TECHNICAL COMMENTARY

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Quality of life

Introduction

Quality of life (QoL) refers to an individual's sense of satisfaction with their circumstances. This can be measured subjectively via interview and objectively via measures of overall health, social and material well-being and access to resources and opportunities. A key focus of QoL research in schizophrenia is to identify factors that influence or predict a person's satisfaction with their circumstances, which may then provide targets for therapeutic focus to improve QoL, The presence of acute psychiatric symptoms may contribute to lower QoL ratings. Other influential factors could include financial situation, living situation (homeless, living in a community setting or in a hospital), and perceived personal safety.

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 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 were given priority 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 six systematic reviews that met our inclusion criteria[3-8].

- Moderate to high quality evidence suggests large effects of poorer psychological, physical, and social quality of life in people with schizophrenia.
- Moderate to high quality evidence finds small to medium-sized associations between

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increased positive symptoms, negative symptoms, and general psychopathology and lower QoL ratings.

- Moderate to high quality evidence finds small associations between better objective QoL scores and better verbal ability, vigilance, short-term memory, executive functioning, working memory, list learning, and processing speed. On subjective rating scales, there is a small association between better QoL and better letter fluency. However, small associations were found from moderate quality evidence between poorer QoL and better verbal ability and processing speed.
- Moderate quality evidence suggests the best predictors of increased well-being ratings are engagement in meaningful leisure activities and having strong social networks.

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Quality of life

Dong M, Lu L, Zhang L, Zhang YS, Ng CH, Ungvari GS, Li G, Meng X, Wang G, Xiang YT

Quality of Life in Schizophrenia: A Meta-Analysis of Comparative Studies

Psychiatric Quarterly 2019; 90: 519-32

View review abstract online

Comparison	**Quality of life in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests large effects of poorer psychological, physical, and social quality of life in people with schizophrenia.**

Psychological quality of life

A large effect shows poorer psychological quality of life in people with schizophrenia;

15 studies, N = 3,703, SMD = -1.18, 95%CI -1.51 to -0.85, $p < 0.00001$, $I^2 = 94\%$

The effect was larger in studies using the SF-36 than the WHOQOL, and in studies with more males.

The effect was larger in studies of patients who had a longer illness duration (>9.6 years), but smaller in studies of older patients.

There were no moderating effects of severity of psychotic symptoms or income level.

Physical quality of life

A large effect shows poorer physical quality of life in people with schizophrenia;

15 studies, N = 3,703, SMD = -1.19, 95%CI -1.42 to -0.85, $p < 0.00001$, $I^2 = 87\%$

The effect was larger in studies using the WHOQOL than the SF-36.

The effect was smaller in studies of older patients.

There were no moderating effects of illness duration, severity of psychotic symptoms, income level, or gender.

Social quality of life

A large effect shows poorer social quality of life in people with schizophrenia;

13 studies, N not reported, SMD = -1.13, 95%CI -1.34 to -0.92, $p < 0.00001$, $I^2 = 83\%$

The effect was larger in studies using the WHOQOL than the SF-36.

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The effect was smaller in studies of older patients, and in studies of lower-middle income groups. There were no moderating effects of illness duration, severity of psychotic symptoms, or gender.	
Consistency in results‡	Inconsistent
Precision in results§	Precise
Directness of results‖	Direct

Eack SM, Newhill CE

Psychiatric symptoms and quality of life in schizophrenia: a meta-analysis

Schizophrenia Bulletin 2007; 33(5): 1225-1237

View review abstract online

Comparison	**Relationships between psychiatric symptoms and QoL ratings.**
Summary of evidence	**Moderate to high quality evidence (large sample sizes, inconsistent, precise, direct) suggests small to medium-sized associations between increased positive and negative symptoms, and general psychopathology and lower QoL ratings.**

Positive symptoms

Significant, small associations between positive symptoms and QoL;

Composite QoL score;

43 studies, N = 3,998, r = -0.20, 95%CI -0.23 to -0.17, $p < 0.05$, Q = 97.21, $p < 0.01$

Subjective QoL;

19 studies, N = 2,256, r = -0.15, 95%CI -0.19 to -0.11, $p < 0.05$, Q = 42.90, $p < 0.01$

Objective QoL;

15 studies, N = 1,150, r = -0.18, 95%CI -0.24 to -0.13, $p < 0.05$, Q = 36.60, $p < 0.01$

General wellbeing;

12 studies, N = 1,198, r = -0.08, 95%CI -0.14 to -0.03, $p < 0.05$, Q = 23.09, $p < 0.05$

Health-related QoL;

15 studies, N = 1,256, r = -0.26, 95%CI -0.31 to -0.21, $p < 0.05$, Q = 37.87, $p < 0.01$

Quality of life

Negative symptoms
Significant, small to medium-sized associations between negative symptoms and QoL outcomes; *Composite QoL score;* 44 studies, N = 4,114, *r* = -0.25, 95%CI -0.28 to -0.22, *p* < 0.05, Q = 170.14, *p* < 0.01 *Subjective QoL;* 20 studies, N = 2,359, *r* = -0.12, 95%CI -0.16 to -0.08, *p* < 0.05Q = 29.54, *p* > 0.05 *Objective QoL;* 16 studies, N = 1,207,*r* = -0.47, 95%CI -0.51 to -0.42, *p* < 0.05, Q = 97.26, *p* < 0.01 *General wellbeing;* 11 studies, N = 1,154, *r* = -0.14, 95%CI -0.20 to -0.08, *p* < 0.05, Q = 23.86, *p* < 0.01 *Health-related QoL;* 15 studies, N = 1,389, *r* = -0.42, 95%CI -0.46 to -0.37, *p* < 0.05, Q = 51.36, *p* < 0.01
General psychopathology
Significant, small to medium-sized associations between general psychopathology and QoL; *Composite QoL score;* 50 studies, N = 5,106, *r* = -0.34, 95%CI -0.36 to -0.31, *p* < 0.05, Q = 121.41, *p* < 0.01 *Subjective QoL;* 25 studies, N = 2,997, *r* = -0.29, 95%CI -0.33 to -0.26, *p* < 0.05, Q = 74.89, *p* < 0.01 *Objective QoL;* 13 studies, N = 1,019, *r* = -0.26, 95%CI -0.32 to -0.20, *p* < 0.05, Q = 41.81, *p* < 0.01 *General wellbeing;* 13 studies, N = 1,434, *r* = -0.27, 95%CI -0.31 to -0.22, *p* < 0.05, Q = 16.91, *p* > 0.05 *Health-related QoL;* 15 studies, N = 1,389, *r* = -0.42, 95%CI -0.46 to -0.37, *p* < 0.05, Q = 32.45, *p* < 0.01
Subgroup analysis: illness duration

Increased positive symptoms was related to poor QoL in people with chronic schizophrenia, but not in people with first-episode schizophrenia; Chronic patients: r = -0.21, $p < 0.0001$ First episode patients: r = -0.08, $p = 0.13$ $Q_B = 4.51$, $p < 0.05$ No differences were reported between people with chronic schizophrenia and people with first-episode schizophrenia in the relationships between general psychopathology or negative symptoms and QoL ratings; $Q_B < 0.76$, $p > 0.38$.
Subgroup analysis: treatment settings
Increased positive and negative symptoms were related to poor QoL in outpatients and inpatients; *Positive symptoms;* Outpatients: r = -0.28, 95%CI and p-value are not reported Inpatients: r = -0.12, 95%CI and p-value not reported *Negative symptoms;* Outpatients: r = -0.32, 95%CI and p-value not reported Inpatients: r = -0.22, 95%CI and p-value not reported For both groups, $Q_B > 7.87$, $p < 0.01$ No differences were reported between inpatients and outpatients in the relationship between general psychopathology and QoL; $Q_B = 0.62$, $p > 0.05$.

Consistency in results	Inconsistent for all outcomes.
Precision in results	Precise for all outcomes except subgroup analysis of treatment settings (unable to assess).
Directness of results	Direct

Lu L, Zeng LN, Zong QQ, Rao WW, Ng CH, Ungvari GS, Li J, An FR, Xiang YT

Quality of life in Chinese patients with schizophrenia: A meta-analysis

Psychiatry Research 2018; 268: 392-9

View review abstract online

Comparison	**QoL in Chinese people with schizophrenia vs. people without**

	schizophrenia.
Summary of evidence	**Moderate to high quality evidence (large sample sizes, inconsistent, precise, direct) shows a large effect of poorer quality of life in people with schizophrenia, particularly poor social functioning.**
QoL	
A large, significant effect showed people with schizophrenia had poorer quality of life; 11 studies, N = 3,234, SMD = -1.07, 95%CI -1.44 to -0.70, $p < 0.001$, $I^2 = 96\%$ Subgroup analyses showed poor social functioning had the largest effect size. Patients diagnosed using the DSM-IV or CCMD-3 showed poorer QOL compared to controls, and compared to patients diagnosed using the ICD-10. There were with no differences in the effect size according to source of patients (inpatients or outpatients), QOL measurement (WHOQOL or other), study location (Chinese economic zone division), or patients' sex or age.	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Tolman AW, Kurtz MM

Neurocognitive Predictors of Objective and Subjective Quality of Life in Individuals With Schizophrenia: A Meta-Analytic Investigation

Schizophrenia Bulletin 2012; 38(2): 304-315

View review abstract online

Comparison 1	**Measuring the relationships between objectively-rated quality of life and cognitive deficits in schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (medium-sized samples, precise, consistent, direct) finds small associations between better objectively-rated QoL and better verbal ability, short-term memory, and executive functioning (categories).** **Moderate to high quality evidence (medium to large samples, inconsistent) finds small associations between better**

	objectively-rated QoL and better working memory, list learning, processing speed and executive functioning (perseverative errors).
Objective QoL and cognitive performance	
A small association was found between better QoL and better verbal ability; WAIS vocabulary: 3 studies, N = 185, *d* = 0.34, 95%CI 0.13 to 0.55, *p* = 0.001, Q = 3.76, *p* > 0.05 *A small association was found between better QoL and better short-term memory;* WAIS digit span: 4 studies, N = 336, *d* = 0.26, 95%CI 0.11 to 0.41, *p* = 0.001, Q = 5.77, *p* > 0.05 *A small association was found between better QoL and better executive functioning;* WCST-categories: 3 studies, N = 271, *d* = 0.55, 95%CI 0.38 to 0.72, *p* = 0.000, Q = 0.85, *p* > 0.05 WCST-perseverative errors: 5 studies, N = 439, *d* = 0.28, 95%CI 0.14 to 0.41, *p* = 0.000, Q = 10.76, *p* < 0.05 *A small association was found between better QoL and better working memory;* WAIS letter-number sequencing: 4 studies, N = 626, *d* = 0.17, 95%CI 0.06 to 0.28, *p* = 0.003, Q = 13.23, *p* < 0.05 *A small association was found between better QoL and better immediate list learning;* CVLT/HVLT/RAVLT: 4 studies, N = 452, *d* = 0.37, 95%CI 0.24 to 0.51, *p* = 0.000, Q = 11.67, *p* < 0.05 *A small association was found between better QoL and better delayed list learning;* CVLT/HVLT/RAVLT: 3 studies, N = 563, *d* = 0.13, 95%CI 0.01 to 0.25, *p* = 0.028, Q = 6.16, *p* <0.05 *A small association was found between better QoL and better processing speed;* Digit Symbol Substitution Test, Trail Making Test-A: 5 studies N = 439, *d* = 0.23, 95%CI 0.10 to 0.36, *p* = 0.000, Q = 19.27, *p* < 0.05 *No significant association was found between QoL and vigilance;* CPT: 3 studies, N = 271, *d* = 0.15, 95%CI -0.02 to 0.32, *p* = 0.089, Q = 1.50, *p* > 0.05 *No significant association was found between QoL and logical memory;* WAIS logical memory-immediate: 4 studies, N = 422, *d* = 0.11, 95%CI -0.02 to 0.25, *p* = 0.099, Q = 4.17, *p* > 0.05 Weschler logical memory- delayed: 3 studies, N = 271, *d* = 0.12, 95%CI -0.05 to 0.29, *p* = 0.176, Q = 1.22, *p* > 0.05	
Consistency in results	Consistent for verbal ability, vigilance, short-term memory, prose recall, and executive function (categories). Inconsistent for working memory, list learning, processing speed and executive function

	(perseverative errors).
Precision in results	Precise for all outcomes
Directness of results	Direct
Comparison 2	**Measuring the relationships between subjectively-rated quality of life and cognitive deficits in schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (medium-sized sample, precise, consistent, direct) finds a small association between better QoL and better letter fluency. Moderate quality evidence (inconsistent) finds small associations between poorer QoL and better verbal ability and processing speed.**
Subjective QoL and cognitive performance	
A small association was found between better QoL and better letter fluency; 5 studies, N = 274, *d* = 0.26, 95% CI 0.09 to 0.43, *p* = 0.002, Q = 32.12, *p* < 0.05 *A small association was found between poorer QoL and better processing speed;* Trail making test-A: 4 studies, N = 272, *d* = -0.19, 95% CI -0.36 to -0.02, *p* = 0.027, Q = 10.58, *p* < 0.05 *A small association was found between poorer QoL and better verbal ability;* WAIS vocabulary: 3 studies, N = 210, *d* = -0.29, 95% CI -0.49 to -0.10, *p* = 0.003, Q = 18.56, *p* < 0.05 *No significant association was found between QoL and short-term memory;* WAIS digit span: 5 studies, N = 310, *d* = 0.01, 95% CI -0.15 to 0.17, *p* = 0.917, Q = 22.00, *p* > 0.05 *No significant association was found between QoL and prose recall;* Weschler logical memory-immediate: 4 studies, N = 272, *d* = -0.16, 95% CI -0.33 to 0.01, *p* = 0.059, Q = -2.25, *p* > 0.05 Weschler logical memory-long delay: 4 studies, N = 272, *d* = -0.06, 95% CI -0.23 to 0.10, *p* = 0.459 Q = 1.15, *p* > 0.05 *No significant association was found between QoL and list learning;* CVLT/HVLT/RAVLT: 4 studies, N = 230, *d* = 0.03, 95% CI -0.15 to 0.21, *p* = 0.762, Q = 0.063, *p* > 0.05 *No significant association was found between QoL and processing speed;* Trail making test-A: 4 studies, N = 272, *d* = -0.06, 95% CI -0.23 to 0.11, *p* = 0.464, Q = 1.13, *p* >	

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0.05 *No significant association was found between QoL and executive functioning;* WCST-perseverative errors: 4 studies, N = 260, *d* = 0.01, 95% CI -0.16 to 0.18, *p* = 0.890, Q = 3.38, *p* > 0.05 WCST-categories: 4 studies, N = 266, *d* = 0.04, 95% CI -0.13 to 0.18, *p* = 0.890, Q = 3.38, *p* > 0.05 *No significant association was found between QoL and executive functioning;* Trail making test-B: 4 studies, N = 272, *d* = -0.04, 95% CI -0.21 to 0.13, *p* = 0.627, Q = 0.50, *p* > 0.05	
Consistency in results	Consistent for all outcomes except verbal ability, letter fluency, and processing speed (digit symbol)
Precision in results	Precise for all outcomes
Directness of results	Direct

Vatne S, Bjorkly S

Empirical evidence for using subjective quality of life as an outcome variable in clinical studies - A meta-analysis of correlates and predictors in persons with a major mental disorder living in the community

Clinical Psychology Review 2008; 28(5): 869-889

View review abstract online

Comparison	**Estimated subjective general well-being (GWB) in people with major mental disorders (mostly schizophrenia) who are living in the community, and predictors of this estimate.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, imprecise, direct) suggests subjective general well-being is good for people with major mental disorders who live in the community. The best predictors of good general well-being are having meaningful leisure activities and strong social networks.**
GWB	
Authors reported that subjective GWB is reported to be good, on average; 49 studies, N = 10,506, pooled estimate of GWB score = 4.558, 95%CI 4.472 to 4.643, Q = 336.771, *p* = 0.000	

Note; Twenty-nine of the studies involved samples containing only patients with schizophrenia. In the other 20 studies the samples also included other diagnoses (schizophrenia: 23% to 94%) *Meta-regression showed that eight QoL domains best predicted GWB estimates, the strongest being leisure and social domains;* Leisure 41 study units, regression coefficient R = 0.7911016, 95%CI 0.5316044 to 1.050599 Social: 43 study units, regression coefficient R = 0.704631, 95%CI 0.4305117 0.9787504 Finances: 44 study units, regression coefficient R = 0.2731748, 95%CI 0.0417648 to 0.5045812 Family: 39 study units, regression coefficient R = 0.4305962, 95%CI 0.1711423 to 0.69005 Work: 31 study units, regression coefficient R = 0.2042235, 95%CI 0.0670581 to 0.3413889 Living: 43 study units, regression coefficient R = 0.4128088, 95%CI 0.1418937 0.6837238 Safety: 38 study units, regression coefficient R = 0.1850072, 95%CI 0.0283799 0.3416345 Health: 41 study units, regression coefficient R = 0.5617022, 95%CI 0.346934 0.7764704

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

Watson P, Zhang JP, Rizvi A, Tamaiev J, Birnbaum ML, Kane J

A meta-analysis of factors associated with quality of life in first episode psychosis

Schizophrenia Research 2018 202: 26-36

View review abstract online

Comparison	**Association between symptoms and duration of untreated psychosis and quality of life in people with first-episode psychosis.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests increased symptom severity and longer duration of untreated psychosis are related to poorer QoL.**
Symptoms	
A medium, significant association between increased symptom severity and poorer QoL;	

Quality of life

10 studies, N = 1,073, *r* = -0.32, 95%CI -0.42 to -0.21, *p* < 0.001, I^2 = 69%, *p* = 0.001 Studies with larger sample sizes and older mean age had weaker correlations, while studies with more people with a schizophrenia diagnosis had stronger correlations. There were no significant moderating effects of ethnicity, sex, and duration of untreated psychosis.
Duration of untreated psychosis
A small, significant association between longer duration of untreated psychosis and poorer QoL; 14 studies, N = 2,733, *r* = -0.21, 95%CI -0.32 to -0.08, *p* < 0.001, I^2 = 90%, *p* < 0.001 Studies with larger samples had stronger correlations, with no significant moderating effects of age, sex, schizophrenia diagnosis, or QoL measure.

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

Explanation of acronyms

CCMD-3 = Chinese Classification of Mental Disorders, CI = Confidence Interval, CPT = Continuous Performance Test, CVLT = California Verbal Learning Test, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, *d* = Cohen's d and *g* = Hedges' g = standardized mean differences (see below for interpretation of effect size), GWB = general well-being, HVLT = Hopkins Verbal Learning Test, N = number of participants, ns = not statistically significant, *p* = statistical probability of obtaining that result (*p* < 0.05 generally regarded as significant), Q = Q statistic (chi-square) for the test of heterogeneity, QB = between group heterogeneity, *r* = correlation coefficient, R/r = regression coefficient, RAVLT = Rey Auditory Verbal Learning Test, SF-36 = 36-item short form survey, vs. = versus, WAIS = Weschler Adult Intelligence Scale, WCST = Wisconsin Card Sorting Test, WHOQOL = World Health Organisation Quality of Life Scale

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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[9].

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† Different effect measures are reported by different reviews.

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.

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 effect[9].

Quality of life

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[10]. 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.

‡ 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[9];

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

§ 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, these criteria should be relaxed[11].

‖ 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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