TECHNICAL COMMENTARY

Suicide and self-harm

Introduction

There has been much research dedicated to determining potential risk factors for suicide, which may have clinically important applications for prevention. Many of the important risk factors for suicide in the general population can apply to people with bipolar disorder, including suffering from depression or having a history of previous suicide attempts. However, factors specific to bipolar disorder may also contribute to an increased risk of suicide or self-harm.

To assess risk factors for suicide in people with bipolar disorder, study samples are ideally followed up over a long period of time. Characteristics such as duration and severity of illness and rates of death due to other causes can impact on suicide rates and these characteristics can change over time.

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 bipolar or 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/or comprehensive version was included. Reviews with pooled data were 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[1]. Reviews with less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large 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)[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 inclusion criteria[3-14].

- Moderate to high quality evidence suggests the overall prevalence of suicide attempts in people with bipolar disorder is around 30%, with the yearly incidence rate being around 4%. Overall prevalence rates increase with increased duration of illness, while yearly incidence rates decreased with increased duration of illness.

In children and adolescents

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Suicide and self-harm

- Moderate to high quality evidence suggests the risk of suicide attempts is higher in children and adolescents with bipolar disorder than children and adolescents with major depression.

- Moderate quality evidence suggests suicide ideation is more prevalent than suicide attempts in children or adolescents with bipolar disorder (~50% vs. ~25%). The only significant predictors of suicide attempts were having bipolar I rather than bipolar II disorder, and having a comorbid diagnosis of attention deficit hyperactivity disorder.

In adults

Self harm

- Moderate to low quality evidence suggests no differences in the risk of self-harm between people with bipolar disorder and people with no mood, anxiety, port-traumatic stress, or obsessive compulsive disorder.

Suicide attempts

- High quality evidence suggests small effects of having an anxiety disorder or being female is associated with greater risk of suicide attempts in people with bipolar disorder.

- Moderate to high quality evidence suggests having a cluster B or borderline personality disorder (medium-sized effect), or a younger age at bipolar onset (< 18yrs, small effect), is associated with greater risk of suicide attempts in people with bipolar disorder.

- Moderate quality evidence suggests a large effect of having a depressive polarity of first illness episode, and small effects of depressive predominance, substance use disorder, and having a family history of suicide being associated with greater risk of suicide attempts in people with bipolar disorder.

- Moderate quality evidence suggests a medium-sized effect of more risky decision making in people with bipolar disorder with a history of suicide attempts compared to people with bipolar disorder without a history of suicide attempts, or compared to controls with no psychiatric disorder.

Suicide completion

- Moderate to high quality evidence suggests a medium-sized effect of having a family history of suicide being associated with greater risk of suicide completion in people with bipolar disorder.

- Moderate quality evidence suggests a small effect of male gender being associated with greater risk of suicide completion in people with bipolar disorder.

- Moderate quality evidence suggests a medium-sized effect of increased risk of suicide completion in prisoners with bipolar disorder vs. prisoners with no psychiatric disorder.

- Moderate quality evidence suggests a large increased risk of suicide completion in psychiatric hospital patients who were assessed as being at high risk of suicide. A history of suicidal behaviour and depressive symptoms or affective disorder was included in the majority of the high-risk models.

Bentley KH, Cassiello-Robbins CF, Vittorio L, Sauer-Zavala S, Barlow DH

The association between nonsuicidal self-injury and the emotional disorders: A meta-analytic review

Clinical Psychology Review 2015; 37: 72-88

View review abstract online

Comparison	Rates of self-harm in people with bipolar disorder vs. mood disorders, anxiety disorders, port-traumatic stress disorder, or obsessive compulsive disorder.
Summary of evidence	Moderate to low quality evidence (unclear sample size, inconsistent, imprecise, direct) suggests no differences between groups in the rates of self-harm.

Self-harm	

No significant difference between groups;	
10 studies, N = unclear, OR = 1.05, 95%CI 0.62 to 1.77, $p = 0.85$, $I^2 = 55\%$, $p < 0.001$	

Consistency in results[‡]	Inconsistent
Precision in results[§]	Imprecise
Directness of results[∥]	Direct

Carra G, Bartoli F, Crocamo C, Brady KT, Clerici M

Attempted suicide in people with co-occurring bipolar and substance use disorders: systematic review and meta-analysis

Journal of Affective Disorders 2014; 167: 125-35

View review abstract online

Comparison	Rates of attempted suicide in people with bipolar and substance use disorders vs. people with bipolar disorder, without a substance use disorder.
Summary of evidence	Moderate quality evidence (large sample size, inconsistent, imprecise, direct) suggests a small, increased risk of suicide attempts in people with bipolar disorder and a history of comorbid substance use disorder.

Suicide attempts
Small, significant increased risk of attempted suicide in people with bipolar disorder and any history of substance use disorders, but not current substance use disorders;
Lifetime use: 13 studies, N = 19,062, OR = 1.96, 95%CI 1.56 to 2.47, $p < 0.01$, $I^2 = 64\%$, $p = 0.001$
Current use: 4 studies, N = 3,418, OR = 1.50, 95%CI 0.87 to 2.59, $I^2 = 88\%$, $p < 0.001$
There were no significant effects of substance type (any substance, cannabis, or alcohol), age, sex, geographic location, publication year, setting, and study quality. Authors report no evidence of publication bias.

Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Carvalho AF, McIntyre RS, Dimelis D, Gonda X, Berk M, Nunes-Neto PR, Cha DS, Hyphantis TN, Angst J, Fountoulakis KN

Predominant polarity as a course specifier for bipolar disorder: a systematic review

View review abstract online

Comparison	**Factors associated with predominance of symptoms in people with bipolar disorder.**
Summary of evidence	**Moderate quality evidence (large sample size, unable to assess precision or consistency, direct) suggests there were more suicide attempts in people with a depressive symptom predominance of bipolar disorder compared to manic or mixed symptom predominance.**

Suicide attempts
More suicide attempts were found in people with depressive rather than manic/mixed symptom predominance;
More suicide attempts: 5 studies, N = 2,049

Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no CIs were reported.

Directness of results	Direct

De Crescenzo F, Serra G, Maisto F, Uchida M, Woodworth H, Casini MP, Baldessarini RJ, Vicari S

Suicide Attempts in Juvenile Bipolar Versus Major Depressive Disorders: Systematic Review and Meta-Analysis

Journal of the American Academy of Child & Adolescent Psychiatry 2017; 56: 825-831

View review abstract online

Comparison	Rates of suicide attempts in children and adolescents with bipolar disorder vs. major depression.
Summary of evidence	**Moderate to high quality evidence (large sample size, consistent, imprecise, direct) suggests the risk of suicide attempts is higher in children and adolescents with bipolar disorder than children and adolescents with major depression.**

Suicide attempts	
Small, significant increased risk of attempted suicide in children and adolescents with bipolar disorder; 6 studies, N = 2,303, OR = 1.71, 95%CI 1.33 to 2.20, *p* < 0.0001, I^2 < 10%	
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Fazel S, Wolf A, Geddes JR

Suicide in prisoners with bipolar disorder and other psychiatric disorders: a systematic review

Bipolar Disorders 2013; 15: 491-495

View review abstract online

Comparison	Suicide rates in prisoners with bipolar disorder compared to prisoners with no psychiatric disorder.
Summary of evidence	Moderate quality evidence (unclear sample size, consistent, imprecise, direct) suggests a medium increased risk of suicide in prisoners with bipolar disorder vs. prisoners with no psychiatric disorder.

Suicide completion	

A significant, medium-sized effect for increased risk of suicide in prisoners with bipolar disorder vs. prisoners without a psychiatric disorder;

5 studies, N = not reported, OR = 2.40, 95%CI 1.60 to 3.60, $p < 0.05$, $I^2 = 0\%$

Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Hauser M, Galling B, Correll CU

Suicidal ideation and suicide attempts in children and adolescents with bipolar disorder: a systematic review of prevalence and incidence rates, correlates, and targeted interventions

Bipolar Disorders 2013; 15: 507-23

View review abstract online

Comparison	Suicide ideation and attempt rates in children and adolescents with bipolar disorder.
Summary of evidence	Moderate quality evidence (large sample size, unable to assess consistency or precision, direct) suggests suicide ideation is more prevalent than suicide attempts in children or adolescents with bipolar disorder (~50% vs. ~25%). The only significant predictors of suicide attempts were having bipolar I rather than bipolar II disorder, and having a comorbid diagnosis of attention deficit hyperactivity disorder.

Suicide ideation	

Suicide ideation was more prevalent than suicide attempts, while incidence rates were similar;

Overall N = 13, N = 1,508

Suicide ideation	
Past prevalence = 57.4%	
Current prevalence = 50.4%	
Incidence (over ~42 months) = 14.6%	
Meta-regression found no significant predictors for suicide ideation.	
Suicide attempts	
Suicide attempts	
Past prevalence = 21.3%	
Current prevalence = 25.5%	
Incidence (over ~42 months) = 14.7%	
Meta-regression found bipolar I disorder (rather than bipolar II disorder) and comorbid attention deficit hyperactivity disorder, were significant predictors of suicide attempts.	
Consistency in results	Unable to assess; no CIs are reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Joslyn C, Hawes DJ, Hunt C, Mitchell PB

Is age of onset associated with severity, prognosis, and clinical features in bipolar disorder? A meta-analytic review

Bipolar Disorders 2016; 18: 389-403

View review abstract online

Comparison	**Suicide attempts in people with an early age of onset of bipolar disorder (≤ 18 years).**
Summary of evidence	**Moderate quality evidence (large sample size, inconsistent, imprecise, direct) suggests a small increased risk of suicide attempts in people with an early age of onset of bipolar disorder.**
Suicide attempts	
Significant, small increased risk of suicide attempts in people with an early age of bipolar onset; 6 studies, N = 4,045, OR = 1.68, 95%CI 1.29 to 2.18, $p < 0.001$, $I^2 = 58\%$	
Consistency in results	Inconsistent

Precision in results	Imprecise
Directness of results	Direct

Large M, Myles N, Myles H, Corderoy A, Weiser M, Davidson M, Ryan CJ

Suicide risk assessment among psychiatric inpatients: a systematic review and meta-analysis of high-risk categories

Psychological Medicine 2017; doi:10.1017/S0033291717002537

View review abstract online

Comparison	**Rate of suicide in psychiatric inpatients (including those on leave) assessed as being at high risk of suicide vs. low risk of suicide.**
	The sample includes patients with psychotic and affective disorders. Studies varied as to how the high-risk group was categorised; however, a history of suicidal behaviour and depressive symptoms or affective disorder was included in the majority of high-risk models.
Summary of evidence	**Moderate quality evidence (large sample size, imprecise, inconsistent, direct) suggests psychiatric hospital patients who are assessed as being at high risk of suicide have a large increased risk of suicide.**

Suicide completion

A significant, large effect of increased risk of suicide in inpatients deemed at high risk of suicide compared to inpatients deemed at low risk of suicide;

18 samples, N = 191,944, OR = 7.10, 95%CI 4.20 to 12.20, $p < 0.05$, I^2 = 88.1%, $p < 0.001$

Adjustment for potential publication bias resulted in similar results;

OR = 5.10, 95%CI 3.10 to 8.60, $p < 0.05$

Sensitivity of a high-risk categorisation = 53.1% indicating moderate sensitivity

Sensitivity of a lower-risk categorisation = 84.2% indicating good sensitivity

The AUC suggests an 83% chance that an inpatient who died by suicide would have been deemed at higher risk of suicide than an inpatient who did not suicide.

There were no significant differences in the effect size according to year of publication, the number of variables in the model, the number of variables in the high-risk model, or how high-risk groups were categorised.

Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Richard-Devantoy S, Gorwood P, Annweiler C, Olie JP, Le Gall D, Beauchet O

Suicidal behaviours in affective disorders: A deficit of cognitive inhibition?

Canadian Journal of Psychiatry 2012; 57: 254-62

View review abstract online

Comparison	Deficits in cognitive inhibition in people with bipolar disorder and suicide attempts.
Summary of evidence	Low quality evidence (small sample sizes, unable to assess consistency or precision, direct) is unclear of the association between cognitive inhibition and suicide attempts in people with bipolar disorder.

Suicide attempts
1 study (N = 109) found greater deficits in cognitive inhibition in people with bipolar II disorder and current suicide attempts than in people with bipolar I disorder and a history of suicide attempts.
1 study (N = 89) found greater deficits in cognitive inhibition in people with bipolar I disorder and a history of suicide attempts than in people with bipolar I disorder without a history of suicide attempts.
1 study (N = 96) found no differences in cognitive inhibition between people with bipolar I disorder with or without a history of suicide attempts or ideation.

Consistency in results	Unable to assess; no measure of heterogeneity is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Richard-Devantoy S, Olie E, Guillaume S, Courtet P

Decision-making in unipolar or bipolar suicide attempters

Journal of Affective Disorders 2016; 190: 128-36

View review abstract online	
Comparison	**Deficits in decision making in people with bipolar disorder and a history of a suicide attempt vs. people with bipolar disorder and no history of a suicide attempt or controls with no psychiatric disorder.**
Summary of evidence	**Moderate to high quality evidence (small to medium sample sizes, consistent, precise, direct) suggests more risky choices in people with bipolar disorder and a history of suicide attempts compared to both healthy controls and people with bipolar disorder and no history of suicide attempts.**
Risky vs. safe decision making	

A medium-sized, significant effect of more risky choices in people with bipolar disorder and a history of suicide attempts compared to people with bipolar disorder and no history of suicide attempts;

4 studies, N = 270, g = -0.40, 95%CI -0.75 to -0.05, p = 0.026

A medium-sized, significant effect of more risky choices in people with bipolar disorder and a history of suicide attempts compared to controls;

2 studies, N = 258, g = -0.50, 95%CI -0.70 to -0.23, p < 0.001

Consistency in results	Authors report the results were consistent.
Precision in results	Precise
Directness of results	Direct

Schaffer A, Isometsa ET, Tondo L, D HM, Turecki G, Reis C, Cassidy F, Sinyor M, Azorin JM, Kessing LV, Ha K, Goldstein T, Weizman A, Beautrais A, Chou YH, Diazgranados N, Levitt AJ, Zarate CA Jr, Rihmer Z, Yatham LN

International Society for Bipolar Disorders Task Force on Suicide: meta-analyses and meta-regression of correlates of suicide attempts and suicide deaths in bipolar disorder

Bipolar Disorders 2015; 17: 1-16

View review abstract online

Comparison	**Risk factors associated with suicide attempts and completion in people with bipolar disorder.**
Summary of evidence	**High quality evidence (large sample sizes, consistent, precise, direct) suggests anxiety disorders and female gender are associated with more suicide attempts in people with bipolar**

	disorder.
	Moderate to high quality evidence (large sample sizes, inconsistent or imprecise, direct) suggests younger age at bipolar onset, cluster B and/or borderline personality disorders, and having a family history of suicide (for completion) are associated with more suicide attempts in people with bipolar disorder.
	Moderate quality evidence (large sample sizes, inconsistent and imprecise, direct) suggests depressive polarity of first illness episode, male gender (for completions), substance use disorder, and having a family history of suicide (for attempts) are associated with more suicide attempts in people with bipolar disorder.

Suicide attempts
Variables significantly associated with more suicide attempts, with large effects; Depressive polarity of current or most recent episode: 3 studies, N = 1,238, OR = 5.99, 95%CI 1.75 to 20.50, p = 0.004, I^2 = 58%, p = 0.09
Variables significantly associated with more suicide attempts, with medium-sized effects; Comorbid cluster B and/or borderline personality disorder: 5 studies, N = 1,293, OR = 2.51, 95%CI 1.91 to 3.31, p < 0.00001, I^2 = 36%, p = 0.18
Variables significantly associated with more suicide attempts, with small effects; Depressive polarity of first illness episode: 7 studies, N = 4,686, OR = 1.92, 95%CI 1.39 to 2.65, p < 0.0001, I^2 = 77%, p = 0.0003 Comorbid anxiety disorder: 13 studies, N = 40,968, OR = 1.81, 95%CI 1.66 to 1.97, p < 0.0001, I^2 = 35%, p = 0.10 Comorbid substance use disorder: 18 studies, N = 39,139, OR = 1.81, 95%CI 1.31 to 2.50, p < 0.0001, I^2 = 89%, p = 0.00001 First-degree family history of suicide: 11 studies, N = 7,452, OR = 1.69, 95%CI 1.25 to 2.27, p = 0.0006, I^2 = 57%, p = 0.009 Female gender: 20 studies, N = 44,242, OR = 1.54, 95%CI 1.44 to 1.66, p < 0.00001, I^2 = 20%, p = 0.20 Younger age at bipolar onset: 16 studies, N = 11,659, SMD = -0.29, 95%CI -0.36 to -0.21, p < 0.00001, I^2 = 56%, p = 0.004
There were no significant effects of bipolar type (bipolar I disorder vs. bipolar II disorder), history of psychotic symptoms, or cannabis use.
Suicide completion

Variables significantly associated with more suicide attempts, with medium-sized effects; First-degree family history of suicide: 4 studies, N = 7,023, OR = 2.91, 95%CI 1.54 to 5.48, $p <$ 0.001, I^2 = 18%, p = 0.30 *Variables significantly associated with more suicide deaths, with small effects;* Male gender: 11 studies, N = 75,055, OR = 1.83, 95%CI 1.41 to 2.39, $p <$ 0.00001, I^2 = 55%, p = 0.01 There were no significant effects of psychotic symptoms, or substance use disorders.	
Consistency in results	Inconsistent for depressive polarity of first illness episode, comorbid substance use disorder, younger age at bipolar onset, first-degree family history of suicide (for attempts), and male gender.
Precision in results	Precise for comorbid anxiety disorder, female gender, younger age at bipolar onset.
Directness of results	Direct

Tondo L, Pompili M, Forte A, Baldessarini RJ

Suicide attempts in bipolar disorders: comprehensive review of 101 reports

Acta Psychiatrica Scandinavica 2016; 133: 174-86

View review abstract online

Comparison	Rates of suicide attempts in people with bipolar disorder.
Summary of evidence	**Moderate to high quality evidence (large sample size, appears precise, direct, unable to assess consistency) suggests the overall prevalence of suicide attempts in people with bipolar disorder is around 30%, with the yearly incidence rate around 4%. Prevalence rates increase with increased duration of illness, while yearly incidence rates decreased with increased duration of illness.**

Suicide attempts
101 studies, N = 79,937
Average prevalence rate (overall rates) = 31.1%, 95%CI 27.9% to 34.3%
Average yearly incident rate = 4.24%, 95%CI 3.78% to 4.70%

Multivariable regression modeling found the prevalence of suicide attempts increased with duration of illness, while the yearly incidence rate decreased. Other variables (publication year, ages at onset and at intake, sample size, % of women and % of bipolar I disorder) were not significant in multivariable modeling.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Appears precise
Directness of results	Direct

Explanation of acronyms

CI = Confidence Interval, g = Hedges' standardised mean difference, I^2 = proportion of heterogeneity across study results, N = number of participants, OR = odds ratio, p = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), 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[15].

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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 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[15].

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[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.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an

indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

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‡ 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. 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 considerable heterogeneity and over this is considerable heterogeneity. I² can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;[15]

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

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§ 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 [17].

‖ 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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