TECHNICAL COMMENTARY

Negative symptoms

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Introduction

The 'negative symptoms' of schizophrenia refer to an absence of normal functions. This may include (but is not limited to); blunted affect, which is a scarcity of facial expressions of emotion, reduced frequency and range of gestures and voice modulation, and restricted eye contact; alogia (poverty of speech); asociality (reduced social interaction); avolition (reduced motivation and often poor hygiene) and anhedonia, which is reduced experience of pleasure, often manifesting as scarcity of recreation, inability to experience closeness, and reduced interest in sexual activity.

Negative symptoms have been further categorised into primary and secondary symptoms. Primary (idiopathic) negative symptoms are part of the disorder proper, whereas secondary negative symptoms may have other causes such as medication side-effects, depression or social isolation.

Deficit schizophrenia is proposed as an illness subtype in which the patient has primary, persisting negative symptoms. This is a subgroup of patients described by specifically defined assessments, and it is not an official classification of symptoms or a diagnostic category.

Negative symptoms have a significant effect on the day-to-day functioning of patients, affecting their ability to manage the disorder and reducing quality of life. Reduced premorbid adjustment and poorer illness outcome are characteristics of patients with negative symptoms. If a patient is both cognitively impaired and shows a lack of emotion, they may be unaware of the true impact of these negative symptoms on their day to day functioning.

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. Priority is given to reviews with pooled data 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, 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)[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 11 systematic reviews that met our inclusion criteria.[3-13]

- Moderate to low quality evidence indicates negative symptoms occur in 50-90% of people with first episode psychosis. This estimate decreases to 35-70% with treatment, and 20-40% of patients have persisting negative symptoms.

- Moderate to high quality evidence shows deficit syndrome is apparent in around one-third of people with schizophrenia. It is associated with greater severity of negative and disorganised symptoms, but less severity of mood symptoms and no association with positive symptoms. Deficit schizophrenia is more likely to occur in males than females.

- Moderate to high quality evidence shows people with schizophrenia report less consummatory and anticipatory pleasure than controls. There were also small associations between increased negative symptoms and increased depression and reduced motivation in patients.

- Moderate quality evidence finds speech deficits are apparent in people with schizophrenia. There were large effects of longer pauses and less spoken time in people with schizophrenia. There were medium-sized effects of lower speech rate and less pitch variability. No differences were found for pitch, intensity variability, duration of utterance and number of pauses. Significant correlations were found in patients between less pitch variability and greater flat affect, less time spoken and more alogia, and more duration of pauses and more negative psychopathology.

- Moderate to low quality evidence finds negative symptoms are associated with structural changes in temporal and frontal lobes, and functional changes in frontal and temporal lobes, and the cerebellum and thalamus.

- High quality evidence shows a small effect of more severe negative symptoms in patients with a family history of psychosis compared to patients without a family history of psychosis. There is also significant concordance of psychomotor poverty in siblings with schizophrenia.

Cohen A, Brown LA, Minor KS

The psychiatric symptomatology of deficit schizophrenia: A meta-analysis

Schizoprenia Research 2010; 118: 122-127

View review abstract online

Comparison	Magnitude of psychiatric symptoms in deficit syndrome of schizophrenia compared with non-deficit schizophrenia patients.
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) suggests deficit syndrome of schizophrenia is associated with greater severity of negative and to a lesser extent with disorganisation symptoms, lesser severity of mood symptoms, and no association with positive symptoms compared to non-deficit schizophrenia.**

Negative symptoms

Large effect size suggests significant association of deficit syndrome with greater severity of negative symptoms compared to non-deficit schizophrenia;

34 studies, N = 1,620, d = 1.01, 95%CI 0.75 to 1.25, Q_w = 38.97, *ns*

Significant variability of effect size when compared between SDS and PDS assessment, Q_B = 11.53, *p* < 0.01. Studies employing the PDS showed only small differences in negative symptom severity between deficit and non-deficit groups, in contrast to SDS which showed a much larger magnitude of difference.

Disorganisation symptoms

Small effect size suggests significant association of deficit syndrome with greater severity of disorganisation symptoms compared to non-deficit schizophrenia;

11 studies, N = 1,320, d = 0.29, 95%CI 0.01 to 0.56, Q_w = 10.40, *ns*

Comparison of SDS and PDS assessment, Q_B = 1.25, *ns*

Patients assessed by the SDS authors showed smaller magnitude of difference in disorganisation than diagnoses by other groups.

Positive symptoms

Negative symptoms

No difference in severity of positive symptoms was reported between deficit and non-deficit schizophrenia;
43 studies, N = 2,856, d = -0.17, 95%CI -0.29 to -0.04, Q_w = 44.65, *ns*
Comparison of SDS and PDS assessment (see below for explanation of acronyms), Q_B = 0.82, *ns*
Mood symptoms, comprising both subjectively and objectively assessed feelings of anxiety, depression, hostility and guilt
Small effect size suggests less severe mood symptoms in deficit syndrome compared to non-deficit schizophrenia;
15 studies, N = 938, d = -0.34, 95%CI -0.58 to -0.08, Q_w = 21.33, *ns*
Significant variability of effect size when compared between SDS and PDS assessment, Q_B = 8.17, p < 0.05. Studies employing the SDS showed only small differences in mood symptom severity between deficit and nondeficit groups, in contrast to PDS which showed a much larger magnitude of difference.
Overall psychiatric symptoms
No difference in severity of global symptoms was reported between deficit and non-deficit schizophrenia;
20 studies, N = 981, d = 0.15, 95%CI -0.08 to 0.37, Q_w = 19.53, *ns*
Comparison of SDS and PDS assessment, Q_B = 2.06, *ns*

Consistency in results[‡]	Consistent, some differences may be apparent depending on the scale used
Precision in results[§]	Precise
Directness of results[∥]	Direct

Edwards CJ, Garety P, Hardy A **The relationship between depressive symptoms and negative symptoms in people with non-affective psychosis: a meta-analysis** **Psychological Medicine 2019; 49: 2486-98** [View review abstract online](#)	
Comparison	Relationship between depression and negative symptoms of schizophrenia.

Negative symptoms

Summary of evidence	Moderate to high quality evidence (large sample, inconsistent, precise, direct) shows a small association between higher ratings of negative symptoms and higher levels of depressive symptoms.
Depression and negative symptoms	
Small effect showed higher ratings of negative symptoms were associated with higher levels of depressive symptoms; 56 studies, N = 8,177, *r* = 0.194, 95%CI 0.141 to 0.247, *p* < 0.001, I^2 = 79.5% There were no moderating effects of measures used,	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Esterberg ML, Trotman HD, Holtzman C, Compton MT, Walker EF	
The impact of a family history of psychosis on age-at-onset and positive and negative symptoms of schizophrenia: A meta-analysis	
Schizophrenia Research 2010; 120: 121-130 [View review abstract online](#)	
Comparison	The impact of a family history of psychosis on severity of negative symptoms of schizophrenia.
Summary of evidence	High quality evidence (large sample, consistent, precise, direct) shows a small effect of more severe negative symptoms in patients with a family history of psychosis compared to patients without a family history of psychosis.
Positive symptoms	
A small, significant effect suggested that patients with a family history of psychosis showed more severe negative symptoms than patients without a family history of psychosis; 12 studies, N = 1,172, *d* = 0.23, 95% CI = 0.11 to 0.35, *p* not reported, Q$_w$ = 13.05, *p* > 0.05	

Meta-regression revealed a medium effect; as the proportion of males increased in the group of patients without a family history of psychosis, the mean effect size for the overall difference between groups decreased ($r = -0.61$, $p < 0.05$).	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Hallford DJ, Sharma MK

Anticipatory pleasure for future experiences in schizophrenia spectrum disorders and major depression: A systematic review and meta-analysis

British Journal of Clinical Psychology 2019; 58: 357-83

View review abstract online

Comparison	Anticipatory pleasure for future experiences in people with schizophrenia vs. controls.
Summary of evidence	Moderate to high quality evidence (large sample, inconsistent, precise, direct) shows less anticipatory pleasure for future experiences in people with schizophrenia.

Anticipatory pleasure
A medium-sized deficit was observed in schizophrenia spectrum disorders vs. controls;   32 studies, N = 3,300, $g = -0.42$, 95%CI -0.53 to -0.31, $p < 0.001$, $I^2 = 59\%$ The effect was significantly larger for depression ($g = -0.87$).   The effect for schizophrenia was larger is studies of people with a longer duration of illness and lower cognitive functioning.

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

Negative symptoms

Lopez-Diaz A, Lara I, Lahera G

Is the prevalence of the deficit syndrome in schizophrenia higher than estimated? Results of a meta-analysis

Psychiatry Investigation 2018; 15: 94-8

View review abstract online

Comparison	Prevalence of deficit syndrome in people with schizophrenia.
	Studies were conducted in Brazil, China, France, Hungary, Italy, Spain, Turkey, and the United States.
Summary of evidence	**Moderate to high quality evidence (large sample, unable to assess consistency, precise, direct) shows deficit syndrome is evident in around one-third of people with schizophrenia.**

Deficit syndrome
Around one-third of people with schizophrenia has deficit syndrome;
13 studies, N = 2,092, prevalence = 32.64%, 95%CI 25.39% to 40.34%, I^2 = 91.31%, *p* < 0.0001
Excluding low quality studies gave similar results.

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

Luther L, Fischer MW, Firmin RL, Salyers MP

Clarifying the overlap between motivation and negative symptom measures in schizophrenia research: A meta-analysis

Schizophrenia Research 2019; 206: 27-36

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Comparison	Association between motivation and negative symptoms in people with schizophrenia.
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent,**

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	precise, direct) shows a small association between reduced motivation and increased negative symptoms.
Motivation	

A small association was found between reduced motivation and increased negative symptoms;

46 studies, N = 2,862, r = -0.18, 95%CI -0.24 to -0.12, p < 0.05, I^2 = 57%

Studies using second-generation measures of negative symptoms showed a larger effect size than studies using first-generation measures (r = -0.38 vs. -0.17).

Effort discounting tasks were most strongly related to negative symptoms (r = -0.44).

The domain of amotivation had a larger effect size than domains of intrinsic or extrinsic motivation (amotivation: r = -0.22, intrinsic: r = -0.12, extrinsic: r = -0.06).

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

Makinen J, Miettunen J, Isohanni M, Koponen H

Negative symptoms in schizophrenia: a review

Nordic Journal of Psychiatry 2008; 62(5): 334-341

View review abstract online

Comparison	**Negative symptoms in people with schizophrenia.**
Summary of evidence	**Moderate to low quality evidence (unclear sample sizes, unable to assess consistency or precision, direct) report negative symptoms occur in 50-90% of patients at the first episode of psychosis, which decreases to 35-70% with treatment; 20-40% of patients have symptoms that persistent permanently. Negative symptoms were associated with structural changes in temporal and frontal lobes, and functional changes in frontal and temporal lobes, cerebellum and thalamus.**
Prevalence of negative symptoms	

Three short term follow-up studies (1-2 years), N not reported, report high prevalence in first-episode psychosis;
At onset, clinically significant symptoms occur in 50-90% of patients.
With treatment, negative symptoms decreased markedly to 35-70% at the end of follow up.
In a long-term follow-up study (N, duration not reported), negative symptoms were the most important factor restricting the normal life of schizophrenia patients.

Persistence of negative symptoms
Two long term follow-up studies (N, duration not reported) report 20-40% of schizophrenia patients have permanent negative symptoms after a first episode of psychosis.
Two studies (N not reported) suggest prominent negative symptoms are associated with economic, professional, social and functional disabilities. One additional study reports longer hospitalization period, slower recovery and poorer treatment outcomes in patients with more negative symptoms.

Physiological associations with negative symptoms
Structural imaging
Two studies (N not reported) used structural magnetic resonance imaging to investigate grey matter volume and reported an association of negative symptoms with reduced volume in the temporal lobe.
Both studies reported grey and white matter loss in the temporal lobe, anterior cingulate, medial frontal cortex compared to healthy controls.
Two studies (N not reported) noted white matter loss in prefrontal and inferior frontal cortex.
One study (N not reported) reported an association of apathy with reduced bilateral frontal lobe volume, one study (N not reported) reported an association of negative symptoms with reduced size of prosencephalon (forebrain).
Functional imaging
One study (N not reported) showed deficit schizophrenia patients only had N1 event-related potential amplitude reduction and reduced current source density in cingulate and parahippocampal gyri.
Two studies (N not reported) used positron emission tomography and reported an association of negative symptoms with reduced blood flow in right prefrontal area, temporal lobe, cerebellum, and left thalamus, compared with positive symptoms.

Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no confidence intervals are reported.
Directness of results	Direct

Parola A, Simonsen A, Bliksted V, Fusaroli R

Voice patterns in schizophrenia: A systematic review and Bayesian meta-analysis

View review abstract online

Comparison	Voice patterns and relationship with symptoms in people with schizophrenia vs. controls.
Summary of evidence	Moderate quality evidence (medium to large samples, inconsistent, imprecise, direct) found large effects of longer pauses and less spoken time in people with schizophrenia. There were medium-sized effects of lower speech rate and less pitch variability. No differences were found for pitch, intensity variability, duration of utterance and number of pauses.
	Significant correlations were found in patients between lower pitch and more positive symptoms, less pitch variability and greater flat affect, less time spoken and more alogia, and more duration of pauses and more negative psychopathology.

Voice patterns

Large effects were found for;

Longer pauses: 9 studies, N = 371, g = 1.89, 95%CI 0.72 to 3.21, p < 0.001, Qp < 0.001

Less spoken time: 11 studies, N = 478, g = -1.26, 95%CI -2.26 to -0.25, p = 0.001, Qp < 0.001

Medium -sized effects were found for;

Slower speech rate: 11 studies, N = 595, g = -0.75, 95%CI -1.51 to -0.04, p = 0.01, Qp < 0.001

Less pitch variability: 11 studies, N = 644, g = -0.55, 95%CI -1.06 to -0.09, p = 0.005, Qp < 0.001

No significant effects were found for;

Pitch mean: 4 studies, N = 198, g = 0.25, 95%CI -0.72 to 1.30, p = 0.273, Qp = 0.04

Intensity variability: 4 studies, N = 169, g = 0.74, 95%CI -2.01 to 3.39, p = 0.164, Qp < 0.001

Duration of utterance: 4 studies, N = 165, g = -0.15, 95%CI -2.56 to 2.26, p = 0.739, Qp < 0.001

Number of pauses: 5 studies, N = 108, g = 0.05, 95%CI -1.23 to 1.13, p = 0.782, Qp = 0.02

Significant correlations were found between lower pitch and more positive symptoms, less pitch variability and greater flat affect, less time spoken and more alogia, and more duration of pauses and more negative psychopathology.

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Moderator analyses revealed that tasks with more demanding cognitive and social components have significantly larger effects.	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Rietkerk T, Boks MPM, Sommer IE, Liddle PF, Ophoff RA, Kahn RS

The genetics and symptom dimensions of schizophrenia: review and meta-analysis

Schizophrenia Research 2008; 102: 197-205

View review abstract online

Comparison	**The heritability of psychomotor poverty symptoms assessed through the concordance of symptoms in twins and siblings with schizophrenia.** **Note: psychomotor poverty includes poverty of speech, flat affect and decreased voluntary movement.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests significant concordance of psychomotor poverty symptoms in siblings with schizophrenia. This effect was not replicated in one study of twins with schizophrenia.**

Symptom heritability
Measured by OPCRIT

1 study of twins concordant for schizophrenia (N = 57 pairs) suggested no significant heritability association with psychomotor poverty in monozygotic twins ($r = 0.27$) and dizygotic twins ($r = -0.03$).
4 studies compared siblings with schizophrenia, N = 967
A small effect size suggests a significant concordance of psychomotor poverty symptoms between siblings with schizophrenia; $r = 0.17$, 95%CI 0.10 to 0.23, $p < 0.0001$, I² < 0.001, $p = 0.71$

Consistency in results	Consistent for siblings, unable to assess for twin studies
Precision in results	Precise for siblings, unable to assess for twin studies
Directness of results	Direct

Roy MA, Maziade M, Labbe A, Merette C

Male gender is associated with deficit schizophrenia: a meta-analysis

Schizophrenia Research 2001; 47(2-3): 141-147

View review abstract online

Comparison	Association of male sex in deficit schizophrenia compared to non-deficit schizophrenia subgroups.
	Note deficit schizophrenia is a descriptive rather than diagnostic term.
Summary of evidence	Moderate to high quality evidence (large sample, consistent, imprecise, direct) suggests significant association of deficit schizophrenia subgroups with the male sex. This effect was not moderated by sampling method, diagnosis criteria, or duration of illness.

Association with sex

Large effect size suggests significant association of male sex with deficit schizophrenia;

23 studies, N = 1,765, OR = 1.75, 95%CI 1.39 to 2.21, p = 0.000002, Q_w = 15.87, p = 0.82

Subgroup analyses

No significant difference in effect size between convenience and systematic sampling: Q_B = 0.04, p = 0.86.

No significant difference in effect size between three assessment methods;

SDS vs. PDS: Q_B = 0.32, p = 0.57

SDS vs. DR: Q_B = 0.85, p = 0.36

PDS vs. DR: Q_B = 0.85, p = 0.18

Unlike SDS and DR, the pooled OR for PDS alone did not yield a significant association with male sex: 3 studies, OR = 1.33, 95%CI 0.86 to 2.05, p > 0.05.

No effect of diagnosis inclusion criteria: no significant difference between schizophrenia or schizoaffective disorder: Q_B = 0.49, p = 0.49

Pooled OR for schizophrenia alone was significantly different to pooled OR including schizoaffective: OR = 1.68, 95%CI 1.29 to 2.19, p < 0.05.

No significant difference between duration less than or greater than 10 years, Q_B = 1.17, p = 0.28

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

Visser KF, Chapman HC, Ruiz I, Raugh IM, Strauss GP

A meta-analysis of self-reported anticipatory and consummatory pleasure in the schizophrenia-spectrum

Journal of Psychiatric Research 2020; 121: 68-81

[View review abstract online](#)

Comparison	Association of anticipatory and consummatory pleasure in people with schizophrenia vs. controls.
Summary of evidence	Moderate to high quality evidence (large sample, some inconsistency, imprecise, direct) showed medium-sized effects that people with schizophrenia reported less consummatory and anticipatory pleasure than controls.

Anticipatory and consummatory pleasure
31 studies, N = 1,771
Medium-sized effects showed people with schizophrenia reported less consummatory and anticipatory pleasure than controls;
Consummatory pleasure: g = -0.46, 95%CI -0.58 to -0.33, $p < 0.001$, $I^2 = 60\%$
Anticipatory pleasure: g = -0.48, 95%CI 0.58 to -0.38, $p < 0.001$, $I^2 = 40\%$
There were no moderating effects of sex, age, medication, ethnicity, or severity of negative symptoms.

Consistency in results	Consistent for anticipatory only.
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

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CI = confidence interval, DR = 'detailed review' method for assessing deficit schizophrenia, g = Hedges's 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, ns = not statistically significant, OPCRIT = Operational Criteria checklist for psychotic disorders, OR = odds ratio, p = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PDS = Proxy Deficit Syndrome, Q_B = test for between group differences (heterogeneity between groups of studies for an outcome of interest), Q_w = test for within group differences (heterogeneity in study results within a group of studies – measure of study consistency), r = correlation coefficient, SDS = Schedule for the Deficit Syndrome, 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[14].

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† Different effect measures are reported by different reviews.

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[15]. 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 are an 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.

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. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large effect[14].

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

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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).

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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 be 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;[14]

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

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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[16].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C 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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