TECHNICAL COMMENTARY

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Oxidative stress

Introduction

While oxygen is a vital component of life, some oxygen-based compounds called free radicals can be toxic due to their highly unstable nature. The key free radical classes are the reactive oxygen species (ROS) and reactive nitrogen species (RNS), and they are formed as by-products of normal metabolism. Under normal conditions, these free radicals are tightly monitored and controlled by stringent protective barriers, such as their rapid removal from cells; and antioxidant enzymes that break them down.

At these tightly maintained concentrations, free radicals play an important role in cellular signalling, immune responses and cell growth. However, excess free radicals can result from interruption of the antioxidant defense barrier, or from excess production. This can cause oxidative stress, resulting in structural damage to cellular proteins, fats, carbohydrates, and nucleic acids (DNA and RNA). Severe oxidative stress can result in failure of cell growth, apoptosis, and cell necrosis.

Oxidative stress mechanisms are proposed to have pathological effects in schizophrenia. This has been investigated through genetic polymorphism of oxidative enzyme genes, and measurement of levels of antioxidant enzymes and markers of oxidative damage.

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, which describes a preferred way to present a meta-analysis[1]. Reviews rated as having 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

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are solely the opinion of staff NeuRA (Neuroscience Research Australia).

Results

We found five systematic reviews that met our inclusion criteria[3-7].

- Moderate quality evidence suggests a large effect of reduced total antioxidant levels in plasma and serum of people with first-episode psychosis compared to controls.
- High quality evidence finds medium-sized effects of reduced glutathione and glutathione peroxidase levels in people with schizophrenia compared to controls, and no differences in glutathione disulfide or gluthatione reductase levels. There were no significant differences in glutathione levels between first-episode patients and controls.
- Moderate quality evidence suggests large effects of reduced catalase, superoxide dismutase, and glutathione peroxidase in red blood cells of people with acute relapse of psychosis compared to controls.
- Moderate quality evidence suggests medium-sized effects of reduced superoxide dismutase in red blood cells, and medium to large effects of increased superoxide dismutase in serum of stable medicated outpatients with schizophrenia compared to controls. There are also increases in thiobarbituric acid reactive substances in serum, catalase in red blood cells, and nitrate in plasma of stable outpatients. There are no differences in thiobarbituric acid reactive substances in plasma or glutathione peroxidase in red blood cells between stable outpatients and controls.
- Moderate quality evidence suggests a large effect of increased malondialdehyde in plasma of chronic inpatients with schizophrenia compared to controls. There were also medium to large effects of decreased catalase in both red blood cells and plasma, decreased vitamins C and E in plasma, decreased glutathione peroxidase in both red blood cells and plasma, and decreased superoxide dismutase in plasma in chronic inpatients. No significant differences were found between inpatients and controls in superoxide dismutase in red blood cells, or thiobarbituric acid reactive substances or uric acid in plasma.
- Moderate quality evidence finds no differences in catalase, glutathione, glutathione peroxidase, superoxide dismutase, total antioxidant status and cell/DNA oxidative damage in people with early-onset schizophrenia.
- High quality evidence suggests a small decrease in glutathione in the anterior cinguate of people with schizophrenia.

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Das TK, Javadzadeh A, Dey A, Sabesan P, Theberge J, Radua J, Palaniyappan L

Antioxidant defense in schizophrenia and bipolar disorder: A meta-analysis of MRS studies of anterior cingulate glutathione

Progress in Neuro Psychopharmacology and Biological Psychiatry 2018; August

View online review abstract

Comparison	**Glutathione in the anterior cinguate of people with schizophrenia vs. controls.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests a small decrease in glutathione in the anterior cinguate of people with schizophrenia.**
Glutathione	
A small, significant decrease in glutathione in the anterior cinguate of people with schizophrenia; 13 studies, N = 726, SMD = 0.26, 95%CI 0.07 to 0.44, p = 0.008, I^2 = 29%, p = 0.11 There was a trend-effect finding that studies with longer echo-time of MRS acquisitions were more likely to report reduced glutathione concentrations in patients compared to controls. There were no moderating effects of medication, sex, scanner strength, repetition time, patient age or duration of illness.	
Consistency in results‡	Consistent
Precision in results§	Precise
Directness of results‖	Direct

Flatow J, Buckley P, Miller BJ

Meta-Analysis of Oxidative Stress in Schizophrenia

Biological Psychiatry 2013; 74(6): 400-409

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Oxidative stress

Comparison 1	**Antioxidant levels in people with first-episode psychosis vs. controls.**
Summary of evidence	**Moderate quality evidence (small to medium-sized samples, mostly precise and inconsistent, direct) suggests a large effect of reduced total antioxidant levels in plasma and serum of people with first-episode psychosis compared to controls. For specific parameters, there are medium-sized decreases in catalase and superoxide dismutase in red blood cells and decreases in nitrate and uric acid in plasma of people with first-episode psychosis. There are medium to large increases in superoxide dismutase, malondialdehyde, and thiobarbituric acid reactive substances in plasma of people with first-episode psychosis. There were no differences between patients and controls in glutathione peroxidase levels.**
Oxidative stress parameters	
Significant, large effects of decreased total antioxidant levels (TAS) in plasma and serum of people with first-episode psychosis; TAS (plasma): 3 studies, N = 239, g = -1.42, -1.70 to -1.13, $p < 0.01$, X^2 $p = 0.04$ TAS (serum): 2 studies, N = 148, g = -1.12, -1.48 to -0.75, $p < 0.01$, X^2 $p < 0.01$ *Significant, medium-sized effects of decreased catalase (CAT) and superoxide dismutase (SOD) in red blood cells, and nitrate and uric acid in plasma in people with first-episode psychosis;* CAT (red blood cell): 4 studies, N = 199, g = -0.48, -0.78 to -0.17, $p < 0.01$, X^2 $p < 0.01$ SOD (red blood cell): 3 studies, N = 133, g = -0.79, -1.16 to -0.41, $p < 0.01$, X^2 $p = 0.02$ Nitrate (plasma): 4 studies, N = 243, g = -0.70, -0.98 to -0.42, $p < 0.01$, X^2 $p < 0.01$ Uric acid (plasma): 3 studies, N = 241, g = -0.55, -0.82 to -0.29, $p < 0.01$, X^2 $p = 0.91$ *Significant, medium to large effects of increased SOD, malondialdehyde (MDA) and thiobarbituric acid reactive substances (TBARS) in plasma in people with first-episode psychosis;* MDA (plasma): 2 studies, N = 143, g = 2.36, 1.88 to 2.83, $p < 0.01$, X^2 $p < 0.01$ SOD (plasma): 3 studies, N = 317, g = 0.45, 0.19 to 0.71, $p < 0.01$, X^2 $p = 0.49$ TBARS (plasma): 4 studies, N = 195, g = 0.88, 0.55 to 1.21, $p < 0.01$, X^2 $p < 0.01$ *No significant differences in glutathione peroxidase (GSH-Px) red blood cell levels between patients and controls;* GSH-Px (red blood cell): 4 studies, N = 199, g = 0.18, -0.13 to 0.49, $p = 0.26$, X^2 $p < 0.01$ Authors report that the heterogeneity was no longer significant, yet findings remained significant, after outliers were removed in the TAS (plasma), SOD (red blood cell), CAT, and TBARS analyses. No statistics are reported for these sensitivity analyses, so quality is assessed on the main analyses above.	

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Consistency in results	Inconsistent, apart from SOD (plasma) and uric acid.
Precision in results	Precise, apart from MDA.
Directness of results	Direct
Comparison 2	**Antioxidant levels in people with acute relapse of psychosis vs. controls.**
Summary of evidence	**Moderate quality evidence (small to medium-sized samples, precise, some inconsistency, direct) suggests large effects of reduced catalase, superoxide dismutase, and glutathione peroxidase in red blood cells of people with acute relapse of psychosis compared to controls.**
Oxidative stress parameters	
Significant, large effects of decreased CAT, SOD, and GSH-Px in red blood cells of people with acute relapse of psychosis; CAT (red blood cell): 3 studies, N = 171, *g* = -0.98, -1.30 to -0.66, $p < 0.01$, X^2 $p = 0.13$ SOD (red blood cell): 3 studies, N = 171, *g* = -0.87, -1.19 to -0.55, $p < 0.01$, X^2 $p < 0.01$ GSH-Px (red blood cell): 3 studies, N = 171, *g* = -0.67, -1.00 to -0.34, $p < 0.01$, X^2 $p < 0.01$ Authors state that the heterogeneity was no longer significant, and SOD and GSH-Px remained significantly decreased, after removal of one outlier. No statistics are reported for these sensitivity analyses, so quality is assessed on the main analyses above.	
Consistency in results	Inconsistent, apart from CAT.
Precision in results	Precise
Directness of results	Direct
Comparison 3	**Antioxidant levels in stable medicated outpatients with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (small to medium-sized samples, precise, mostly inconsistent, direct) suggests medium-sized effects of reduced superoxide dismutase in red blood cells, and medium to large effects of increased superoxide dismutase in serum of stable medicated outpatients with schizophrenia compared to controls. There are also increases in thiobarbituric acid reactive substances in serum, catalase in red blood cells, and nitrate in plasma. There are no differences in thiobarbituric acid reactive substances in plasma or glutathione peroxidase in red blood cells between patients and controls.**

Oxidative stress

Oxidative stress parameters	
Significant, medium-sized effect of decreased SOD in red blood cells of stable outpatients with schizophrenia; SOD (red blood cell): 5 studies, N = 392, *g* = -0.37, -0.57 to -0.11, *p* < 0.01, X^2 *p* < 0.01 *Significant, medium to large effects of increased SOD and TBARS in serum, increased CAT in red blood cells, and increased nitrate in plasma in stable outpatients with schizophrenia;* SOD (serum): 2 studies, N = 154, *g* = 1.75, 1.34 to 2.16, *p* < 0.01, X^2 *p* = 0.10 TBARS (serum): 3 studies, N = 272, *g* = 1.14, 0.86 to 1.41, *p* < 0.01, X^2 *p* < 0.01 CAT (red blood cell): 5 studies, N = 392, *g* = 0.30, 0.07 to 0.53, *p* < 0.01, X^2 *p* < 0.01 Nitrate (plasma): 2 studies, N = 302, *g* = 0.37, 0.04 to 0.70, *p* < 0.01, X^2 *p* = 0.40 *No significant differences in GSH-Px in red blood cells or TBARS in plasma between patients and controls;* GSH-Px (red blood cell): 5 studies, N = 392, *g* = -0.03, -0.26 to 0.20, *p* = 0.82, X^2 *p* < 0.01 TBARS (plasma): 3 studies, N = 194, *g* = 0.20, -0.10 to 0.50, *p* = 0.20, X^2 *p* < 0.01 Authors report that heterogeneity was no longer significant, and serum TBARS remained significantly increased after removal of one outlier. In all other sensitivity analyses, the heterogeneity remained significant after removing each single study as well as all combinations of two studies.	
Consistency in results	Inconsistent, apart from SOD (serum) and nitrate.
Precision in results	Precise
Directness of results	Direct
Comparison 4	**Antioxidant levels in chronic inpatients with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (small to medium-sized sample, precise, some inconsistency, direct) suggests a large effect of increased malondialdehyde in plasma of chronic inpatients with schizophrenia compared to controls. There were also medium to large effects of decreased catalase in both red blood cells and plasma, decreased vitamins C and E in plasma, decreased glutathione peroxidase in both red blood cells and plasma, and decreased superoxide dismutase in plasma in chronic inpatients. No significant differences were found between patients and controls in superoxide dismutase in red blood cells, or thiobarbituric acid reactive substances or uric acid in plasma.**
Oxidative stress parameters	

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Significant, medium to large effects of decreased CAT in both red blood cell and plasma, vitamins C and E in plasma, GSH-Px in both red blood cells and plasma, and SOD in plasma in chronic inpatients with schizophrenia; CAT (red blood cell): 2 studies, N = 146, *g* = -1.02, -1.36 to -0.67, *p* < 0.01, X^2 *p* = 0.45 CAT (plasma): 2 studies, N = 317, *g* = -0.56, -0.90 to -0.22, *p* < 0.01, X^2 *p* < 0.01 Vitamin E (plasma): 2 studies, N = 58, *g* = -0.88, -1.34 to -0.43, *p* < 0.01, X^2 *p* = 0.33 Vitamin C (plasma): 2 studies, N = 102, *g* = -0.85, -1.25 to -0.44, *p* < 0.01, X^2 *p* = 0.51 GSH-Px (red blood cell): 2 studies, N = 146, *g* = -0.56, -0.90 to -0.22, *p* < 0.01, X^2 *p* < 0.01 GSH-Px (plasma): 3 studies, N = 468, *g* = -0.50, -0.70 to -0.30, *p* < 0.01, X^2 *p* < 0.01 SOD (plasma): 2 studies, N = 652, *g* = -0.29, -0.47 to -0.12, *p* < 0.01, X^2 *p* < 0.01 *Significant, large effect of increased MDA in plasma of chronic inpatients with schizophrenia;* MDA (plasma): 3 studies, N = 349, *g* = 1.14, 0.90 to 1.38, *p* < 0.01, X^2 *p* = 0.35 *No significant differences in SOD in red blood cells, TBARS in plasma or uric acid in plasma between patients and controls;* SOD (red blood cell): 2 studies, N = 146, *g* = -0.05, -0.40 to 0.29, *p* = 0.77, X^2 *p* < 0.01 TBARS (plasma): 2 studies, N = 203, *g* = 0.08, -0.21 to 0.37, *p* = 0.59, X^2 *p* < 0.01 Uric acid (plasma): 2 studies, N = 274, *g* = -0.18, 0.43 to 0.07, *p* = 0.15, X^2 *p* = 0.25 Authors report that the heterogeneity was no longer significant, and plasma GSH-Px and SOD remained significantly decreased after removal of one outlier.

Consistency in results	Inconsistent, apart from CAT (red blood cell), Vitamin C and E, MDA, and uric acid.
Precision in results	Precise
Directness of results	Direct

Fraguas D, Diaz-Caneja CM, Rodriguez-Quiroga A, Arango C

Oxidative Stress and Inflammation in Early Onset First Episode Psychosis: A Systematic Review and Meta-Analysis

International Journal of Neuropsychopharmacology 2017; 20: 435-44

View review abstract online

Comparison	**Assessment of levels of oxidative stress markers in people with early-onset schizophrenia (<18 years) vs. age-matched controls.**

Summary of evidence	**Moderate quality evidence (medium-sized samples, some inconsistency and imprecision, direct) finds no differences in oxidative stress markers (catalase, glutathione, glutathione peroxidase, superoxide dismutase, total antioxidant status and cell/DNA oxidative damage) in people with early-onset schizophrenia.**
Oxidative stress markers	
There were no significant differences in; Catalase: 2 studies, N = 261, SMD = -0.122, 95%CI -0.379 to 0.136, p = 0.354, I^2 = 5%, p = 0.304 Glutathione: 2 studies, N = 260, SMD = -0.240, 95%CI -0.694 to 0.214, p = 0.299, I^2 = 60%, p = 0.115 Glutathione peroxidase: 3 studies, N = 245, SMD = 0.557, 95%CI -1.181 to 2.295, p = 0.530, I^2 = 96%, p = 0.000 Superoxide dismutase: 3 studies, N = 302, SMD = -0.051, 95%CI -0.617 to 0.515, p = 0.860, I^2 = 77%, p = 0.012 Total antioxidant status: 2 studies, N = 260, SMD = -0.328, 95%CI -1.052 to 0.396, p = 0.374, I^2 = 83%, p = 0.014 Cell/DNA oxidative damage: 2 studies, N = 196, SMD = 1.641, 95%CI -1.688 to 4.971, p = 0.334, I^2 = 99%, p = 0.000	
Consistency in results	Inconsistent, apart from catalase and glutathione.
Precision in results	Imprecise, apart from catalase and glutathione.
Directness of results	Direct

Fraguas D, Diaz-Caneja CM, Ayora M, Hernandez-Alvarez F, Rodriguez-Quiroga A, Recio S, Leza JC, Arango C

Oxidative stress and inflammation in first-episode psychosis: A Systematic Review and Meta-analysis

Schizophrenia Bulletin 2019; 45(4): 742-51

View review abstract online

Comparison	**Oxidative stress markers in people with first-episode psychosis vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, imprecise,**

	direct) finds a large effect of reduced total antioxidant status in the serum or plasma of people with first-episode psychosis. There were no significant differences in catalase, glutathione (serum/plasma), glutathione peroxidase (blood cells and serum/plasma), superoxide dismutase (blood cells and serum/plasma), or thiobarbituric acid reactive substances (serum/plasma) levels.
Oxidative stress markers	
A large effect of reduced total antioxidant status in serum/plasma of people with first-episode psychosis; 9 studies, N = 773, *d* = -1.020, 95%CI -1.516 to -0.524, *p* = 0.001, I^2 = 90%, *p* < 0.001 There were no significant differences in catalase, glutathione (serum/plasma), glutathione peroxidase (blood cells and serum/plasma), superoxide dismutase (blood cells and serum/plasma), or thiobarbituric acid reactive substances (serum/plasma).	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Tsugawa S, Noda Y, Tarumi R, Mimura Y, Yoshida K, Iwata Y, Elsalhy M, Kuromiya M, Kurose S, Masuda F, Morita S, Ogyu K, Plitman E, Wada M, Miyazaki T, Graff-Guerrero A, Mimura M, Nakajima S

Glutathione levels and activities of glutathione metabolism enzymes in patients with schizophrenia: A systematic review and meta-analysis

Journal of Psychopharmacology 2019; 33: 1199-214

View review abstract online

Comparison	**Glutathione in people with schizophrenia vs. controls.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) finds medium-sized effects of reduced glutathione and glutathione peroxidase levels in people with schizophrenia, and no differences in glutathione disulfide or gluthatione reductase levels. There were no significant differences in glutathione levels in first-episode patients.**

Oxidative stress

Glutathione	
Medium-sized effects of reduced glutathione and glutathione peroxidase levels in people with schizophrenia; Glutathione: 47 studies, N = 3,722, SMD = -0.67, 95%CI -0.88 to -0.45, $p < 0.001$, $I^2 = 18\%$ Glutathione peroxidase: 38 studies, N = 3,138, SMD = -0.69, 95%CI -1.07 to -0.30, $p = 0.002$, $I^2 = 28\%$ The effect was larger in the subgroup analysis of unmedicated patients (SMD = -1.45). The effect sizes were similar for whole blood and plasma/serum. There were no significant differences in glutathione disulfide or gluthatione reductase levels. There were no significant differences in glutathione in first-episode patients.	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

CAT = Catalase, CI = confidence interval, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences (see below for interpretation of effect sizes), GSH = Glutathione, GSH-Px = Glutathione peroxidise, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MDA = malondialdehyde, N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RR = relative risk, SOD = Superoxide dismutase, TBARS = Thiobarbituric acid reactive substances, 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[8].

† 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) which 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[8].

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[9]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios

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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 dependent 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 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;

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

§ 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, this criteria should be relaxed[10].

‖ 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, which 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.

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