



## Criminal offending, aggression and violence

### Introduction

Criminal offending covers a wide range of behaviours from destructive acts, stealing, sexual assaults, to physical assaults causing injury or death. The majority of patients with a mental illness will never commit a crime, however, the few who do may help perpetuate a negative public stereotype that mental illness is associated with violent behaviour.

It is difficult to determine whether the violent acts of an individual with bipolar disorder are a consequence of the illness, or are traits of that particular individual. This ambiguity is confounded by the fact that people with mental illness may be at particularly high risk for exposure to the social factors that contribute to violent or homicidal tendencies in the general population, including social disadvantage and substance abuse. Furthermore, any increase in violent behaviour seen in an individual with bipolar disorder could be the result of a co-morbid psychiatric disorder such as antisocial personality disorder.

### 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 for people with a diagnosis of bipolar or related disorders. We have prioritised reviews with pooled data for inclusion. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found that assessed the same topic, only the most recent review was included.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses ([PRISMA](#)) checklist 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 (RCT) 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)<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>.

#### *Criminal offending*

- Moderate to low quality evidence suggests arrest rates in people with schizophrenia or



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bipolar disorder are around 40%, which is similar to people with other mental disorders.

### *Violence*

- Moderate quality evidence suggests no significant differences in rates of violent criminal behaviour between people with bipolar disorder and general population rates. Rates of violent criminal behavior were higher in people with bipolar disorder than in people with major depression or anxiety disorders, and were lower in people with bipolar disorder than in people with a psychotic disorder. There were no significant differences in violent criminal behaviour between people with bipolar disorder and people with a substance use or personality disorder.
- Moderate to high quality evidence suggests the overall prevalence of violence in psychiatric inpatients is 17%, but having a diagnosis of bipolar disorder was not associated with risk of inpatient violence. For all inpatients, there was a strong association between increased inpatient violence and having a history of violence. Weaker associations were found between increased inpatient violence and being male, or having an alcohol abuse disorder.

### *Aggression*

- Moderate to high quality evidence suggests no significant differences in risk of inpatient aggression in people with an affective disorder, including bipolar disorder, and people with other psychiatric disorders. Moderate quality evidence suggests a large increased risk of inpatient aggression in people with any psychiatric disorder with increased previous admissions. There were small to medium-sized effects of increased risk of inpatient aggression in people with a history of illicit substance abuse or involuntary admissions, and small effects of increased risk of inpatient aggression in males, people with a history of self-destructive behavior, and people who were not married. Moderate to low quality

evidence suggests small increased risk of inpatient aggression in people with a history of violence, or those who were young.



*Dack C, Ross J, Papadopoulos C, Stewart D, Bowers L*

**A review and meta-analysis of the patient factors associated with psychiatric inpatient aggression**

Acta Psychiatrica Scandinavica 2013; 127: 255-268

[View review abstract online](#)

<p><b>Comparison</b></p>	<p><b>Assessment of factors associated with psychiatric inpatient aggression.</b></p> <p>The sample included people with affective disorders (bipolar disorder, depression, mania), schizophrenia, personality disorders, or organic brain syndrome.</p>
<p><b>Summary of evidence</b></p>	<p><b>Moderate to high quality evidence (consistent, precise, indirect, large samples) suggests no significant differences in risk of inpatient aggression in people with an affective disorder, including bipolar disorder, and people with other psychiatric disorders.</b></p> <p><b>Moderate quality evidence (inconsistent, imprecise or indirect, large samples) suggests a large increased risk of inpatient aggression in people with any psychiatric disorder with increased number of previous admissions. There were small to medium-sized effects of increased risk of inpatient aggression in people with a history of illicit substance abuse or involuntary admissions, and small effects of increased risk of inpatient aggression in males, people with a history of self-destructive behavior, and people who were not married. Moderate to low quality evidence (inconsistent, imprecise, indirect, large samples) suggests small increased risk of inpatient aggression in people with a history of violence, or those who were young.</b></p>
<p align="center"><b>Factors associated with inpatient aggression</b></p>	
<p><i>No significant differences in inpatient aggression between people with affective vs. other diagnoses; 11 studies, N = 12,974, RR = 0.94, 95%CI 0.82 to 1.08, p &gt; 0.05, I<sup>2</sup> = 44%</i></p> <p align="center"><u>For all patients, regardless of diagnosis</u></p> <p><i>A large effect of increased inpatient aggression in patients with more previous admissions vs. fewer previous admissions;</i></p>	



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2 studies, N = 2,300, SMD = 1.20, 95%CI 1.05 to 1.35,  $p < 0.001$ ,  $I^2 = 98.50\%$

*A small effect of increased inpatient aggression with younger age vs. older age;*

18 studies, N = 9,584, SMD = -0.32, 95%CI -0.39 to 0.25,  $p < 0.001$ ,  $I^2 = 51.10\%$

*A small to medium-sized effect of increased inpatient aggression in patients with a history of any violence vs. no history of violence;*

5 studies, N = 1,013, RR = 2.27, 95%CI 1.90 to 2.69,  $p < 0.001$ ,  $I^2 = 75.80\%$

*A small to medium-sized effect of increased inpatient aggression in patients with involuntary admissions vs. patients with voluntary admissions;*

8 studies, N = 6,520, RR = 2.17, 95%CI 2.01 to 2.34,  $p < 0.001$ ,  $I^2 = 98.50\%$

*A small to medium-sized effect of increased inpatient aggression in patients with a history of illicit substance abuse vs. patients with no history of illicit substance abuse;*

3 studies, N = 296, RR = 2.09, 95%CI 1.46 to 3.00,  $p < 0.01$ ,  $I^2 = 7.80\%$

*A small effect of increased inpatient aggression in patients with a history of any substance abuse vs. patients without a history of any substance abuse;*

6 studies, N = 1,113, RR = 1.15, 95%CI 1.00 to 1.31,  $p < 0.05$ ,  $I^2 = 76.40\%$

*A small effect of increased inpatient aggression in male patients vs. female patients;*

21 studies, N = 16,309, RR = 1.10, 95%CI 1.03 to 1.17,  $p < 0.01$ ,  $I^2 = 48\%$

*A small effect of increased inpatient aggression in patients who are single vs. patients who are married or in a de facto relationship;*

6 studies, N = 6,570, RR = 0.72, 95%CI 0.63 to 0.83,  $p < 0.001$ ,  $I^2 = 2.3\%$

*A small effect of increased inpatient aggression in patients with a history of self-destructive behavior vs. patients without a history of self-destructive behavior;*

3 studies, N = 567, RR = 1.24, 95%CI 1.03 to 1.50,  $p < 0.05$ ,  $I^2 = 95.30\%$

*A small effect of increased inpatient aggression in patients with a history of violent convictions vs. patients without a history of violent convictions;*

4 studies, N = 362, RR = 0.80, 95%CI 0.65 to 0.98,  $p < 0.05$ ,  $I^2 = 87.90$

The following factors were not associated with a risk of inpatient aggression: ethnicity, education, and having an affective disorder.

**Factors associated with repetitive inpatient aggression**

For all patients, regardless of diagnosis

*A small effect of increased repetitive inpatient aggression in patients with a history of any violence vs. patients without a history of any violence;*

2 studies, N = 703, RR = 1.58, 95%CI 1.45 to 1.73,  $p < 0.01$ ,  $I^2 = 99.1\%$



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*A small effect of increased repetitive inpatient aggression in male patients vs. female patients;*

9 studies, N = 1,694, RR = 0.83, 95%CI 0.75 to 0.93,  $p < 0.01$ ,  $I^2 = 56.7\%$

*A small effect of increased repetitive inpatient aggression in patients with a history of any substance abuse vs. patients without a history of any substance abuse;*

3 studies, N = 702, RR = 1.28, 95%CI 1.04 to 1.59,  $p < 0.05$ ,  $I^2 = 11.3\%$

The following factors were not associated with a risk of repetitive inpatient aggression: age, ethnicity, diagnosis, and having a history of violent convictions.

<b>Consistency in results<sup>†</sup></b>	Reasonably consistent
<b>Precision in results<sup>§</sup></b>	Precise
<b>Directness of results<sup>  </sup></b>	Indirect; mixed diagnostic samples for other comparisons.

*Iozzino L, Ferrari C, Large M, Nielssen O, De Girolamo G*

**Prevalence and risk factors of violence by psychiatric acute inpatients: A systematic review and meta-analysis**

PLoS ONE 2015; 10 (6): e0128536

[View review abstract online](#)

<b>Comparison</b>	<p><b>Prevalence and risk factors for violence in psychiatric inpatients.</b></p> <p>The sample predominately included people with schizophrenia, but also included people with bipolar disorder or personality disorders.</p>
<b>Summary of evidence</b>	<p>Moderate to high quality evidence (inconsistent or indirect, precise, large sample) suggests the overall prevalence of violence in psychiatric inpatients is 17%, but having a diagnosis of bipolar disorder was not associated with risk of inpatient violence. There was a strong association between increased inpatient violence and having a history of violence. Weaker associations were found between increased inpatient violence and being male, or having an alcohol abuse disorder.</p>
<b>Prevalence and risk factors</b>	



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*The pooled prevalence of inpatients who committed at least one act of violence was 17%;*

35 studies, N = 23,972 patients, prevalence = 17%, 95%CI 14% to 20%,  $I^2 = 98%$ ,  $p < 0.001$

Univariate analyses showed bipolar disorder was not a significant predictor of increased inpatient violence ( $\beta = -0.06$ ,  $p = 0.739$ ). The factors significantly associated with increased inpatient violence were; being male ( $\beta = 0.48$ ), having an alcohol abuse disorder ( $\beta = 0.32$ ), having a history of violence ( $\beta = 0.27$ ), having a diagnosis of schizophrenia ( $\beta = 0.26$ ), and involuntary admission ( $\beta = 0.11$ ).

A multivariate analyses, which explained 68% of study heterogeneity, included having male gender, a diagnosis of schizophrenia, an alcohol abuse disorder, and involuntary admission showed only male gender ( $\beta = 0.28$ ) and having an alcohol abuse disorder ( $\beta = 0.21$ ) were significant predictors.

A multivariate analyses, which explained 100% of study heterogeneity, included having a history of violence, male gender, a diagnosis of schizophrenia, and having an alcohol abuse disorder, showed only having a history of violence was a significant predictor ( $\beta = 0.42$ ).

Authors report no evidence of publication bias.

<b>Consistency in results</b>	Inconsistent for overall prevalence rates, consistent for the multivariate models.
<b>Precision in results</b>	Precise
<b>Directness of results</b>	Direct for the bipolar assessment only; mixed samples otherwise.

*Livingstone JD*

**Contact Between police and people with mental disorders: A Review of Rates**

Psychiatric Services 2016; 67: 850-857

[View review abstract online](#)

<b>Comparison</b>	Arrest rates in people with bipolar disorder, schizophrenia or other mental disorders.
<b>Summary of evidence</b>	Moderate to low quality evidence (unable to assess consistency or precision, indirect, large samples) suggests arrest rates in people with schizophrenia or bipolar disorder are around 40%, which is similar to people with other mental disorders.



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<b>Arrest rates</b>	
Schizophrenia and bipolar disorder: 12 studies, N = 121,467, average rate = 40%	
Other mental disorders: 10 studies, N = 5,385, average rate = 41%	
<b>Consistency in results</b>	Unable to assess – no measure of consistency is reported.
<b>Precision in results</b>	Unable to assess – no measure of precision is reported.
<b>Directness of results</b>	Indirect; mixed diagnosis samples.

*Verdolini N, Pacchiarotti I, Kohler CA, Reinares M, Samalin L, Colom F, Tortorella A, Stubbs B, Carvalho AF, Vieta E, Murru A*

**Violent criminal behavior in the context of bipolar disorder: Systematic review and meta-analysis**

**Journal of Affective Disorders 2018; 239: 161-70**

[View review abstract online](#)

<b>Comparison 1</b>	<b>Violent criminal behaviour in people with bipolar disorder vs. the general population.</b>
<b>Summary of evidence</b>	<b>Moderate quality evidence (large sample, inconsistent, imprecise, direct) suggests no differences in rates of violent criminal behaviour in people with bipolar disorder and general population rates. Rates were significantly higher in people with bipolar disorder in studies using self-report measures of violence, in cross-sectional studies, and in studies conducted in the USA. There were no differences in studies using record-based measures of violence, in retrospective or case-control studies or in studies conducted in Europe or Oceania.</b>

**Violent criminal behaviour**

*Large, significant effect of more violent criminal behavior in people with bipolar disorder;*

12 studies, N = 58,475, OR = 5.21, 95%CI 1.34 to 20.25,  $p = 0.01$ ,  $I^2 = 100\%$

*This effect was not significant with one extreme outlier removed;*



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<p>11 studies, N = 38,493, OR = 2.78, 95%CI 0.69 to 11.29, <math>p = 0.152</math>, <math>I^2 = 100\%</math></p> <p>Subgroup analyses found rates were significantly higher in people with bipolar disorder in studies using self-report measures of violence and not record-based measures, in cross-sectional studies and not retrospective or case-control studies, and in studies conducted in the USA and not in Europe or Oceania.</p> <p>There were no moderating effects of study quality, publication year, sex or substance use.</p> <p>There was no evidence of publication bias.</p>	
<b>Comparison 2</b>	<b>Violent criminal behaviour in people with bipolar disorder vs. people with any other psychiatric disorder.</b>
<b>Summary of evidence</b>	<b>Moderate quality evidence (large sample, inconsistent, imprecise, direct) suggests no differences in rates of violent criminal behaviour in people with bipolar disorder and people with any other psychiatric disorders. Subgroup analyses found rates were significantly higher in people with bipolar disorder in studies using self-report measures of violence, in cross-sectional studies, and in studies conducted in the USA. Rates were significantly lower in people with bipolar disorder in studies conducted in Europe, in studies using record-based measures, and in case-control studies.</b>
<b>Violent criminal behaviour</b>	
<p><i>There was no significant differences between groups;</i></p> <p>9 studies, N = 260,011, OR = 0.78, 95%CI 0.44 to 1.49, <math>p = 0.41</math>, <math>I^2 = 98\%</math></p> <p>Subgroup analyses found rates were significantly higher in people with bipolar disorder in studies using self-report measures of violence and were lower in record-based measures. Rates were higher in people with bipolar disorder in cross-sectional studies and lower in case-control studies. Rates were in higher in people with bipolar disorder in studies conducted in the USA, and lower in studies conducted in Europe.</p> <p>There were no moderating effects of study quality, publication year, or sex.</p> <p>There was no evidence of publication bias.</p>	
<b>Comparison 3</b>	<b>Violent criminal behaviour in people with bipolar disorder vs. people with major depression.</b>
<b>Summary of evidence</b>	<b>Moderate quality evidence (large samples, inconsistent, imprecise, direct) suggests a small effect of increased rates of violent criminal behaviour in people with bipolar disorder compared to people with major depression.</b>



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<b>Violent criminal behaviour</b>	
<p><i>A significant, small effect of more violent criminal behavior in people with bipolar disorder;</i> 7 studies, N = 141,345, OR = 2.313, 95%CI 1.721 to 3.110, <math>p &lt; 0.001</math>, <math>I^2 = 59\%</math></p> <p>Subgroup analyses found rates were significantly higher in people with bipolar disorder in studies using self-report measures of violence, in cross-sectional studies, and in studies conducted in the USA.</p> <p>There were no moderating effects of study quality or publication year.</p> <p>There was evidence of publication bias.</p>	
<b>Comparison 4</b>	<b>Violent criminal behaviour in people with bipolar disorder vs. people with psychotic disorders.</b>
<b>Summary of evidence</b>	<b>Moderate quality evidence (large samples, inconsistent, imprecise, direct) suggests a medium-sized effect of decreased rates of violent criminal behaviour in people with bipolar disorder compared to people with a psychotic disorder.</b>
<b>Violent criminal behaviour</b>	
<p><i>A significant, medium-sized effect of less violent criminal behavior in people with bipolar disorder;</i> 8 studies, N = 55,285, OR = 0.498, 95%CI 0.329 to 0.751, <math>p = 0.001</math>, <math>I^2 = 79\%</math></p> <p>Subgroup analyses found rates were significantly lower in people with bipolar disorder in studies using record-based measures, case-control design, and in studies conducted in the USA.</p> <p>There were no moderating effects of study quality, publication year, or sex.</p> <p>There was no evidence of publication bias.</p>	
<b>Comparison 5</b>	<b>Violent criminal behaviour in people with bipolar disorder vs. people with an anxiety disorder.</b>
<b>Summary of evidence</b>	<b>Moderate quality evidence (large samples, inconsistent, imprecise, direct) suggests a small trend effect of increased rates of violent criminal behaviour in people with bipolar disorder than in people with an anxiety disorder.</b>
<b>Violent criminal behaviour</b>	
<p><i>Small, trend effect of increased rates of violent criminal behavior in people with bipolar disorder;</i> 5 studies, N = 11,391, OR = 1.771, 95%CI 0.978 to 3.207, <math>p = 0.059</math>, <math>I^2 = 75\%</math></p> <p>Subgroup analyses found rates were significantly higher in people with bipolar disorder in studies</p>	



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<p>using self-report measures of violence, in cross-sectional studies, and in studies conducted in the USA.</p> <p>There were no moderating effects of study quality or publication year.</p> <p>There was no evidence of publication bias.</p>	
<b>Comparison 6</b>	<b>Violent criminal behaviour in people with bipolar disorder vs. people with substance use disorders.</b>
<b>Summary of evidence</b>	<b>Moderate quality evidence (large samples, inconsistent, imprecise, direct) suggests no significant differences in rates of violent criminal behaviour between people with bipolar disorder and people with a substance use disorder.</b>
<b>Violent criminal behaviour</b>	
<p><i>There were no significant differences between groups;</i></p> <p>Alcohol: 5 studies, N = 13,572, OR = 0.454, 95%CI 0.093 to 2.213, <math>p = 0.328</math>, <math>I^2 = 97\%</math></p> <p>Drugs: 6 studies, N = 12,668, OR = 0.980, 95%CI 0.609 to 1.576, <math>p = 0.933</math>, <math>I^2 = 88\%</math></p> <p>There was no evidence of publication bias.</p>	
<b>Comparison 7</b>	<b>Violent criminal behaviour in people with bipolar disorder vs. people with a personality disorder.</b>
<b>Summary of evidence</b>	<b>Moderate quality evidence (large sample, inconsistent, imprecise, direct) suggests no significant differences in rates of violent criminal behaviour between people with bipolar disorder and people with a personality disorder.</b>
<b>Violent criminal behaviour</b>	
<p><i>There were no significant differences between groups;</i></p> <p>2 studies, N = 5,764, OR = 0.388, 95%CI 0.022 to 6.742, <math>p = 0.516</math>, <math>I^2 = 98\%</math></p>	
<b>Consistency in results</b>	Inconsistent
<b>Precision in results</b>	Imprecise
<b>Directness of results</b>	Direct



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### Explanation of acronyms

$\beta$  = coefficient, CI = confidence interval,  $I^2$  = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, OR = odds ratio,  $p$  = statistical probability of obtaining that result ( $p < 0.05$  generally regarded as significant), 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; 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.

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† 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 randomized 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. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large treatment 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, an 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. An 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 an 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 indicate the strength of association or relationship between



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variables. They are an indication of prediction, but do not confirm causality due to possible and often unforeseen confounding variables. An  $r^2$  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 independent 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.

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<sup>9</sup>.

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‡ Inconsistency refers to differing estimates of treatment 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 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;

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

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|| 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.

§ 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



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