from geographical centre)

Explanation of acronyms

B, b = beta coefficient, CI = confidence interval, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, OR = odds ratio (see below for interpretation of effect size), *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q = Q statistic (chi-square) for the test of heterogeneity, *r* = correlation, RR = relative risk, SDS = Schedule for the Deficit Syndrome, vs. = versus

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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results, publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[10].

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† Different effect measures are reported by different reviews.

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, an RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. An RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[11]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg r) indicate the strength of association or relationship between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the dependent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 and over represents a large treatment effect[10].

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the

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number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

‡ Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity and 75% to 100%: considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test oheterogeneity with the following formula;

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, this criteria should be relaxed[12].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available so is inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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