

Personality and temperament

Introduction

Personality and temperament are thought to be relatively stable over time and include innate emotional, reactive, and attentional traits. These traits may differ according to genetic differences and the extent of the risk a person has to psychiatric disorders such as schizophrenia.

Personality and temperament are thought to be relatively stable over time and include emotional, reactive, and attentional traits. Studies assessing personality and temperament use “positive” stimuli, which generates pleasurable emotional states, “negative” stimuli evokes avoidant, threat, sadness, or other negative emotional states, and “neutral” stimuli generally provokes no response. Hedonic and aversive emotions refer to the positive or negative emotions following stimuli presentation.

One of the main personality models is the Five-Factor Model which includes five traits of; 1) neuroticism: vulnerability to emotional instability and self-consciousness, 2) extraversion: predisposition towards sociability, assertiveness and social interaction, 3) openness: cognitive disposition to new experiences, creativity and aesthetics, 4) agreeableness: tendency towards being sympathetic, trusting and altruistic, and 5) conscientiousness: tendency towards dutifulness and competence.

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. 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. 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-analysis¹. Reviews reporting less than 50% of items 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

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objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

was associated with increased positive but not negative symptoms.

- Moderate to high quality evidence finds medium to large effects of more negative emotion and less positive emotion in people with schizophrenia than controls.

Results

We found eight systematic reviews that met our inclusion criteria³⁻¹⁰.

- Moderate to high quality evidence suggests a large effect of increased neuroticism and decreased extraversion, and medium-sized effects of decreased openness, agreeableness and conscientiousness in people with schizophrenia compared to controls.
- High quality evidence shows a large effect of more harm avoidance, and small effects of less novelty seeking, reward dependence and persistence in people with schizophrenia compared to controls.
- High quality evidence suggests a medium effect of greater aversion and arousal to neutral stimuli, greater aversion to positive stimuli and greater hedonic (pleasure) response to negative stimuli.
- Moderate to high quality evidence suggests a large effect of more trait anhedonia (inability to feel pleasure) in people with schizophrenia than controls.
- Moderate to high quality evidence suggests a medium to large effect of poor emotion regulation, and more dissociation and alexithymia (inability to identify and describe one's own emotions).
- Moderate to high quality evidence finds the prevalence insecure attachment style is higher in people with psychosis than controls (76% vs. 38%), with fearful attachment style being the most prevalent followed by avoidant then anxious. Increased prevalence

Carr SC, Hardy A, Fornells-Ambrojo M

Relationship between attachment style and symptom severity across the psychosis spectrum: A meta-analysis

Clinical Psychology Review 2018; 59: 145-58

[View review abstract online](#)

Comparison	Attachment style in people with psychosis vs. controls.
Summary of evidence	Moderate to high quality evidence (large samples, inconsistent, precise, direct) finds the prevalence rate of insecure attachment style was significantly higher in people with psychosis than controls (76% vs. 38%), with fearful attachment style being the most prevalent followed by avoidant then anxious. Increased prevalence was associated with increased positive but not negative symptoms.

Attachment style

The prevalence rate of insecure attachment style was significantly higher in people with psychosis;

Psychosis: 10 studies, N = 1,305, prevalence = 76%, 95%CI 0.65% to 0.84%, I² = 86%

Control: 6 studies, N = 10,391, prevalence = 38%, 95%CI 0.31% to 0.44%, I² = 59%

Q = 29.24, p < 0.001

Subgroup analysis within the clinical sample showed fearful attachment style was the most prevalent, followed by avoidant attachment style then anxious attachment style.

Small, significant associations were found between increased positive symptoms (or psychotic-like symptoms in controls) and increased anxious attachment style;

Psychosis: 11 studies, r = 0.23, 95%CI 0.14 to 0.33, p < 0.001, I² ≥ 50%

Control: 11 studies, r = 0.28, 95%CI 0.21 to 0.35, p < 0.001, I² ≥ 80%

Small, significant associations were found between increased positive symptoms (or psychotic-like symptoms in controls) and increased avoidant attachment style;

Psychosis: 11 studies, r = 0.15, 95%CI 0.04 to 0.25, p = 0.006, I² ≥ 50%

Control: 11 studies, r = 0.19, 95%CI 0.13 to 0.25, p < 0.001, I² ≥ 80%

A small, significant association was found between increased negative-like symptoms in controls and increased anxious attachment style, with no association in clinical samples;

Psychosis: 7 studies, r = 0.11, 95%CI -0.03 to 0.25, p = 0.057, I² ≥ 50%

Control: 5 studies, r = 0.25, 95%CI 0.12 to 0.37, p < 0.001, I² ≥ 80%

A small, significant association was found between increased negative-like symptoms in controls

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and increased avoidant attachment style, with no association in clinical samples;
 Psychosis: 7 studies, $r = 0.11$, 95%CI -0.03 to 0.25, $p = 0.133$, $I^2 \geq 50\%$
 Control: 5 studies, $r = 0.38$, 95%CI 0.28 to 0.48, $p < 0.001$, $I^2 \geq 80\%$

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

Cho H, Gonzalez R, Lavaysse LM, Pence S, Fulford D, Gard DE

Do people with schizophrenia experience more negative emotion and less positive emotion in their daily lives? A meta-analysis of experience sampling studies

Schizophrenia Research 2017; 183: 49-55
[View review abstract online](#)

Comparison	Negative and positive emotion in people with schizophrenia vs. controls.
Summary of evidence	Moderate to high quality evidence (large samples, some inconsistency, precise, direct) finds medium to large effects of more negative emotion and less positive emotion in people with schizophrenia.
Attachment style	
<i>Medium to large effects of more negative emotion and less positive emotion in people with schizophrenia;</i> Negative emotion: 12 studies, N = 1,349, SMD = 0.84, 95%CI, 0.73 to 0.95, $p < 0.0001$, $I^2 = 23\%$ Positive emotion: 12 studies, N = 1,349, SMD = -0.75, 95%CI, -1.03 to -0.46, $p < 0.0001$, $I^2 = 71\%$	
Consistency in results	Consistent for negative emotion, inconsistent for positive emotion.
Precision in results	Precise
Directness of results	Direct

Cohen AS, Minor KS

Emotional experience in patients with schizophrenia revisited: Meta-analysis of laboratory studies

Schizophrenia Bulletin 2010; 36(1): 143-150

[View review abstract online](#)

<p>Comparison</p>	<p>Emotional response following positive, negative or neutral stimuli in people with schizophrenia vs. controls.</p> <p>Note: “Positive” refers to stimuli generating pleasure. “Negative” refers to stimuli evoking avoidant, threat, sadness, or other negative emotional states. “Neutral” refers to stimuli that are neither positive nor negative. Hedonic and aversive emotions refer to positive or negative emotions following stimuli presentation. “Bipolar ratings” refers to a subjective rating scale set up with hedonic and aversive emotions on opposing ends of a spectrum.</p>
<p>Summary of evidence</p>	<p>High quality evidence (large samples, consistent, precise, direct) suggests a medium-sized effect of greater aversion to positive and neutral stimuli, and greater hedonic response to negative stimuli in people with schizophrenia. There were similar hedonic responses to positive and neutral stimuli, and similar aversive responses to negative stimuli.</p>
<p>Positive stimuli</p>	
<p><i>A medium to large-sized effect suggests people with schizophrenia experienced greater aversion to positive stimuli, compared with controls;</i></p> <p>11 studies, N = 605, $d = 0.72$, 95%CI 0.53 to 0.91, no p-value reported, $Q = 5.36$</p> <p><i>A small to medium-sized effect suggests people with schizophrenia experienced greater aversion (lower ‘bipolar ratings’) to positive stimuli, compared with controls;</i></p> <p>12 studies, N = 627, $d = -0.33$, 95%CI -0.57 to -0.10, no p-value reported, $Q = 10.68$</p> <p><i>No difference was reported in hedonic response to positive stimuli between people with schizophrenia and controls;</i></p> <p>14 studies, N = 770, $d = -0.16$, 95%CI -0.40 to 0.07, no p-value reported, $Q = 13.72$</p>	
<p>Negative stimuli</p>	

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A small effect suggests people with schizophrenia experienced greater hedonic response to negative stimuli, compared with controls;

10 studies, N = 544, $d = 0.28$, 95%CI 0.03 to 0.59, no p -value reported, $Q = 10.86$

No difference was reported in aversive response to negative stimuli between people with schizophrenia and controls;

9 studies, N = 697, $d = 0.24$, 95%CI -0.03 to 0.45, no p -value reported, $Q = 8.56$

No difference was reported in 'bipolar ratings' to negative stimuli between people with schizophrenia and controls;

12 studies, N = 594, $d = 0.12$, 95%CI -0.12 to 0.36, no p -value reported, $Q = 11.80$

Neutral stimuli

A medium effect suggests that people with schizophrenia experienced greater aversion to neutral stimuli, compared with controls;

7 studies, N = 321, $d = 0.64$, 95%CI 0.34 to 0.93, no p -value reported, $Q = 4.76$

No difference was reported in hedonic response to neutral stimuli between people with schizophrenia and controls;

7 studies, N = 321, $d = 0.25$, 95%CI -0.25 to 0.73, no p -value reported, $Q = 6.24$

No difference was reported in 'bipolar ratings' to neutral stimuli between people with schizophrenia and controls;

9 studies, N = 452, $d = 0.07$, 95%CI -0.15 to 0.29, no p -value reported, $Q = 8.01$

Subgroup analysis suggests stimulus type, gender and medication did not significantly affect emotion induction.

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

Llerena K, Strauss GP, Cohen AS

Looking at the other side of the coin: A meta-analysis of self-reported emotional arousal in people with schizophrenia

Schizophrenia Research 2012; 142(1-3): 65-70

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Comparison	Emotional arousal in people with schizophrenia vs. controls.
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Summary of evidence	High quality evidence (large samples, consistent, precise, direct) shows a medium-sized effect of increased arousal to neutral emotive stimuli compared to controls, but no differences with positive or negative emotive stimuli.
Emotional arousal using subjective arousal ratings	
<p><i>A medium effect of increased arousal to neutral emotive stimuli in patients compared to controls;</i> 22 studies, N = 1,588, $g = 0.43$, 95%CI 0.23 to 0.63, $p < 0.001$, $Q = 22.29$, $p > 0.05$ <i>No differences between in arousal for positive or negative emotive stimuli;</i> Positive 24 studies, N = 1,530, $g = -0.05$, 95%CI -0.19 to 0.09, $p > 0.05$, $Q = 22.19$, $p > 0.05$ Negative 26 24 studies, N = 1,827, $g = -0.14$, 95%CI -0.32 to 0.04, $p > 0.05$, $Q = 26.93$, $p > 0.05$ Authors report no evidence of publication bias.</p>	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

<p><i>Miettunena J, Raevuoric A</i> A meta-analysis of temperament in axis I psychiatric disorders Comprehensive Psychiatry 2012; 53: 152-166 View review abstract online</p>	
Comparison	Temperament in people with schizophrenia vs. controls.
Summary of evidence	High quality evidence (large samples, consistent, precise, direct) suggests a large effect of more harm avoidance, and small effects of less novelty seeking, reward dependence, and persistence in people with schizophrenia compared to controls.
Harm avoidance	
<p><i>A large effect of more harm avoidance in people with schizophrenia than controls;</i> 13 studies, N = 6,481, $d = 1.15$, $p < 0.05$</p>	
Novelty seeking or risk taking	

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<p><i>A small effect of less novelty seeking in people with schizophrenia;</i> 13 studies, N = 6,481, $d = -0.16$, $p < 0.05$</p>	
<p>Reward dependence</p>	
<p><i>A small to medium-sized effect of less reward dependence in people with schizophrenia;</i> 10 studies, N = not reported, $d = -0.36$, $p < 0.05$</p>	
<p>Persistence</p>	
<p><i>A small effect of less persistence in people with schizophrenia;</i> 10 studies, N = not reported, $d = -0.23$, $p < 0.05$</p>	
Consistency in results	Authors report results are consistent.
Precision in results	Graphs indicate data are precise.
Directness of results	Direct

<p><i>O'Driscoll C, Laing J, Mason O</i></p> <p>Cognitive emotion regulation strategies, alexithymia and dissociation in schizophrenia, a review and meta-analysis</p> <p>Clinical Psychology Review 2014; 34: 482-495 View review abstract online</p>	
Comparison	Cognitive emotion regulation, alexithymia (inability to identify and describe own emotions), and dissociation (detachment from reality) in people with schizophrenia vs. controls.
Summary of evidence	Moderate to high quality evidence (large samples, mostly inconsistent or imprecise, direct) suggests a medium to large effect of poor emotion regulation, more dissociation and more alexithymia in people with schizophrenia than controls.
<p>Cognitive emotion regulation</p>	
<p><i>A medium to large-sized effect of poor emotion regulation in people with schizophrenia, with less emotion management and cognitive reappraisal, and more attentional deployment, worry, rumination, and experiential avoidance;</i></p>	

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<p>Emotion management: 13 studies, N = 1,204, $g = 0.96$, 95%CI 0.77 to 1.14, $p < 0.00001$, $I^2 = 45%$, $p = 0.06$</p> <p>Cognitive reappraisal: 11 studies, N = 1,395, $g = 0.49$, 95%CI 0.32 to 0.66, $p < 0.00001$, $I^2 = 51%$, $p = 0.03$</p> <p>Attentional deployment: 17 studies, N = 2,001, $g = -0.96$, 95%CI -1.18 to -0.75, $p < 0.00001$, $I^2 = 76%$, $p < 0.00001$</p> <p>Worry: 12 studies, N = 1,559, $g = -1.06$, 95%CI -1.33 to -0.79, $p < 0.00001$, $I^2 = 80%$, $p < 0.00001$</p> <p>Rumination: 5 studies, N = 442, $g = -0.67$, 95%CI -0.86 to -0.47, $p < 0.00001$, $I^2 = 0%$, $p = 0.41$</p> <p>Experiential avoidance: 9 studies, N = 713, $g = -0.44$, 95%CI -0.59 to -0.29, $p < 0.00001$, $I^2 = 1%$, $p = 0.42$</p>	
Dissociation	
<p><i>A large effect of more dissociation in people with schizophrenia;</i></p> <p>Overall: 7 studies, N = 767, $g = -0.86$, 95%CI -1.13 to -0.60, $p < 0.00001$, $I^2 = 50%$, $p = 0.06$</p> <p>Amnesia: 4 studies, N = 545, $g = -0.73$, 95%CI -1.03 to -0.44, $p < 0.05$, $I^2 = 36%$, p-value not reported</p> <p>Absorption: 5 studies, N = 587, $g = -0.70$, 95%CI -1.03 to -0.37, $p < 0.05$, $I^2 = 54%$, p-value not reported</p> <p>Depersonalisation / derealisation: 4 studies, N = 545, $g = -0.95$, 95%CI -1.19 to -0.72, $p < 0.05$, $I^2 = 0%$, p-value not reported</p>	
Alexithymia	
<p><i>A large effect of more alexithymia in people with schizophrenia;</i></p> <p>8 studies, N = 710, $g = -1.05$, 95%CI -1.45 to -0.65, $p < 0.00001$, $I^2 = 83%$, $p < 0.00001$</p>	
Consistency in results	Consistent for rumination, experiential avoidance, depersonalisation and dissociation.
Precision in results	Imprecise for amnesia, absorption and alexithymia.
Directness of results	Direct

Ohji K, Shimada T, Nitta Y, Kihara H, Okubo H, Uehara T, Kawasaki Y

The Five-Factor Model personality traits in schizophrenia: A meta-analysis

Psychiatry Research 2016; 240: 34-41

[View review abstract online](#)

Comparison	Assessment of the five-factor model of personality (neuroticism, extraversion, openness, agreeableness and conscientiousness) in people with schizophrenia vs. controls.
Summary of evidence	Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests large effects of increased neuroticism and decreased extraversion, and medium-sized effects of decreased openness, agreeableness and conscientiousness in people with schizophrenia compared to controls.
<p>Five-factor model of personality Assessed using the NEO Five-Factor Inventory</p>	
<p><i>Large effects of higher scores on neuroticism and lower scores on extraversion in people with schizophrenia compared to controls;</i></p> <p style="text-align: center;">9 studies, N = 946</p> <p style="text-align: center;">Neuroticism: $g = 1.10$, 95%CI 0.77 to 1.43, $p < 0.05$</p> <p style="text-align: center;">Extraversion: $g = -0.79$, 95%CI -1.00 to -0.59, $p < 0.05$</p> <p><i>Medium-sized effects of lower scores on openness, agreeableness and conscientiousness in people with schizophrenia compared to controls;</i></p> <p style="text-align: center;">8 studies, N = 870</p> <p style="text-align: center;">Openness: $g = -0.38$, 95%CI -0.62 to -0.14, $p < 0.05$</p> <p style="text-align: center;">Agreeableness: $g = -0.51$, 95%CI -0.86 to -0.15, $p < 0.05$</p> <p style="text-align: center;">Conscientiousness: $g = -0.59$, 95%CI -0.87 to -0.31, $p < 0.05$</p> <p>Moderator analysis showed that having more males in the study was associated with lower levels of agreeableness compared to controls. There were no moderating effects of age.</p> <p style="text-align: center;">Authors report no evidence of publication bias.</p>	
Consistency in results	Authors state all results are inconsistent, although removing one study from each of the extraversion, openness and agreeableness analyses reduced heterogeneity.
Precision in results	Precise
Directness of results	Direct

Yan C, Cao Y, Zhang Y, Song L, Cheung EFC, Chan RCK

Trait and State Positive Emotional Experience in Schizophrenia: A Meta-

Analysis

PLoS ONE 2012; 7(7): e40672

[View review abstract online](#)

Comparison	Positive emotional experience in people with schizophrenia vs. controls.
Summary of evidence	Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests a large effect of more trait anhedonia in people with schizophrenia compared with controls.
Positive emotional experience	
<p><i>A large effect of more trait anhedonia symptoms (inability to experience pleasure) in people with schizophrenia compared with controls;</i> 47 studies, N = 3,722, $d = 0.81$, 95%CI 0.73 to 0.90, $p < 0.05$, $Q = 113.30$, $p < 0.001$</p> <p><i>A small effect of less hedonia, and no differences in exciting experience;</i> Hedonic: 40 studies, N = 2,264, $d = -0.24$, 95%CI -0.37 to -0.11, $p < 0.05$, $Q = 106.61.30$, $p < 0.001$ Exciting: 21 studies, N = 1,258, $d = 0.01$, 95%CI -0.14 to 0.16, $p > 0.05$, $Q = 38.14$, $p = 0.009$</p> <p>Authors report no evidence of publication bias.</p>	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

CI = Confidence Interval, d = Cohen's d and g = Hedges' g = standardised mean differences, 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 = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q = Q statistic for the test of 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.¹¹

† 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).

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 effect¹¹.

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 ¹². 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.

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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 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;¹¹

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

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the

effect estimate. Based on GRADE recommendations, a result for continuous data 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 relaxed¹³.

|| 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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