

## Cognition in bipolar disorder vs. schizophrenia

### Introduction

Bipolar disorder is characterised by intermittent periods of mania and depression. Mania involves elevated or irritable mood, which is often accompanied by inflated self-esteem or grandiosity, decreased need for sleep, distractibility, psychomotor agitation or excessive involvement in pleasurable activities. Manic episodes may involve psychotic symptoms such as grandiose delusions. Depressive episodes may be characterised by extended periods of sadness, a loss of interest in activities, loss of appetite, decreased energy, feelings of worthlessness, difficulty concentrating and suicidal ideation. Bipolar I disorder is mostly characterised by manic symptoms whereas Bipolar II disorder is mostly characterised by depressive episodes.

Schizophrenia is characterised by positive, negative and disorganised symptoms. Positive symptoms refer to experiences additional to what would be considered normal experience, such as hallucinations and delusions. Negative symptoms feature an absence of normal function, and may include blunted affect, impoverished thinking, alogia, asociality, avolition and anhedonia. Alogia is often manifested as poverty of speech; asociality involves reduced social interaction; avolition refers to poor hygiene and reduced motivation; and anhedonia is defined as an inability to experience pleasure. Disorganised symptoms include disorganised thought and speech. Depressive symptoms are also common, with many individuals experiencing depression after a psychotic episode.

Neurocognitive deficits are a core feature of both schizophrenia and bipolar disorder. People with either disorder may perform poorly on cognitive tasks assessing intelligence, memory, executive functioning, language, information processing and attention. Establishing differences in these cognitive domains may

assist correct diagnosis and treatment of the two disorders.

### 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 2010 that report results separately for people with a diagnosis of bipolar and related disorders. 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 review topics were found, only the most recent and comprehensive review was included. Reviews with pooled data are prioritised 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<sup>1</sup>. 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



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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 or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)<sup>2</sup>. 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 four systematic reviews that met our inclusion criteria<sup>3-6</sup>.

- Moderate to high quality evidence shows a medium-sized effect of poorer premorbid IQ in people with first-episode schizophrenia compared to people with first-episode bipolar disorder. Moderate to low quality evidence also shows a medium-sized effect of poorer current IQ in people with first-episode schizophrenia.
- Moderate to high quality evidence finds a small effect of poorer pre-onset cognitive functioning and a medium-sized effect of poorer post-onset cognitive functioning in people with bipolar disorder compared to controls. In people with schizophrenia compared to controls, there was a medium-sized effect of poorer pre-onset cognitive functioning and a large effect of poorer post-onset cognitive functioning.
- Moderate to high quality evidence shows medium-sized effects of poorer verbal memory in people with first-episode schizophrenia compared to people with first-episode bipolar disorder. Moderate quality evidence also shows a small effect of poorer working memory, with no differences in visual memory.
- Moderate to high quality evidence shows a medium-sized effect of poorer verbal fluency in people with first-episode schizophrenia compared to people with first-episode bipolar disorder.
- Moderate quality evidence shows a small effect of poorer processing speed in people with first-episode schizophrenia compared to people with first-episode bipolar disorder.
- Moderate to high quality evidence suggests a medium-sized effect of poorer social cognition in people with schizophrenia than in people with bipolar disorder on Theory of Mind and negative facial emotion recognition tasks, particularly in male patients. There were no differences on positive (happy) facial emotion recognition tasks.
- Moderate quality evidence suggests similar, medium to large effects of poor semantic inhibition performance in people with bipolar disorder or schizophrenia when compared to controls.



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*Bora E, Pantelis C*

**Meta-analysis of Cognitive Impairment in First-Episode Bipolar Disorder: Comparison With First-Episode Schizophrenia and Healthy Controls**

Schizophrenia Bulletin 2015; 41(5): 1095-1104

[View review abstract online](#)

<p><b>Comparison</b></p>	<p>Cognitive functioning in people with first-episode bipolar disorder vs. people with first-episode schizophrenia.</p>
<p><b>Summary of evidence</b></p>	<p><b>Memory:</b> Moderate to high quality evidence (medium to large samples, consistent, precise, direct) shows a medium-sized effect of poorer verbal memory in people with first-episode schizophrenia compared to people with first-episode bipolar disorder. Moderate quality evidence (inconsistent) also shows a small effect of poorer working memory. There were no significant differences in digit span or visual memory.</p> <p><b>Verbal fluency:</b> Moderate to high quality evidence (medium to large samples, consistent, precise, direct) shows a medium-sized effect of poorer verbal fluency in people with first-episode schizophrenia compared to people with first-episode bipolar disorder.</p> <p><b>Processing speed:</b> Moderate quality evidence (medium to large samples, inconsistent) shows a small effect of poorer processing speed in people with first-episode schizophrenia compared to people with first-episode bipolar disorder.</p> <p><b>IQ:</b> Moderate to high quality evidence (medium to large samples, consistent, precise, direct) shows a medium-sized effect of poorer premorbid IQ in people with first-episode schizophrenia compared to people with first-episode bipolar disorder. Moderate to low quality evidence (imprecise and inconsistent) also shows a medium-sized effect of poorer current IQ in people with first-episode schizophrenia.</p> <p><b>Global cognition:</b> Moderate to high quality evidence (large sample, inconsistent, precise, direct) shows a small effect of poorer global cognition in people with first-episode schizophrenia compared to people</p>



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	<p><b>with first-episode bipolar disorder.</b></p> <p><b>No differences in attention or reasoning are reported.</b></p>
<b>Global cognition</b>	
<p><i>A significant, small effect of poorer global cognition in people with first-episode schizophrenia compared with first-episode bipolar disorder;</i></p> <p>14 studies, N = 1,427, <math>d = 0.28</math>, 95%CI 0.12 to 0.44, <math>p &lt; 0.001</math>, <math>I^2 = 48.8%</math>, <math>p = 0.02</math></p> <p>Authors report no publication bias.</p> <p>No differences were found for males vs. females or younger vs. older patients.</p>	
<b>Memory</b>	
<p><i>Significant, small to medium-sized effects of poorer verbal memory, working memory and verbal working memory in people with first-episode schizophrenia compared with first-episode bipolar disorder;</i></p> <p>All verbal memory tasks: 7 studies, N = 832, <math>d = 0.47</math>, 95%CI 0.28 to 0.65, <math>p &lt; 0.001</math>, <math>I^2 = 39.5%</math>, <math>p = 0.13</math></p> <p>Working memory: 8 studies, N = 774, <math>d = 0.35</math>, 95%CI 0.11 to 0.59, <math>p = 0.005</math>, <math>I^2 = 59.2%</math>, <math>p = 0.02</math></p> <p>Verbal working memory: 8 studies, N = 774, <math>d = 0.33</math>, 95%CI 0.08 to 0.57, <math>p = 0.009</math>, <math>I^2</math> not reported</p> <p><i>No significant differences in;</i></p> <p>Digit span forwards: 4 studies, N = 435, <math>d = 0.18</math>, 95%CI -0.03 to 0.38, <math>p = 0.09</math>, <math>I^2</math> not reported</p> <p>Digit span backwards: 6 studies, N = 536, <math>d = 0.13</math>, 95%CI -0.04 to 0.31, <math>p = 0.14</math>, <math>I^2</math> not reported</p> <p>Visual memory: 4 studies, N = 406, <math>d = 0.28</math>, 95%CI -0.05 to 0.60, <math>p = 0.09</math>, <math>I^2 = 66.2%</math>, <math>p = 0.05</math></p> <p>Authors report no publication bias.</p> <p>Meta-regression analysis revealed between-group differences in working memory were more significant in studies that included younger people with first-episode schizophrenia. No differences were found for males vs. females.</p>	
<b>Processing speed</b>	
<p><i>Significant, small to medium-sized effects of poorer processing speed in people with first-episode schizophrenia compared with first-episode bipolar disorder;</i></p> <p>All speed tasks: 6 studies, N = 679, <math>d = 0.33</math>, 95%CI 0.08 to 0.59, <math>p = 0.009</math>, <math>I^2 = 58.9%</math>, <math>p = 0.03</math></p> <p>TMT A: 3 studies, N = 328, <math>d = 0.45</math>, 95%CI 0.23 to 0.68, <math>p &lt; 0.001</math></p> <p>TMT B: 3 studies, N = 328, <math>d = 0.47</math>, 95%CI 0.14 to 0.80, <math>p = 0.006</math></p> <p>Digit symbol: 3 studies, N = 450, <math>d = 0.71</math>, 95%CI 0.36 to 1.06, <math>p &lt; 0.001</math></p> <p>Authors report no publication bias.</p> <p>No differences were found for males vs. females or younger vs. older patients.</p>	



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<b>IQ</b>	
<p><i>Significant, medium-sized effects of lower premorbid and current IQ in people with first-episode schizophrenia compared with first-episode bipolar disorder;</i></p> <p>Premorbid IQ: 7 studies, N = 728, <math>d = 0.50</math>, 95%CI 0.30 to 0.69, <math>p &lt; 0.001</math>, <math>I^2 = 36.8%</math>, <math>p = 0.15</math></p> <p>Current IQ: 6 studies, N = 533, <math>d = 0.63</math>, 95%CI 0.36 to 0.91, <math>p &lt; 0.001</math>, <math>I^2 = 67.9%</math>, <math>p = 0.05</math></p> <p>Authors report no publication bias.</p> <p>No differences were found for males vs. females or younger vs. older patients.</p>	
<b>Fluency</b>	
<p><i>Significant, medium-sized effects of poorer fluency in people with first-episode schizophrenia compared with first-episode bipolar disorder;</i></p> <p>All fluency tasks: 7 studies, N = 865, <math>d = 0.50</math>, 95%CI 0.33 to 0.66, <math>p &lt; 0.001</math>, <math>I^2 = 22.0%</math>, <math>p = 0.26</math></p> <p>Letter: 5 studies, N = 542, <math>d = 0.42</math>, 95%CI 0.24 to 0.60, <math>p &lt; 0.001</math></p> <p>Category: 3 studies, N = 328, <math>d = 0.77</math>, 95%CI 0.0 to 1.53, <math>p = 0.05</math></p> <p>Authors report no publication bias.</p> <p>No differences were found for males vs. females or younger vs. older patients.</p>	
<b>Attention</b>	
<p><i>No significant differences in attention;</i></p> <p>2 studies, N = 101, <math>d = 0.05</math>, 95%CI -0.38 to 0.47, <math>p = 0.83</math>, <math>I^2 = 0%</math>, <math>p = 0.62</math></p> <p>Authors report no publication bias.</p> <p>No differences were found for males vs. females or younger vs. older patients.</p>	
<b>Reasoning</b>	
<p><i>No significant differences in reasoning;</i></p> <p>2 studies, N = 218, <math>d = 0.23</math>, 95%CI -0.09 to 0.56, <math>p = 0.16</math>, <math>I^2 = 26.3%</math>, <math>p = 0.24</math></p> <p>Authors report no publication bias.</p> <p>No differences were found for males vs. females or younger vs. older patients.</p>	
<b>Consistency in results<sup>‡</sup></b>	<p>Consistent for verbal memory, premorbid IQ, fluency, attention and reasoning.</p> <p>Inconsistent for global cognition, working memory, visual memory, psychomotor speed, and current IQ.</p>
<b>Precision in results<sup>§</sup></b>	<p>Precise for global cognition, verbal memory, working memory, visual memory, digit span, psychomotor tasks, TMT A, premorbid IQ, and</p>



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	fluency (all and letter). Imprecise for TMT B, digit symbol, current IQ, category fluency, attention, and reasoning.
<b>Directness of results</b>	Direct

*Bora E, Pantelis C*

**Social cognition in schizophrenia in comparison to bipolar disorder: A meta-analysis**

Schizophrenia Research 2016; 175: 72-8

[View review abstract online](#)

<b>Comparison</b>	<b>Social cognition in people with bipolar disorder vs. people with schizophrenia.</b>
<b>Summary of evidence</b>	<b>Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests a medium-sized effect of poorer social cognition in people with schizophrenia than in people with bipolar disorder on Theory of Mind and negative facial emotion recognition tasks, particularly for male patients. There were no differences on positive (happy) facial emotion recognition tasks.</b>
<b>Social cognition</b>	
<p><i>A significant, medium-sized effect of poorer social cognition in people with schizophrenia;</i></p> <p>Overall social cognition: 26 studies, N = 2,376, <math>d = 0.45</math>, 95%CI 0.31 to 0.60, <math>p &lt; 0.001</math>, <math>Qp &lt; 0.001</math></p> <p>The effect size was slightly smaller when the analysis included only samples of patients with bipolar disorder I (<math>d = 0.39</math>).</p> <p>The effect size was larger for Theory of Mind tests than for facial emotion recognition tests (<math>d = 0.57</math> vs. <math>d = 0.39</math>). The effect was significant only for negative, angry, and sad facial emotion recognition tests, and not happy facial emotion recognition tests.</p> <p>Effect sizes were larger in studies that had a higher percentage of males in their schizophrenia sample.</p> <p>There were no effects of diagnostic tool (DSM-IV/IV-TR vs. DSM-III-R), study setting (acute vs. non-acute), age, negative or positive symptoms, and age of onset and duration of bipolar disorder.</p>	
<b>Consistency in results</b>	Inconsistent
<b>Precision in results</b>	Precise



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<b>Directness of results</b>	Direct
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*Trotta A, Murray RM, MacCabe JH*

**Do premorbid and post-onset cognitive functioning differ between schizophrenia and bipolar disorder? A systematic review and meta-analysis**

**Psychological Medicine 2015; 45: 381-94**

[View review abstract online](#)

<b>Comparison</b>	<b>Pre- and post-illness onset cognitive functioning in people with bipolar disorder or schizophrenia vs. controls.</b>
<b>Summary of evidence</b>	<b>Moderate to high quality evidence (large samples, inconsistent, precise, direct) finds a small effect of poorer pre-onset cognitive functioning and a medium-sized effect of poorer post-onset cognitive functioning in people with bipolar disorder. In people with schizophrenia, there was a medium-sized effect of poorer pre-onset cognitive functioning and a large effect of poorer post-onset cognitive functioning.</b>

**Pre-onset cognitive functioning**

*Significant, medium-sized effect of poorer pre-onset cognitive functioning in people with schizophrenia than controls;*

17 studies, N = 774,131, SMD = -0.597, 95%CI -0.707 to -0.487,  $p < 0.0001$ ,  $I^2 = 72%$ ,  $p < 0.0001$   
 Subgroup analysis found a smaller effect in prospective than retrospective studies (-0.406 vs. -0.675).

*Significant, small effect of poorer pre-onset cognitive functioning in people with bipolar disorder than controls;*

17 studies, N = 773,408, SMD = -0.113, 95%CI -0.202 to -0.024,  $p = 0.013$ ,  $I^2 = 34%$ ,  $p = 0.06$   
 Subgroup analysis found a smaller effect in prospective than retrospective studies (-0.029 vs. -0.147).

There were no moderating effects of medications, age at time of assessment, duration of illness, clinical status, source population, year of publication and cognitive test used.

**Post-onset cognitive functioning**

*Significant, large effect of poorer post-onset cognitive functioning in people with schizophrenia than controls;*



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17 studies, N = 2,487, SMD = -1.369, 95%CI -1.578 to -1.160,  $p < 0.0001$ ,  $I^2 = 78%$ ,  $p < 0.0001$

Subgroup analysis found a smaller effect in patients during their first episode of psychosis than those not in their first episode of psychosis (-1.111 vs. -1.432).

*Significant, medium-sized effect of poorer pre-onset cognitive functioning in people with bipolar disorder than controls;*

17 studies, N = 2,211, SMD = -0.623, 95%CI -0.717 to -0.529,  $p < 0.0001$ ,  $I^2 = 82%$ ,  $p < 0.0001$

Subgroup analysis found a smaller effect in patients during their first episode of psychosis than those not in their first episode of psychosis (-0.277 vs. -0.691).

Potential effect modifiers

There were no moderating effects of medications, age at time of assessment, duration of illness, clinical status, source population, year of publication and cognitive test used.

<b>Consistency in results</b>	Inconsistent
<b>Precision in results</b>	Precise
<b>Directness of results</b>	Direct

*Wang K, Song LL, Cheung EFC, Lui SSY, Shum DHK, Chan RCK*

**Bipolar disorder and schizophrenia share a similar deficit in semantic inhibition: A meta-analysis based on hayling sentence completion test performance**

**Progress in Neuro-Psychopharmacology and Biological Psychiatry 2013; 46: 153-60**

[View review abstract online](#)

<b>Comparison</b>	<b>Semantic inhibition in people with bipolar disorder vs. controls compared to people with schizophrenia vs. controls</b>
<b>Summary of evidence</b>	<b>Moderate quality evidence (medium-sized samples, mostly consistent and precise, direct) suggests similar, medium to large effects of poor semantic inhibition in people with bipolar disorder and schizophrenia when compared to controls.</b>
<b>Semantic inhibition</b>	
<i>Significant, medium to large effects of poor semantic inhibition in both bipolar disorder and schizophrenia compared to controls on the following tasks;</i>	
<u>Total Latency of Task A</u>	
Bipolar disorder: 6 studies, N = 341, $d = 0.719$ , 95%CI 0.231 to 1.207, $p < 0.05$ , $Qp < 0.01$	



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<p>Schizophrenia: 7 studies, N = 405, <math>d = 0.749</math>, 95%CI 0.367 to 1.132, <math>p &lt; 0.05</math>, <math>Qp &lt; 0.01</math></p> <p style="text-align: center;"><u>Total Latency of Task B</u></p> <p>Bipolar disorder: 5 studies, N = 253, <math>d = 0.930</math>, 95%CI 0.403 to 1.457, <math>p &lt; 0.05</math>, <math>Qp &lt; 0.05</math></p> <p>Schizophrenia: 4 studies, N = 245, <math>d = 0.840</math>, 95%CI 0.566 to 1.113, <math>p &lt; 0.05</math>, <math>Qp &gt; 0.05</math></p> <p style="text-align: center;"><u>Total Error of Task B</u></p> <p>Bipolar disorder: 5 studies, N = 253, <math>d = 0.866</math>, 95%CI 0.402 to 1.330, <math>p &lt; 0.05</math>, <math>Qp &lt; 0.05</math></p> <p>Schizophrenia: 8 studies, N = 447, <math>d = 0.944</math>, 95%CI 0.698 to 1.190, <math>p &lt; 0.05</math>, <math>Qp &gt; 0.05</math></p> <p style="text-align: center;"><u>Type A Error of Task B</u></p> <p>Bipolar disorder: 2 studies, N = 146, <math>d = 0.678</math>, 95%CI 0.336 to 1.021, <math>p &lt; 0.05</math>, <math>Qp &lt; 0.05</math></p> <p>Schizophrenia: 6 studies, N = 395, <math>d = 0.639</math>, 95%CI 0.431 to 0.847, <math>p &lt; 0.05</math>, <math>Qp &gt; 0.05</math></p> <p style="text-align: center;"><i>Significant, small effect of poor task performance in schizophrenia vs. controls only;</i></p> <p style="text-align: center;"><u>Type B Error of Task B</u></p> <p>Bipolar disorder: 2 studies, N = 146, <math>d = 0.869</math>, 95%CI -0.472 to 2.211, <math>p &gt; 0.05</math>, <math>Qp &lt; 0.05</math></p> <p>Schizophrenia: 6 studies, N = 395, <math>d = 0.170</math>, 95%CI 0.578 to 0.247, 0.912, <math>p &lt; 0.05</math>, <math>Qp &lt; 0.05</math></p> <p style="text-align: center;"><i>No significant differences between bipolar disorder or schizophrenia vs. controls;</i></p> <p style="text-align: center;"><u>Suppression Time</u></p> <p>Bipolar disorder: 4 studies, N = 218, <math>d = 0.156</math>, 95%CI 0.240 to -0.313, <math>p &gt; 0.05</math>, <math>Qp &lt; 0.05</math></p> <p>Schizophrenia: 5 studies, N = 285, <math>d = 0.325</math>, 95%CI -0.065 to 0.549, <math>p &gt; 0.05</math>, <math>Qp &lt; 0.05</math></p>	
<b>Consistency in results</b>	Inconsistent, apart from Total Latency of Task B, Total Error of Task B, and Type A Error of Task B in schizophrenia.
<b>Precision in results</b>	Precise, apart from Type B Error of Task B in bipolar disorder.
<b>Directness of results</b>	Direct

**Explanation of acronyms**

CI = confidence interval,  $d$  = Cohen’s  $d$  standardised mean difference,  $I^2$  = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants,  $p$  = probability of rejecting a null hypothesis of no differences between groups,  $Q$  = test for heterogeneity. SMD = standardised mean difference, 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<sup>7</sup>.

† Different effect measures are reported by different reviews.

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 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).

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. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect<sup>7</sup>.

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  $< 0.2$ <sup>8</sup>. InOR stands for logarithmic OR where a InOR 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



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between variables. They can provide an indirect 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. 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 effect across studies (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<sup>7</sup>;

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

§ 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, these criteria should be relaxed<sup>9</sup>.

|| 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 and is therefore 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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