TECHNICAL COMMENTARY

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Urbanicity

Introduction

Most studies define urbanicity by degrees of population density, defined either as population per square kilometer or as the number of inhabitants within a defined location (e.g., capital, city, or town). It is not clear whether urban living itself is associated with a higher risk for schizophrenia, as other factors may influence this association such as social class and access to treatment. Exposure to urbanicity may be assessed at birth, during upbringing or at illness onset.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are given priority for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[1]. Reviews with less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[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 to high quality evidence suggests a small increase in the incidence, but not the prevalence, of schizophrenia with increased urbanicity measured prior to, or after illness onset.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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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.**
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

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 of schizophrenia in the UK relative to urban environment.**

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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Summary of evidence	**Moderate to high quality evidence (large sample, precise, direct, unable to assess consistency) suggests a small effect of increased incidence of schizophrenia with increased urbanicity in the UK.**
Schizophrenia	
Increased urbanicity was related to increased incidence: Population-level studies, IRR = 1.03, 95%CI 1.01 to 1.03, p = 0.01 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	Unable to assess; no measure of consistency is reported.
Precision in results	Precise
Directness of results	Direct

Linscott RJ, van Os J

An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders

Psychological Medicine 2013; 43: 1133-1149

View review abstract online

Comparison	**Prevalence and incidence of subclinical psychotic symptoms in people living in urban vs. rural environments.**
Summary of evidence	**Moderate quality evidence (inconsistent or imprecise, direct, unclear sample sizes) suggests no differences in the prevalence or incidence of subclinical psychotic symptoms.**
Subclinical psychotic symptoms	
No differences in prevalence or incidence of subclinical psychotic symptoms: Prevalence: 8 studies, N not reported, OR = 1.09, 95%CI 0.93 to 1.27, $p > 0.05$, $I^2 = 91\%$, $p < 0.01$ Incidence: 2 studies, N not reported, OR = 0.62, 95%CI 0.32 to 1.23, $p > 0.05$, $I^2 = 57\%$, $p > 0.05$	

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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Consistency in results	Inconsistent for prevalence, consistent for incidence rates
Precision in results	Precise for prevalence, imprecise for incidence rates
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 (number of inhabitants, city dwelling) and neighbourhoods (districts, electoral wards and municipalities) in developed countries.**
Summary of evidence	**Moderate quality evidence (large samples, unable to assess consistency or precision, direct) suggests an association between increased levels of urban living and increased rates of psychosis. Neighbourhood factors such as lower socioeconomic status may further increase risk, while increased social capitol and ethnic density levels may decrease this risk.**

Schizophrenia

Urbanicity (20 population-level studies from USA and Western Europe) is associated with an approximately twofold increased risk of psychosis, and up to fourfold risk in early-onset cases, not attributable to drift and selection or service utilization. This association appears to be specific to non-affective psychoses as distinct from affective psychoses.

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

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Comparison	**Incidence of schizophrenia according to level of urbanicity.**

Summary of evidence	**Moderate quality evidence (large samples, unable to assess consistency or precision, direct) suggests that the incidence of schizophrenia is higher in urban regions compared to mixed urban/rural areas.**
Schizophrenia	
Significantly increased incidence of schizophrenia for those living in urban regions compared to mixed urban/rural: 68 population-level studies, difference in harmonic means, $F_{1,50} = 6.06$, $p = 0.02$	
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	Direct

Saha S, Chant D, Welham J, McGrath J

A systematic review of the prevalence of schizophrenia

PLoS Medicine / Public Library of Science 2005; 2(5): e141

View review abstract online

Comparison	**Distribution rates of the prevalence of schizophrenia with influence of urbanicity levels.**
Summary of evidence	**Moderate quality evidence (large samples, unable to assess consistency or precision, direct) suggests no differences in the prevalence of schizophrenia between urban, rural or mixed urban/rural areas.**
Schizophrenia	
No significant difference in prevalence of schizophrenia between urban and rural regions; 99 population-level studies, $F_{1,120} = 0.95$, $p = 0.33$ No significant difference was found between rates in mixed urban/rural areas compared to either urban or rural areas separately.	
Consistency in results	Unable to assess; no measure of consistency is reported.

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Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Vassos E, Pedersen CB, Murray RM, Collier DA, Lewis CM

Meta-Analysis of the Association of Urbanicity With Schizophrenia

Schizophrenia Bulletin 2012; 38(6): 1118-1123

View review abstract online

Comparison	**Risk of schizophrenia and urbanicity prior to the earliest stage of the disorder (at birth or under 15 years of age).**
Summary of evidence	**Moderate to high quality evidence (large sample, precise, inconsistent, direct) suggests increases the incidence of schizophrenia with increases in levels of urbanicity measured before illness onset.**
Schizophrenia	
Significant, medium-sized increased risk of schizophrenia with increased premorbid urbanicity; 4 studies, N = 46,820, OR = 2.37, 95%CI 2.01 to 2.81, I^2 = 82%, Q-test *p* = 0.18	
Consistency in results	Inconsistent – heterogeneity (I^2) not significant, but high.
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, *F* = one-way ANOVA F-test for (harmonic) means, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), IRR = incidence rate ratio, N = number of participants, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q = Q statistic for the test of heterogeneity, 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].

† Different effect measures are reported by different reviews.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified - 100% sensitivity = predict all people who are at high risk as developing psychosis and specificity is the proportion of negatives that are correctly identified - 100% specificity = not predicting anyone as being at high risk if they are truly not.

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. Standardized 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 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 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, a 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. A 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 independent 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.

‡ Inconsistency refers to differing estimates of treatment effect across trials (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 be considerable heterogeneity and over this is 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 sized are of lower quality than those gained from head-to-head comparisons of A and B.

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