TECHNICAL COMMENTARY

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Spatial variation in incidence

Introduction

The incidence of schizophrenia refers to how many new cases there are per population in a specified time-period. It is different from prevalence, which refers to how many existing cases there are at a particular point in time. Incidence is usually reported as the 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 developing schizophrenia. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Differences in the incidence of a disorder can provide clues to its possible causes. For example, a population register with information gained from consensus data helps to identify all adults in a defined area who were born within a certain time-period (an age cohort). Cross linking this information with a mental health register can be used to identify those who received treatment for schizophrenia over particular times. This can provide information of the incidence of a disorder for various age groups within that cohort. The incidence of schizophrenia can also be examined in subgroups defined by other criteria such as environmental and genetic risk factors to investigate their influence on the risk of the disorder. This table summarises the evidence regarding how the incidence of schizophrenia varies between regions. The majority of studies have focused on rural – urban differences but comparisons of results have been limited by a lack of consistent criteria for defining rural or urban regions.

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[3-9].

- Moderate quality evidence finds the incidence of schizophrenia or schizophreniform disorder is higher in urban regions than in rural areas or mixed urban/rural areas.
- Moderate quality evidence shows rates were higher for males than females who were born at higher latitudes.
- Moderate to low quality evidence suggests no differences in incidence rates according to a country's per capita gross national product and mean income.

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Castillejos MC, Martín-Pérez C, Moreno-Küstner B

A systematic review and meta-analysis of the incidence of psychotic disorders: the distribution of rates and the influence of gender, urbanicity, immigration and socio-economic level

Psychological Medicine 2018; 48: 2101–15

View review abstract online

Comparison	**Incidence of schizophrenia in urban vs. rural populations.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency, imprecise, direct) suggests the incidence rate of schizophrenia or schizophreniform disorder is higher in urban regions than in rural areas.**
Diagnosis of schizophrenia or schizophreniform disorder	
A significant increased rate of schizophrenia or schizophreniform disorder in urban regions; 3 population-based studies, IRR = 1.89, 95%CI 1.38 to 1.95, $p < 0.01$	
Consistency in results‡	Unable to assess – heterogeneity measure is not reported.
Precision in results§	Imprecise
Directness of results‖	Direct

Goldner EM, Hsu L, Waraich P, Somers JM

Prevalence and incidence studies of schizophrenic disorders: a systematic review of the literature

Canadian Journal of Psychiatry 2002; 47(9): 833-843

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Comparison	**Spatial variation in the incidence of schizophrenia.**
Summary of evidence	**Moderate quality evidence (large samples, unable to assess precision or consistency, direct) indicates there is spatial variation in the incidence of schizophrenia.**

Spatial variation in incidence

Incidence of schizophrenia diagnosed by ICD-9 or DSM-III and later criteria	
7 population-level studies Canada: 1 study, rates using ICD diagnosis = 7.7 per 100,000, rates using DSM = 3.6 per 100,000 Spain: 1 study, rates using ICD diagnosis = 13.5 per 100,000 UK: 4 studies, 3 studies using ICD and 1 study using DSM diagnosis, rates = 4.8 to 22.6 per 100,000 US: 1 study, rates using DSM diagnosis = 200 per 100,000	
Consistency in results	No measure of consistency within regions is reported
Precision in results	No measure of precision is reported
Directness of results	Direct

Kirkbride JB, Errazuriz A, Croudace TJ, Morgan C, Jackson D, Boydell J, Murray RM, Jones PB

Incidence of Schizophrenia and Other Psychoses in England, 1950–2009: A Systematic Review and Meta-Analyses

PLoS One 2012; 7(3): e1660

View review abstract online

Comparison	**Incidence in the UK relative to urban environment.**
Summary of evidence	**Moderate to high quality evidence (large sample, precise, unable to assess consistency, direct) suggests an incidence rate of 15.2 per 100,000 person years, and a small effect of urbanicity on increased incidence in the UK.**
Incidence in the UK	
15 studies, N = 2,305, pooled incidence rate = 15.2, 95%CI 11.9 to 19.5 per 100,000 person years Increased urbanicity was related to increased incidence: IRR1.03, 95%CI 1.01 to 1.03, $p = 0.01$ Note that authors report a similar relationship between urbanicity and increased incidence of all non-affective psychoses, but not with affective psychoses or substance induced psychosis.	
Consistency in results	No measure of consistency within regions is reported

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Precision in results	Precise
Directness of results	Direct

March D, Hatch SL, Morgan C, Kirkbride JB, Bresnahan M, Fearon P, Susser E

Psychosis and place

Epidemiologic Reviews 2008; 30: 84-100

View review abstract online

Comparison	**Incidence of psychosis relative to urban environment (population, city dwelling), neighbourhoods (districts, electoral wards and municipalities) in developed countries.** **Most studies include people with schizophrenia, some studies include all psychotic disorders.**
Summary of evidence	**Moderate quality evidence (large samples, unable to assess precision or consistency, direct) indicates an association between urban life, neighbourhood factors and incidence of psychosis, mainly schizophrenia.**
Incidence of schizophrenia diagnosed by ICD-9 or DSM-III and later criteria in urban regions compared to rural regions in developed countries	
20 population-level studies conducted in USA and Western Europe Authors state that the evidence indicates an association between urban life and rates of psychosis; in most studies, urbanicity is associated with an approximately two-fold increase in risk, with associations indicating a risk increase as high as fourfold in early-onset cases. Urbanicity does not seem attributable to drift and selection or service utilization.	
Incidence of schizophrenia diagnosed by ICD-9 or DSM-III in neighbourhood regions compared to rural regions in developed countries	
24 population-level studies conducted in USA and Western Europe Authors state that a number of studies reported spatial variation in psychoses at the neighbourhood level. Drift and selection cannot be ruled out conclusively as an explanation. Socioeconomic deprivation of neighbourhoods may be an increased risk and levels of social capital and ethnic density may decrease risk.	
Consistency in results	No measure of consistency within regions is reported

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Precision in results	No measure of precision is reported
Directness of results	Direct

McGrath J, Saha S, Welham J, El Saadi O, MacCauley C, Chant D

A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology

BMC Medicine 2004; 2: 13

View review abstract online

Comparison	**Distribution rates of the incidence of schizophrenia with influence of urbanicity.**
Summary of evidence	**Moderate quality evidence (large samples, unable to assess precision or consistency, direct) indicates the incidence of schizophrenia is higher in those living in urban regions compared to mixed urban/rural areas.**

Differences in incidence rates via any diagnostic criteria for urban vs. rural and mixed urban/rural place of residence

68 population-level studies conducted worldwide

Significantly increased incidence of schizophrenia for those living in urban regions compared to mixed urban/rural regions:

Difference in harmonic means; $F_{1,50} = 6.06$, $p = 0.02$

Heterogeneity explored via differences in study quality, case identification, diagnostic criteria, age-standardized vs. raw rates and year of first intake. Only year of first intake showed significant variability across studies.

Consistency in results	No measure of consistency within regions is reported
Precision in results	No measure of precision is reported
Directness of results	Direct

Saha S, Chant DC, Welham JL, McGrath JJ

The incidence and prevalence of schizophrenia varies with latitude

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Acta Psychiatrica Scandinavica 2006; 114 (1): 36-39 View review abstract online	
Comparison	**Association of the incidence of schizophrenia by latitude. Based on absolute latitude; low = 0 to 30°, medium = 30 to 60° and high = > 60°.**
Summary of evidence	**Moderate quality evidence (large samples, unable to assess precision or consistency, direct) suggests increased incidence of schizophrenia for males who were born at higher latitudes, with no differences for females.**

Relationship between latitude and incidence of schizophrenia via any diagnostic criteria

68 population-level studies conducted 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

No difference in incidence rates (log-transformed harmonic means) for all persons;

$F_{2,79} = 0.37$, $p = 0.69$

For all persons, incidence rates (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 latitude studies adjusted harmonic mean: 18.8, 95%CI 10.9 to 32.4

Significantly higher incidence rates (log-transformed harmonic means) for males in higher latitudes;

$F_{2,55} = 3.56$, $p = 0.04$

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

No difference between in incidence rates (log-transformed harmonic means) for females;

$F_{2,48} = 2.92$, $p = 0.06$

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

Consistency in results	No measure of consistency within regions is reported

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Precision in results	Unable to assess (harmonic means)
Directness of results	Direct

Saha S, Welham J, Chant D, McGrath J

Incidence of schizophrenia does not vary with economic status of the country. Evidence from a systematic review

Soc Psychiatry Psychiatr Epidemiol 2006; 41: 338-340

View review abstract online

Comparison	**Distribution rates of the incidence of schizophrenia with influence of socioeconomic status of countries.**
Summary of evidence	**Moderate to low quality evidence (large samples, unable to assess consistency or precision, indirect) suggests no association between level of per capita gross national product and mean income and incidence rates of schizophrenia.**

Differences in incidence rates for developed vs. emerging vs. least developed countries

52 population-level studies

Approximated measure of socioeconomic status, using per capita gross national product of the study site and World Bank definitions of mean income: < US$2,995 per annum = least developed, US$2,995 to 9266 = emerging economy, >US$9,266 = developed.

There was no significant difference in incidence rates between groups;

$F_{2,52} = 0.20$, $p = 0.82$

The median (and 10 to 90% quantiles) incidence rates per 100,000 persons for least developed countries (3 studies) = 20.0 (0.4 to 35.0), emerging economies (9 studies) = 11.0 (5.0 to 26.0) and developed countries (42 studies) = 16.0 (8.0 to 48.0).

When developing countries' incidence rates were compared to emerging and least developed countries' incidence rates combined, there was also no significant group difference.

Consistency in results	No measure of consistency within regions is reported
Precision in results	Unable to assess (quantiles)
Directness of results	Direct measure of incidence, indirect measure of individual socioeconomic status

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Explanation of acronyms

CI = confidence interval, DSM = Diagnostic and Statistical Manual, *F* = one-way ANOVA F-test for difference in means, ICD = International Classification of Diseases, IRR = incidence rate ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), 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.

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 medium effect, and 0.8 and over represents a large treatment effect[10].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in the treatment group 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. 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 certain 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.

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.

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 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

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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) which 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 of heterogeneity 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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