TECHNICAL COMMENTARY

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Sex differences

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 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 regarding the incidence of schizophrenia for each sex.

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, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. Reviews with pooled data were given priority for inclusion. When multiple copies of reviews were found, only the most recent version was included.

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).

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Results

We found three systematic reviews that met our inclusion criteria[3-5].

- Moderate to high quality evidence suggests the incidence rate of schizophrenia is higher in men than in women. This is only apparent in men up until 39 years of age, then the incidence is higher in females after 50 years of age. These results remain after adjusting for year of study, sample size, sampling method (admission or contact), case ascertainment (clinical, systematic or interview), and diagnostic classification system.

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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 males vs. females.**
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 men than in women.**
Diagnosis of schizophrenia or schizophreniform disorder	
A significant increased rate of schizophrenia or schizophreniform disorder in men; 4 population-based studies, IRR = 8.42, 95%CI 3.25 to 32.22, $p < 0.01$	
Consistency in results	Unable to assess – heterogeneity measure is not reported.
Precision in results	Imprecise
Directness of results	Direct

Jongsma HE, Turner C, Kirkbride JB, Jones PB

International incidence of psychotic disorders, 2002-17: a systematic review and meta-analysis

The Lancet Public Health 2019; 4: e229-e44

View review abstract online

Comparison	**Incidence of schizophrenia in males vs. females.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests the incidence rate of schizophrenia is**

	higher in men than in women.
Diagnosis of schizophrenia	
A significant increased rate of schizophrenia or schizophreniform disorder in men; 11 studies (population and other designs), IRR = 1.70, 95%CI 1.46 to 1.97, $p < 0.05$, $I^2 = 95\%$	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

van der Werf M, Hanssen M, Kohler S, Verkaaik M, Verhey FR, RISE Investigators, van Winkel R, van Os J, Allardyce J

Systematic review and collaborative recalculation of 133693 incident cases of schizophrenia

Psychological Medicine 2014; 44(1): 9-16

Link to review abstract

Comparison	**Incidence of schizophrenia in males vs. females.**
Summary of evidence	**Moderate to high quality evidence (large samples, unable to assess consistency, precise, direct) suggests higher incidence of schizophrenia in males up until 39 years. Moderate quality evidence (imprecise) suggests no differences in incidence between 40 to 49 years, and higher incidence of schizophrenia in females over 50 years.**
Diagnosis of schizophrenia	
The risk of schizophrenia was significantly greater in men aged 20 to 39 years, and in women aged over 50 years, after adjusting for year of study, sample size, sampling frame (admission or contact), case ascertainment (clinical, systematic or interview) and diagnostic classification system. No differences were found between males and females aged 40 to 49 years; 33 samples (N = 63,550 incident cases of schizophrenia) < 20 years: IRR 0.53, 95%CI 0.41 to 0.69, $p < 0.05$ 20–29 years: IRR 0.47, 95%CI 0.41 to 0.54, $p < 0.05$	

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30–39 years: IRR 0.80, 95%CI 0.71 to 0.91, $p < 0.05$ 40–49 years: IRR 1.18, 95%CI 0.99 to 1.41, $p > 0.05$ 50–59 years: IRR 1.50, 95%CI 1.25 to 1.80, $p < 0.05$ 60–69 years: IRR 1.50, 95%CI 1.13 to 1.99, $p < 0.05$ ≥ 70 years: IRR 1.38, 95%CI 0.93 to 2.05, $p > 0.05$	
Consistency in results	No consistency measures are reported within age groups.
Precision in results	Precise for 20 to 39-year age groupings only.
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, IRR = incidence rate ratio, N = number of participants, p = probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q = test for 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[6].

† 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 medium effect, and 0.8 and over represents a large effect[6].

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[7]. 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

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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 represent 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[8].

‖ 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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