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Sex differences

Introduction

Sex differences have been reported in schizophrenia, including differences between sexes in the age of illness onset, in premorbid functioning, in symptom profile, and in the course of illness. This summary table assesses differences in the risk of schizophrenia between males and females as differences in incidence (number of new cases in the population at risk over a specified period of time) and prevalence (proportion of individuals who have the disorder in the population at risk at a specified time point or over a specified time period). Any sex differences in rates of schizophrenia could be due to genetic and/or environmental influences.

Method

We have included only systematic reviews 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 12 reviews that met our inclusion criteria[3-14].

- Moderate to high quality evidence shows a small increase in the incidence, but not the prevalence of schizophrenia in males. This effect was found only up until around 40 years of age, with no sex differences between 40 and 50 years of age, then there was higher incidence in females after 50 years of age, possibly due to reductions in oestrogen. These results remained after adjusting for year of study, sample size, sampling frame (admission or contact), case ascertainment (clinical, systematic or interview), and diagnostic classification system.
- Moderate quality evidence finds male sex was more common in people assessed as being at ultra high-risk for psychosis; having attenuated psychotic symptoms or brief and limited intermittent psychotic symptoms, as well as genetic risk and functional deterioration.

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

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Sex differences

Aleman A, Kahn RS, Selten JP

Sex differences in the risk of schizophrenia: evidence from meta-analysis

Archives of General Psychiatry 2003; 60(6): 565-571

Link to review abstract

Comparison	**Differences in risk of schizophrenia in males vs. females.**
Summary of evidence	**Moderate to high quality evidence (unclear sample sizes, mostly consistent and precise, direct) shows the risk of schizophrenia is higher for males vs. females in developed countries, regardless of study age cut-off, study quality or diagnostic tool.**

Sex differences

38 studies (N unclear)

A small, significant increased risk of schizophrenia in males vs. females;

RR = 1.42, 95%CI 1.30 to 1.56, $p < 0.05$, $Q_W = 50.7$, $p > 0.05$

Subgroup analysis assessing sex differences based on studies from developed countries with a high World Health Organization human development index (e.g., England or Sweden) vs. studies from developing countries with a medium development index (e.g., India or Brazil).

A small, significant increased risk of schizophrenia in males vs. females in developed countries, but not in developing countries;

Developed: 42 effect sizes, RR = 1.48, 95% CI 1.34 to1.63, $p < 0.05$, $Q_W = 40.7$, $p > 0.05$

Developing: 7 effect sizes, RR = 1.09, 95% CI 0.79 to 1.49, $p > 0.05$, $Q_W = 5.1$, $p > 0.05$

The difference between these effect sizes was significant ($Q_B = 4.9$, $p = 0.03$).

Subgroup analysis assessing time trends by comparing studies with sample years before 1980 vs. those with sample years after 1980.

Small, significant increased risks of schizophrenia in males vs. females in both time periods;

<1980: 25 effect sizes, RR = 1.27, 95%CI 1.15 to 1.41, $p < 0.05$, $Q_W = 34.9$, $p > 0.05$

>1980: 24 effect sizes, RR = 1.54, 95%CI 1.39 to 1.71, $p < 0.05$, $Q_W = 36.4$, $p < 0.05$

The difference between these effect sizes was significant ($Q_B = 9.1$, $p \leq 0.01$)

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Subgroup analysis assessing sex differences based on studies using different diagnostic criteria: DSM-III-R or DSM-IV criteria compared to ICD-8, ICD-9 or ICD-10 criteria. *Small, significant increased risks of schizophrenia in males vs. females in both diagnostic criteria;* ICD-8, ICD-9, ICD-10: 29 effect sizes, RR = 1.45, 95%CI 1.29 to 1.63, $p < 0.05$, $Q_W = 32.1$, $p > 0.05$ DSM-III-R, DSM-IV: 8 effect sizes, RR = 1.58, 95%CI 1.21 to 2.08, $p < 0.05$, $Q_W = 6.1$, $p > 0.05$ The difference between these effect sizes was not significant ($Q_B = 0.5$, $p > 0.05$)
Subgroup analysis assessing sex differences based on studies that included older participants, with an age cut-off of 64 years or older compared to studies with an age cut-off of less than 64 years. *Small, significant increased risks of schizophrenia in males vs. females in both age cut-offs;* < 64 years: 32 effect sizes, RR = 1.50, 95%CI 1.33 to 1.68, $p < 0.05$, $Q_W = 29.4$, $p > 0.05$ ≥ 64 years: 16 effect sizes, RR = 1.32, 95%CI 1.13 to 1.55, $p < 0.05$, $Q_W = 19.7$, $p > 0.05$ The difference between these effect sizes was not significant ($Q_B = 1.7$, $p > 0.05$)
Subgroup analysis assessing sex differences based on studies that minimised selection bias i.e. age cut-off of ≥54 years and inclusion of both inpatient and outpatient services. *Small, significant increased risks of schizophrenia in males vs. females in both biased and unbiased studies;* Unbiased: 24 effect sizes, RR = 1.35, 95%CI 1.17 to 1.56, $p < 0.05$, $Q_W = 26.8$, $p > 0.05$ Biased: 25 effect sizes, RR = 1.48, 95%CI 1.30 to 1.69, $p < 0.05$, $Q_W = 24.5$, $p > 0.05$ The difference between these effect sizes was not significant ($Q_B = 1.0$, $p > 0.05$)
Subgroup analysis assessing sex differences based on high-quality studies only i.e. age cut-off of ≥54 years, inclusion of both inpatient and outpatient services, ICD classification of schizophrenia or CATEGO “broad schizophrenia”, use of semi-structured diagnostic interviews and inclusion of at least 50 cases of schizophrenia. *Small, significant increased risks of schizophrenia in males vs. females in high quality studies;* 11 effect sizes, RR = 1.39, 95%CI 1.15 to 1.68, $p < 0.05$, $Q_W = 9$, $p > 0.05$

Consistency in results‡	Mostly consistent
Precision in results§	Mostly precise
Directness of results‖	Direct

Beauchamp G, Gagnon A

Sex differences

Influence of diagnostic classification on gender ratio in schizophrenia

Social Psychiatry and Psychiatric Epidemiology 2004; 39: 1017-1022

View review abstract online

Comparison	**Differences in risk for schizophrenia vs. other psychoses, according to the diagnostic tool used.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, imprecise, direct) suggests a male with psychosis is significantly more likely to obtain a diagnosis of schizophrenia (rather than any other psychotic disorder) than a female with psychosis. This was only apparent with DSM and not ICD-9 diagnostic criteria.**
Sex differences	
A male with psychosis was significantly more likely to obtain a diagnosis of schizophrenia than a female with psychosis; 12 studies, N = 827, OR = 1.70, 95%CI 1.27 to 2.30, $p = 0.0003$, $Q_w = 11.1$, $p = 0.43$ *Only the DSM criteria assigned significantly greater proportions of males to schizophrenia;* DSM: OR = 2.41, 95%CI 1.60 to 3.61 ICD-9: OR = 1.13, 95%CI 0.69 to 1.85 The difference between these effect sizes was significant ($Q_B = 5.7$, $p = 0.017$)	
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Cascio MT, Cella M, Preti A, Meneghelli A, Cocchi A

Gender and duration of untreated psychosis: A systematic review and meta-analysis

Early Intervention in Psychiatry 2012; 6(2): 115-127

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Comparison	**Sex differences in the duration of untreated psychosis (DUP) and age at first contact with treatment.**
Summary of evidence	**Moderate quality evidence (unclear sample size, inconsistent, mostly precise, direct) suggests no sex differences in the length of DUP.**
Sex differences in DUP and age at first contact	
A medium, significant effect of more males than females presenting with a first-episode of psychosis; 23 samples, unclear N, OR = 2.1, 95%CI 1.6 to 2.9, p = 0.0001 *There were no differences in the length of DUP;* 23 samples, g = -0.05, 95%CI -0.23 to 0.13, p = 0.58 *Males had a younger age at first contact with treatment in studies using any definition of DUP, and in samples from Western countries;* DUP by any definition: 16 samples, g = -0.18, 95%CI -0.37 to 0.001, p = 0.051 Samples from Western countries: 15 samples, g = -0.37, 95%CI -0.56 to -0.17, p = 0.0001 Samples from non-Western countries: 7 samples: g = -0.08, 95%CI -0.33 to 0.11, p = 0.54	
Consistency in results	Authors state that the results are inconsistent.
Precision in results	Mostly precise
Directness of results	Direct

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**

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	schizophrenia or schizophreniform disorder is higher in men than in women.
Sex differences	
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

Fusar-Poli P, Tantardini M, De Simone S, Ramella-Cravaro V, Oliver D, Kingdon J, Kotlicka-Antczak M, Valmaggia L, Lee J, Millan MJ, Galderisi S, Balottin U, Ricca V, McGuire P

Deconstructing vulnerability for psychosis: Meta-analysis of environmental risk factors for psychosis in subjects at ultra high-risk

European Psychiatry 2017; 40: 65-75

View review abstract online

Comparison	**Sex differences in people with ultra high-risk (UHR) mental states, determined as; attenuated psychotic symptoms, brief and limited intermittent psychotic symptoms, and genetic risk and functional deterioration.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, precise, direct) suggests increased rates of males in people with ultra high-risk mental states.**
Sex differences	
A significant, small increase in male sex in people with UHR mental states; 23 studies, N = 3,352, OR = 1.381, 95%CI 1.147 to 1.663, $p < 0.001$, $I^2 = 44\%$, $p = 0.014$ There was no evidence of publication bias.	
Consistency in results	Inconsistent

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Precision in results	Precise
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

View review abstract online

Comparison	**Sex differences in worldwide incidence and prevalence rates.**
Summary of evidence	**Moderate quality evidence (large samples, consistent, unable to assess precision, direct) suggests that the incidence, but not prevalence of schizophrenia is higher for males in the UK and Canada than for females.**
Sex differences	
Annual incidence rates per 100,000 persons 3 population-level studies *2 of the 3 studies reported male rates about twice that of female rates;* UK study – males: 10.0, females: 5.0 Canadian study – males: 10.9, females: 4.12 Spanish study - males: 12.7, females: 14.4 *Lifetime prevalence rates per 100 persons* 10 community surveys (samples ranged from 500 to 20,000) Male range: 0.12 in Hong Kong to 1.9 in Puerto Rico Female range: 0.07 in Taiwan to 2.6 in US	
Consistency in results	Authors state that male and female subjects were found to have very similar rates across most studies and differences are not reported to be significant.

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Precision in results	Unable to assess; no CIs are reported.
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, unable to assess consistency, precise, direct) suggests the incidence rate of schizophrenia is higher in men than in women.**
Sex differences	
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, $p < 0.05$	
Consistency in results	Unable to assess – heterogeneity measure is not reported.
Precision in results	Precise
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

Sex differences

Comparison	**Effects of sex on age of onset of schizophrenia in the UK.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, unable to assess consistency, imprecise, direct) suggests a medium effect of increased risk of schizophrenia in men up until 45 years of age, with no differences after 45 years.**
Sex differences	
A small, significant effect of increased risk of schizophrenia in men up until 45 years of age; < 45 years: 5 studies (N not reported), HR = 1.99, 95%CI 1.70 to 2.33, $p < 0.05$ > 45 years: HR = 0.98, 95%CI 0.70 to1.36, $p > 0.05$	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Imprecise
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	**Sex differences in the prevalence and incidence of subclinical psychotic symptoms.**
Summary of evidence	**Moderate quality evidence (inconsistent, precise, direct) suggests no differences in incidence or prevalence of subclinical psychotic symptoms between males and females.**
Sex differences	
No significant differences in the prevalence and incidence of subclinical psychotic symptoms; Prevalence: 25 studies, N not reported, OR = 1.01, 95%CI 0.91 to 1.12, $p > 0.05$, $I^2 = 70\%$, $p < 0.01$ Incidence: 2 studies, N not reported, OR = 1.06, 95%CI 0.64 to 1.75, $p > 0.05$, $I^2 = 79\%$, $p < 0.01$	

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Consistency in results	Inconsistent
Precision in results	Precise for prevalence
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	**Sex differences in the incidence of schizophrenia.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, unable to assess precision, direct) suggests that the incidence of schizophrenia is higher in males.**
Sex differences	
61 worldwide population-level studies *Significantly higher incidence of schizophrenia for males compared to females;* Differences in harmonic means: $F_{1,30} = 76.8$, $p < 0.001$ Median rate ratio (10% and 90% quantiles) = 1.4 (0.9, 2.4) Heterogeneity was explored via study quality, case identification, diagnostic criteria, age-standardised vs. raw rates and year of first intake. Only year of first intake showed significant variability across studies.	
Consistency in results	Inconsistent
Precision in results	Unable to assess; no CIs were reported.
Directness of results	Direct

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Sex differences

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	**Sex difference in the prevalence of schizophrenia.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, unable to assess precision, direct) suggests no differences in the prevalence of schizophrenia in males compared to females.**
Sex differences	
42 worldwide population-level studies *No difference in the prevalence estimates for schizophrenia between males and females*; $F_{1,72} = 0.68$, $p = 0.41$ Median rate ratio (10% and 90% quantiles) = 1.11 (0.50 to 1.69)	
Consistency in results	Inconsistent
Precision in results	Unable to assess; CIs are not reported.
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

View review abstract online

Comparison	**Sex differences in the incidence of schizophrenia and age effects.**

Sex differences

Summary of evidence	**Moderate to high quality evidence (large samples, unable to assess consistency, precise, direct) finds greater incidence of schizophrenia in males up until 39 years. Moderate quality evidence (imprecise) finds no differences in incidence between 40 to 49 years, and higher incidence of schizophrenia in females over 50 years.**
Sex differences	
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 < 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, $p < 0.05$ 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	Unable to assess; no measure of consistency is reported within age groups.
Precision in results	Precise for 20-39 year age groupings only.
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, DSM = Diagnostic and Statistical Manual of Mental Disorders, *g* = Hedges standardised mean difference, ICD = International Classification of Diseases, IRR = incidence rate ratio, F = F-test of difference in variance between groups, HR = hazard ratio, IRR = incidence rate ratio, N = number of participants, *p* = probability of obtaining that result ($p < 0.05$ generally regarded as significant), OR = odds ratio, Q_w = test for within group differences (heterogeneity in study results within a group of studies – measure of study consistency), Q_B = test for between group differences (heterogeneity between groups of studies for an outcome of interest), RR = risk ratio, 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 which 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[15].

† 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, 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 large effect is considered if RR > 2 or < 0.5 and a very large effect if RR > 5 or < 0.2 [16]. 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.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomized 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) which 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[15].

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 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 which are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives which are correctly identified (100% specificity = not

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identifying anyone as positive if they are truly not).

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. Unstandardized (*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. Standardized 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 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[15];

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

§ 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[16].

‖ 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 which 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.

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

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