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 and 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).

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. We also included reviews of psychotic symptoms. Due to the high volume of systematic reviews we have now limited inclusion to systematic meta-analyses. Where no systematic meta-analysis exists for a topic, systematic reviews without meta-analysis are included for that topic. 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. 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. 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). 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 ten studies that met our inclusion criteria.

- High quality evidence shows a small increased risk of schizophrenia for males compared with females in developed countries, regardless of study quality or
Sex differences

diagnostic criteria. Moderate to high quality evidence suggests this increased risk for males is not observed in developing countries.

- Moderate to high quality evidence suggests the incidence, but not prevalence, of schizophrenia is higher in males than females, but only up until 39 years of age, then higher incidence in females is found after 50 years of age. 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 to high quality evidence 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. However, this may depend on the diagnostic tool used as the DSM diagnostic criteria assigns significantly more males with psychosis to a schizophrenia diagnosis, while the ICD-9, shows no differences in sex distribution.

- Moderate quality evidence suggests no differences in incidence or prevalence rates of subclinical psychotic symptoms between males and females, although moderate to low quality evidence suggests male sex is more common in people with ultra high-risk mental states.
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

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Risk of schizophrenia for males vs. females.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>High quality evidence (large samples, consistent, 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. Moderate to high quality evidence (imprecise) suggests this increased risk is not observed in developing countries.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk of schizophrenia for males vs females</th>
</tr>
</thead>
<tbody>
<tr>
<td>38 studies (N unclear), 49 effect sizes (several studies reported on multiple groups)</td>
</tr>
<tr>
<td>Overall, the risk ratio shows a small effect for increased risk for men;</td>
</tr>
<tr>
<td>Weighted mean risk ratio = 1.42, 95%CI 1.30 to 1.56, no p-value reported, QW = 50.7 (NS)</td>
</tr>
</tbody>
</table>

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).

The risk ratio for schizophrenia is significantly higher for men vs. women in developed countries, but not in developing countries;

Developed countries: 42 effect sizes. Weighted mean risk ratio = 1.48, 95% CI 1.34 to 1.63, no p-value, QW = 40.7 (NS)

Developing countries: 7 effect sizes. Weighted mean risk ratio = 1.09, 95% CI 0.79 to 1.49 (NS), QW = 5.1 (NS)

Qb = 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.

The weighted mean risk ratio for schizophrenia is significantly higher for men in both time periods. Post-1980 studies reported a significantly larger risk ratio than the pre-1980 studies;

Studies before 1980: 25 effect sizes, weighted mean risk ratio = 1.27, 95%CI 1.15 to 1.41, no p-value, QW = 34.9 (NS)
Sex differences

Studies after 1980: 24 effect sizes. Weighted mean risk ratio = 1.54, 95%CI 1.39 to 1.71, no p-value, $Q_W = 36.4, p \leq 0.05$

$Q_B = 9.1, p \leq 0.01$

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.

The risk ratio for schizophrenia is significantly higher for men regardless of diagnostic criteria employed:

ICD-8, ICD-9 & ICD-10: 29 effect sizes. Weighted mean risk ratio = 1.45, 95%CI 1.29 to 1.63, no p-value, $Q_W = 32.1$ (NS)

DSM-III-R, DSM-IV: 8 effect sizes. Weighted mean risk ratio = 1.58, 95%CI 1.21 to 2.08, no p-value, $Q_W = 6.1$ (NS)

$Q_B = 0.5$ (NS)

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.

The risk ratio for schizophrenia is significantly higher for men regardless of age cut-off;

< 64 years: 32 effect sizes. Weighted mean risk ratio = 1.50, 95%CI 1.33 to 1.68, no p-value, $Q_W = 29.4$ (NS)

$\geq 64$ years: 16 effect sizes. Weighted mean risk ratio = 1.32, 95%CI 1.13 to 1.55, no p-value, $Q_W = 19.7$ (NS)

$Q_B = 1.7$ (NS)

Subgroup analysis assessing sex differences based on studies that minimized selection bias i.e. age cut-off of ≥54 years and inclusion of both inpatient and outpatient services.

The risk ratio for schizophrenia is significantly higher for men in both biased and unbiased studies;

Unbiased studies: 24 effect sizes. Weighted mean risk ratio = 1.35, 95% CI 1.17 to 1.56, no p-value, $Q_W = 26.8$ (NS)

Biased studies: 25 effect sizes. Weighted mean risk ratio = 1.48, 95% CI 1.30 to 1.69, no p-value, $Q_W = 24.5$ (NS)

$Q_B = 1.0$ (NS)

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.

The risk ratio for schizophrenia is significantly higher for men vs. women in high quality studies;

High quality studies: 11 effect sizes. Weighted mean risk ratio = 1.39, 95%CI 1.15 to 1.68, no p-value, $Q_W = 9$ (NS)
Sex differences

The study reported within-category homogeneity statistics for all comparisons. The only significant result was for the pre-and post-1980 study comparison indicating significant heterogeneity of individual study effect sizes.

Consistency in results

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex distribution</td>
<td>Assessment of the sex distribution in schizophrenia vs. other psychoses, depending on the diagnostic tool used.</td>
</tr>
<tr>
<td></td>
<td>Moderate to high quality evidence (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. However, this may depend on the diagnostic tool used as the DSM diagnostic criteria assigns significantly more males with psychosis to a schizophrenia diagnosis, while the ICD-9, shows no differences in sex distribution.</td>
</tr>
</tbody>
</table>

Beauchamp G, Gagnon A

Influence of diagnostic classification on gender ratio in schizophrenia

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

Comparison: Assessment of the sex distribution in schizophrenia vs. other psychoses, depending on the diagnostic tool used.

Summary of evidence: Moderate to high quality evidence (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. However, this may depend on the diagnostic tool used as the DSM diagnostic criteria assigns significantly more males with psychosis to a schizophrenia diagnosis, while the ICD-9, shows no differences in sex distribution.

Sex distribution

A male with psychosis is 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, Qw = 11.1, p = 0.43

However, this finding depends on the diagnostic tool used as when the ICD-9 and DSM were analysed separately, only the DSM criteria assigned significantly greater proportions of males to a schizophrenia diagnosis;

ICD-9: OR = 1.13, 95%CI 0.69 to 1.85
DSM: OR = 2.41, 95%CI 1.60 to 3.61

Q_B = 5.7, p = 0.017
Sex differences

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Consistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>Imprecise</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>

*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*

View review abstract online

**Comparison**

Sex differences in duration of untreated psychosis (DUP) and age at first contact with treatment for patients with a schizophrenia spectrum disorder.

**Summary of evidence**

Moderate quality evidence (mostly precise, inconsistent) suggests there are no sex differences in the length of DUP.

**DUP and age at first episode**

Overall, medium size effect suggests a significantly higher number of males than females across first episode psychosis samples;

23 samples (size unclear), OR 2.1 (CI 1.6 to 2.9), p = 0.0001

No differences were found between sexes in the length of DUP;

DUP by any definition: 23 samples: $g = -0.05$ (CI -0.23 to 0.13), $p = 0.58$

DUP defined as the start of psychotic symptoms to first treatment: 13 samples, $g = -0.11$ (CI -0.41 to 0.18), $p = 0.45$

Samples from Western countries: 20 samples: $g = -0.06$ (CI -0.28 to 0.16), $p = 0.60$

Samples from non-Western countries: 10 samples: $g = -0.03$ (CI -0.20 to 0.14), $p = 0.76$

Males had a younger age at first contact with a mental health professional, but only in studies using ‘any definition’ of DUP, and only in samples from Western countries;

DUP by any definition: 16 samples: $g = -0.18$ (CI -0.37 to 0.001), $p = 0.051$

DUP defined as the start of psychotic symptoms to first treatment, 7 samples: $g = -0.11$ (CI -0.41 to 0.20), $p = 0.49$

Samples from Western countries: 15 samples, $g = -0.37$ (CI -0.56 to -0.17), $p = 0.0001$
Sex differences

Samples from non-Western countries: 7 samples: $g = -0.08$ (CI -0.33 to 0.11), $p = 0.54$

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Authors state that heterogeneity was substantial &gt; 60% for all analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>Mostly precise</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>


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, which are determined as; attenuated psychotic symptoms, brief and limited intermittent psychotic symptoms, and genetic risk and functional deterioration.

Summary of evidence

Moderate to low quality evidence (inconsistent, precise and direct) suggests increased rates of male sex in people with ultra high-risk mental states.

Sex

A significant, small increase in male sex in people with UHR mental states;

23 studies, $N = 3352$, 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.

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Inconsistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>Precise</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>
Sex differences

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

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Sex differences in worldwide incidence and prevalence rates.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>Moderate quality evidence (large samples, direct) suggests that the incidence of a schizophrenia spectrum diagnosis may be higher for males in the UK and Canada than for females. Moderate to high quality evidence (large samples, direct, consistent) suggests no differences in the prevalence of schizophrenia for males compared to females.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis of schizophrenia, schizoaffective or schizophreniform disorder via Diagnostic Interview Schedule (DIS) or the Composite International Diagnostic Interview (CIDI) via key-informant surveys (clinician)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual incidence rates per 100,000 persons</td>
</tr>
<tr>
<td>2 of the 3 studies reported male rates about twice that of female rates;</td>
</tr>
<tr>
<td>Spanish study - males: 12.7, females: 14.4</td>
</tr>
<tr>
<td>UK study – males: 10.0, females: 5.0</td>
</tr>
<tr>
<td>Canadian study – males: 10.9, females: 4.12</td>
</tr>
<tr>
<td>Lifetime prevalence rates per 100 persons</td>
</tr>
<tr>
<td>10 community surveys (N = unclear – samples ranged from 500 to 20,000)</td>
</tr>
<tr>
<td>Male range: 0.12 in Hong Kong to 1.9 in Puerto Rico</td>
</tr>
<tr>
<td>Female range: 0.07 in Taiwan to 2.6 in US</td>
</tr>
</tbody>
</table>

Consistency in results | No measure of heterogeneity, however for prevalence, 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. |

Precision in results | No measure of precision |
Sex differences

<table>
<thead>
<tr>
<th>Directness of results</th>
<th>Direct</th>
</tr>
</thead>
</table>

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


[View review abstract online](#)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Effects of sex on age of onset.</th>
</tr>
</thead>
</table>

**Summary of evidence**

Moderate to low quality evidence (direct, imprecise) suggests a medium effect of increased incidence rates in men compared to women, with no differences after 45 years old.

**Age of onset**

*Overall incidence declined with age for both men and women, with a steeper decline reported in men;*

In participants below age 45 years, a medium effect size shows increased incidence rates in men compared to women.

5 studies (N not reported), HR = 1.99, 95%CI 1.70 to 2.33, *p* not reported

No differences were reported in participants aged over 45 years: HR = 0.98, 95%CI 0.70 to 1.36, *p* not reported.

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Unable to assess</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>Imprecise</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>

**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
Sex differences

across mental disorders

Psychological Medicine 2013; 43: 1133-1149

Prevalence and incidence of subclinical psychotic symptoms in males vs. females.

Summary of evidence

Moderate quality evidence (inconsistent, precise, direct) suggests no differences in incidence or prevalence rates of subclinical psychotic symptoms between males and females.

<table>
<thead>
<tr>
<th>Prevalence and incidence of subclinical psychotic symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>No differences in the prevalence and incidence of subclinical psychotic symptoms between males and females;</td>
</tr>
<tr>
<td>Prevalence: (25 studies, N not reported) OR 1.01, 95%CI 0.91 to 1.12, p &gt; 0.05, I² 70%, p &lt; 0.01</td>
</tr>
<tr>
<td>Incidence: (2 studies, N not reported) OR 1.06, 95%CI 0.64 to 1.75, p &gt; 0.05, I² 79%, p &lt; 0.01</td>
</tr>
</tbody>
</table>

Consistency in results

Inconsistent

Precision in results

Precise for prevalence only

Directness of results

Direct


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


<table>
<thead>
<tr>
<th>Distribution of rates of the incidence of schizophrenia by sex.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate to high quality evidence (large samples, direct, appears consistent) suggests that the incidence of schizophrenia is higher for males compared to females.</td>
</tr>
</tbody>
</table>

Incidence rates for males vs. females
Sex differences

61 studies in total (worldwide), N = unclear, population level data

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)

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Heterogeneity 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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>Unable to assess</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>

Saha S, Chant D, Welham J, McGrath J

A systematic review of the prevalence of schizophrenia


Link to review abstract

Comparison | Distribution of rates of the prevalence of schizophrenia by sex.
Summary of evidence | Moderate quality evidence (large samples, direct) suggests no differences in the prevalence of schizophrenia for males compared to females.

Prevalence rates for males vs. females

42 studies in total (worldwide), N = unclear, population level data

No difference in the distribution of 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 | Heterogeneity due to study quality explored and found consistent results, other areas not able to be calculated
Precision in results | CIs not reported
Sex differences

Directness of results | Direct


Systematic review and collaborative recalculation of 133693 incident cases of schizophrenia

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

Comparison | Distribution of rates of the incidence of schizophrenia by age and sex;

Summary of evidence | Moderate to high quality evidence (large samples, direct, unable to assess consistency, precise) suggests higher incidence of schizophrenia in males up until 39 years;
Moderate quality evidence (large samples, direct, unable to assess consistency, imprecise) suggests no differences in incidence between 40 to 49 years, and higher incidence of schizophrenia in females over 50 years;

Incidence rates for males vs. females by age

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), females vs. males

- < 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 | No consistency measures reported within age groups
Sex differences

<table>
<thead>
<tr>
<th>Precision in results</th>
<th>Precise for 20 to 39 year age groupings only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>

Explanation of acronyms

CI = Confidence Interval, DSM = Diagnostic and Statistical Manual of Mental Disorders, \( g \) = Hedges standardised mean difference, ICD = International Classification of Diseases, \( F \) = F-test of difference in variance between groups, HR = hazard ratio, IRR = incidence rate ratio, \( N \) = number of participants, NS = non-significant, \( p \) = 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), 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.

† 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. InOR 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.

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
Sex differences

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 unforeseen 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. I² 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. I² can be calculated from Q (chi-square) for the test of heterogeneity with the following formula:\textsuperscript{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\textsuperscript{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.
Sex differences

References