Integrated care



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Introduction

Integrated care refers to the association of multiple treatment paradigms to produce a single unified program. The idea is to deliver seamless care to the patient to ensure high treatment continuity and improve patient Integrated programs satisfaction. typically involve multi-element psychosocial therapies for mental illness. For example, integrated integrated psychological therapy and neurocognitive therapy involve a combination of cognitive training, social skills training, problemsolving training and cognitive remediation. Integrated care can also refer to the formal liaison of typically distinct services such as medical practitioners and dedicated mental health teams, or the incorporation of mental health and substance use treatments into a single program.

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 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 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-analysis¹. 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 or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent. precise and direct with low associated risks (see end of table for an explanation of these terms)². The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

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

 Moderate to high quality evidence finds integrated psychological therapy provides benefit for symptoms, global state, functioning and cognition. Moderate to low quality evidence finds integrated



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psychological therapy provides benefit regardless of treatment settings or assessment format and is most effective for patients with stabilised symptoms.

- Moderate quality evidence finds integrated neurocognitive therapy provides a benefit for negative symptoms and functioning posttreatment and at 12 months follow up, with no lasting benefit for positive symptoms.
- Moderate to low quality evidence suggests benefit of integrated medical and mental health care for improving health outcomes and treatment needs, increasing contact with services, and improving patient satisfaction.

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Cleary M, Hunt GE, Matheson SL, Walter G

Psychosocial treatments for people with co-occurring severe mental illness and substance misuse: systematic review

Journal of Advanced Nursing 2009; 65(2): 238-258

View review abstract online

Comparison	Integrated care for patients with dual diagnosis (substance abuse treatment combined with assertive community treatment) vs. standard care.
	Results are reported here for samples containing a majority schizophrenia.
Summary of evidence	Moderate to low quality evidence (small to medium-sized samples, unable to assess consistency or precision, direct) is unclear of the benefit of integrated care for patients with dual diagnosis.

Mental state and hospitalisation

2 RCTs (N = 198 and 216) reported reduced hospitalisation rates with integrated care.

1 non-randomised study (N = 179) reported no differences between groups in hospitalisation rates.

2 RCTs (N = 223 and 95) reported no differences between groups in mental state scales.

Substance use

1 RCT (N = 223) and 1 non-randomised study (N = 179) reported reductions in substance use with integrated care.

3 RCTs (N = 198, 216 and 95) reported no differences between groups in substance use.

Treatment retention

1 RCT (N = 223) and 1 non-randomised study (N = 179) reported increased treatment retention with integrated care.

3 RCTs (N = 198, 216 and 95) reported no differences between groups in study retention.

Consistency in results	Unable to assess, no measure of consistency is reported. Appears
	inconsistent.



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Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct

De Mare A, Cantarella M, Galeoto G

Effectiveness of Integrated Neurocognitive Therapy on Cognitive Impairment and Functional Outcome for Schizophrenia Outpatients

Schizophrenia Research and Treatment 2018: 2360697

View review abstract online

Comparison	Integrated neurocognitive therapy (15 weeks of biweekly sessions each lasting 90 minutes) vs. treatment as usual.
Summary of evidence	Moderate quality evidence (small to medium-sized samples, consistent, imprecise, direct) suggests integrated neurocognitive therapy provides a benefit for negative symptoms and functioning post-treatment and at 12 month follow up, with no lasting benefit for positive symptoms.

Negative symptoms

Significant improvement in negative symptoms post-treatment and at follow up; At 15 weeks: 2 studies, N = 195, MD = -2.99, 95%Cl -4.41 to -1.57, p < 0.0001, $l^2 = 0$ % At 9-12 months: 2 studies, N = 170, MD = -2.47, 95%Cl -4.11 to -0.83, p = 0.003, $l^2 = 0$ %

Positive symptoms

Trend effect of improvement in positive symptoms post-treatment but not at follow up; At 15 weeks: 2 studies, N = 195, MD = -1.26, 95%Cl -2.56 to -0.05, p = 0.06, l^2 = 0% At 9-12 months: 2 studies, N = 170, MD = -0.97, 95%Cl -2.30 to 0.36, p = 0.15, l^2 = 0%

Functioning

Significant improvement in functioning post-treatment and at follow up;
At 15 weeks: 2 studies, N = 195, MD = 2.38, 95%Cl 0.02 to 4.74, p = 0.05, $l^2 = 0\%$ At 9-12 months: 2 studies, N = 170, MD = 4.58, 95%Cl 2.03 to 7.12, p = 0.0004, $l^2 = 0\%$



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Consistency in results	Consistent
Precision in results	Appears imprecise (MD not standardised)
Directness of results	Direct

De Silva MJ, Cooper S, Li HL, Lund C, Patel V

Effect of psychosocial interventions on social functioning in depression and schizophrenia: meta-analysis

The British Journal of Psychiatry 2013; 202: 253-260

View review abstract online

Integrated treatments for social functioning vs. standard care. Treatment duration ranged from 1 month to 2 years.
Moderate quality evidence (medium to large samples, inconsistent or imprecise, direct) suggests a large effect of improved social functioning following integrated psychotherapies, and a small to medium-sized effect following community based integrated treatments compared to standard care.

Social functioning

A significant, large effect of improved social functioning following multicomponent structured psychotherapies comprising psychoeducation + at least two additional therapies (skills training, cognitive behavioural therapy, interpersonal therapy or family therapy);

4 RCTs, N = 893, SMD = 0.93, 95%Cl 0.23 to 1.63, p = 0.009, l^2 = 89%, p < 0.00001 Authors state 3 of the 4 trials were of good quality.

A significant, small to medium-sized effect of improved social functioning following multicomponent community care (mostly psychoeducation + family therapy);

2 RCTs, N = 316, SMD = 0.33, 95%Cl 0.10 to 0.55, p = 0.004, l^2 = 0%, p < 0.49 Authors state that all trials were of poor quality.

Consistency in results	Inconsistent for structured psychotherapies, consistent for community care.
Precision in results	Imprecise for structured psychotherapies, precise for community



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	care.
Directness of results	Direct

Donald M, Dower J, Kavanagh D

Integrated versus non-integrated management and care for clients with cooccurring mental health and substance use disorders: a qualitative systematic review of randomised controlled trials

Social Science & Medicine 2005; 60(6): 1371-1383

View review abstract online

Comparison	Integrated care programs incorporating psychotherapy, cognitive behavioural therapy, psychoeducation, case management and pharmacological components vs. standard care. Results are reported here for schizophrenia samples only.
Summary of evidence	Moderate to low quality evidence (small samples, unable to assess consistency or precision, direct) suggests unclear benefit of integrated care for reducing substance use or psychiatric symptoms.

Symptoms, functioning and substance use

- 1 study (N = 32) reported significant improvement in global function at 9 and 12 months for integrated care compared to routine care.
- 3 studies (total N = 103) reported no significant difference between groups for symptoms or substance use.

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

Hunt GE, Morley K, Sitharthan T, Siegfried N, Cleary M

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Psychosocial interventions for people with both severe mental illness and substance misuse

Cochrane Database of Systematic Reviews 2013, Issue 10. Art. No.: CD001088. DOI: 10.1002/14651858.CD001088.pub3

View review full text online

Comparison	Integrated care models for dual diagnosis patients (IC, incorporating substance abuse treatments, assertive community treatment, family psychoeducation, crisis intervention and skills training) vs. treatment as usual.
Summary of evidence	Moderate quality evidence (medium to large samples, consistent where applicable, imprecise, direct) suggests integrated care had no significant benefit over treatment as usual for study retention, hospitalisation or service use, substance use, quality of life or functioning.
	Study retention, lost to treatment

Study retention: lost to treatment

No significant effect of IC on retention rates;

By 36 months, N = 603, 3 RCTs, RR = 1.09, 95%CI 0.82 to 1.45, p = 0.57, $I^2 = 0\%$, p = 0.38

Study retention: lost to evaluation

No significant effect of IC on evaluation rates;

By 3 months, N = 132, 1 RCT, RR = 0.54, 95%CI 0.27 to 1.08, p = 0.081

By 6 months, N = 330, 2 RCTs, RR = 0.69, 95%Cl 0.27 to 1.73, p = 0.42, $l^2 = 67\%$, p = 0.08

By 9 months, N = 132, 1 RCT, RR = 0.76, 95%CI 0.49 to 1.19, p = 0.23

By 12 months, N = 198, 1 RCT, RR = 0.54, 95%CI 0.22 to 1.29, p = 0.17

By 24 months, N = 198, 1 RCT, RR = 1.00, 95%CI 0.47 to 2.12, p = 1.0

By 36 months, N = 603, 3 RCTs, RR = 0.76, 95%CI 0.35 to 1.66, p = 0.50, $I^2 = 74\%$, p = 0.02

Substance use

No significant effect of IC on remission rates;

For alcohol users, N = 143, 1 RCT, RR = 1.15, 95%CI 0.84 to 1.56, p = 0.38

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For drug users, N = 85, 1 RCT, RR = 0.89, 95%Cl 0.63 to 1.25, p = 0.49 No significant effect of IC on SATS scores;

By 6 months, N = 203, 1 RCT, WMD = 0.07, 95%CI -0.28 to 0.42, p = 0.69

By 36 months, N = 203, 1 RCT, WMD = 0.11, 95%CI -0.41 to 0.63, p = 0.68

Service use

No significant effect of IC on number of days in community residences;

By 12 months, N = 378, 2 RCTs, WMD = -10.00, 95%CI -38.61 to 18.60, p = 0.49, I^2 = 60%, p = 0.11

By 24 months, N = 203, 1 RCT, WMD = 7.40, 95%CI -6.32 to 21.12, p = 0.29 By 36 months, N = 364, 2 RCTs, WMD = 5.17, 95%CI -9.20 to 19.55, p = 0.48, I^2 = 0%, p = 0.58 No significant effect of IC on hospitalisation rates;

During 36 month study period, N = 198, 1 RCT, RR = 0.88, 95%CI 0.64 to 1.19, p = 0.39

Functioning

No significant effect of IC on global functioning;

By 6 months, N = 162, 1 RCT, WMD = 1.10, 95%CI -1.58 to 3.78, p = 0.42

By 12 months, N = 171, 1 RCT, WMD = 0.70, 95%CI -2.07 to 3.47, p = 0.62

By 18 months, N = 176, 1 RCT, WMD = 1.00, 95%CI -1.58 to 3.58, p = 0.45

By 24 months, N = 166, 1 RCT, WMD = 1.70, 95%CI -1.18 to 4.58, p = 0.25

By 30 months, N = 164, 1 RCT, WMD = -0.60, 95%Cl -3.56 to 2.36, p = 0.69

By 36 months, N = 170, 1 RCT, WMD = 0.40, 95%CI -2.47 to 3.27, p = 0.78

Quality of Life

No significant effect of IC on general life satisfaction (QOLI);

By 6 months, N = 361, 2 RCTs, WMD = -0.11, 95%CI -0.41 to 0.20, p = 0.49, $I^2 = 0\%$, p = 0.56

By 12 months, N = 372, 2 RCTs, WMD = 0.02, 95%CI -0.28 to 0.32, p = 0.91, $I^2 = 0\%$, p = 0.65

By 18 months, N = 377, 2 RCTs, WMD = 0.09, 95%CI -0.27 to 0.44, p = 0.64, $I^2 = 30\%$, p = 0.23

By 24 months, N = 370, 2 RCTs, WMD = 0.02, 95%CI -0.29 to 0.33, p = 0.91, $I^2 = 8\%$, p = 0.30

By 30 months, N = 366, 2 RCTs, WMD = 0.02, 95%CI -0.27 to 0.32, p = 0.87, $I^2 = 0\%$, p = 0.90

By 36 months, N = 373, 2 RCTs, WMD = 0.10, 95%CI -0.18 to 0.38, p = 0.49, $I^2 = 0\%$, p = 1.00

Risks

No differences in death rates. No other adverse effects reported.



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Consistency in results	Most outcomes have 1 RCT, consistent for all other outcomes except lost to evaluation at 36 months.
Precision in results	Imprecise for dichotomous outcomes (RR), unable to assess continuous outcomes (WMD not standardised measure).
Directness of results	Direct

Mitchell G, Del Mar C, Francis D

Does primary medical practitioner involvement with a specialist team improve patient outcomes? A systematic review

British Journal of General Practice 2002; 52(484): 934-939

View review abstract online

Comparison	Formal liaison between medical practitioner and specialist community mental health team vs. community care alone.
Summary of evidence	Moderate to low quality evidence (small sample, unable to assess precision, direct) suggests benefit of integrated care for improving medical health outcomes and treatment needs, increasing contact with services and for improving patient satisfaction.

Treatment needs

At one year, the number of unmet treatment needs were significantly lower in the integrated group (N = 89, p < 0.001) and the number of met treatment needs were significantly higher (p < 0.001). At two years, the number of correctible needs being met were all significantly higher in the integrated treatment group, including daily living needs (p < 0.01), public facilities (p < 0.03) and managing finances (p < 0.05).

Contact with services

During the intervention period (up to 2 years), the integrated treatment group showed significantly higher contact with community psychiatric nurses (p < 0.01), social workers (p < 0.01), and occupational therapists (p < 0.01). No difference was reported in the number of patients who had no contact with services.

Patient satisfaction



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Patients in the integrated treatment group showed lower CSQ scores (significance not reported) compared to community care alone, and the integrated group were significantly more likely (*p* < 0.01) to report better accessibility for appointments and less disruption from staff changes during treatment.

Cost

Cost per capita for patients in the integrated treatment group was higher compared to community care alone (significance not reported), though authors report high within-group variability.

Consistency in results	Not applicable, 1 RCT
Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct

Roder V, Mueller DR, Schmidt SJ

Effectiveness of Integrated Psychological Therapy (IPT) for Schizophrenia Patients: a Research Update

Schizophrenia Bulletin 2011; 37 Suppl 2: 71-79

View review abstract online

Comparison	Pre-post analyses of integrated psychological therapy (combining group cognitive behavioural therapy with cognitive remediation and social skills training), nonspecific group activities, and standard care.
Summary of evidence	Moderate to high quality evidence (large samples, consistent, precise, indirect) suggests integrated psychological therapy provides benefit for symptoms, global state, functioning and cognition (including social cognition), and effects may be greater than in control conditions, apart from symptoms.
	Global state

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A significant, small to medium-sized effect of better global state with integrated psychological therapy, with no significant improvements with nonspecific group activities or standard care;

Integrated psychological therapy: 34 studies, N ~ 1,575, g = 0.52, 95%CI 0.52 to 0.62, p < 0.01, $Q_w = 13.78$, p > 0.05

Nonspecific group activities: 10 studies, g = 0.23, 95%CI 0.03 to 0.42, p > 0.05, $Q_w = 1.83$, p > 0.05

Standard care: 16 studies, g = -0.01, 95%CI -0.18 to 0.17, p > 0.05, $Q_w = 11.7$, p > 0.05

$$Q_B = 29.7, p < 0.01$$

8 month follow-up analysis found similar results;

Integrated psychological therapy: g = 0.57, 95%CI 0.39 to 0.74, p < 0.01, $Q_w = 6.27$, p > 0.05

Nonspecific group activities: 2 studies, g = 0.15, 95%CI -0.31 to 0.62, p > 0.05, $Q_w = 0.00$, p > 0.05

Standard care: 3 studies, g = -0.07, 95%CI -0.52 to 0.38, p > 0.05, $Q_w = 1.94$, p > 0.05

$$Q_B = 8.31, p < 0.05$$

Symptoms

Integrated psychological therapy showed a medium-sized effect of improved symptoms;

General psychopathology: 27 studies, g = 0.52, 95%Cl 0.42 to 0.63, p < 0.01, $Q_w = 20.19$, p > 0.05

Positive symptoms: 21 studies, g = 0.45, 95%CI 0.32 to 0.57, p < 0.01, $Q_w = 9.93$, p > 0.05

Negative symptoms: 11 studies, q = 0.42, 95%CI 0.25 to 0.59, p < 0.01, $Q_w = 11.79$, p > 0.05

No significant differences in effect sizes were found between integrated psychological therapy and control conditions ($Q_B < 3.3$, p > 0.05).

Cognition and functioning

Integrated psychological therapy showed a small to medium-sized effect of improved cognition and functioning:

Overall cognition: 29 studies, g = 0.53, 95%Cl 0.43 to 0.64, p < 0.01, $Q_w = 22.85$, p > 0.05

Neurocognition: 27 studies, g = 0.52, 95%CI 0.41 to 0.63, p < 0.01, $Q_w = 11.85$, p > 0.05

Social cognition: 15 studies, q = 0.70, 95%CI 0.54 to 0.87, p < 0.01, $Q_w = 32.77$, p > 0.05

Psychosocial functioning: 24 studies, g = 0.42, 95%CI 0.31 to 0.54, p < 0.01, $Q_w = 13.63$, p > 0.05

Integrated psychological therapy showed significantly higher effect sizes than control conditions ($Q_B > 13.7$, p < 0.01).

Consistency in results	Consistent
Precision in results	Precise
Directness of results	Indirect comparison between interventions.

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Zygmunt A, Olfson M, Boyer CA, Mechanic D

Interventions to improve medication adherence in schizophrenia.

American Journal of Psychiatry 2002; 159(10): 1653-64

View review abstract online

Comparison	Integrated interventions (various combinations of individual and family interventions, psychoeducation, cognitive therapy, and skills training) for improving medication adherence vs. various comparison groups, including standard care, supportive therapy, or non-specific leisure time.
Summary of evidence	Moderate to low quality evidence (small to medium-sized samples, unable to assess consistency or precision, direct) is unclear of the benefit of multi-modal interventions for improving medication adherence.

Medication adherence

9 randomised studies (sample sizes ranged from 30 to 304), investigated multi-modal interventions compared to standard care or placebo interventions, assessed by either clinician or self-report, or pill count.

Four of eight studies reported interventions incorporating both individual and family therapies were more effective than either psychoeducation or standard care for improving adherence, based on both self- and clinician reports. Psychoeducation also showed no benefit in one study when combined with cognitive therapy and family therapy compared with non-specific group leisure time.

One study reported significant benefit of social skills training, either alone or in combination with family therapy, over standard care for improving treatment adherence.

In-home individual behavioural therapy showed benefit over standard care, compared to clinic-based behavioural therapy which showed no difference to standard care for treatment adherence

Consistency in results	Not applicable, all 1 study.
Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct





Explanation of acronyms

CI = Confidence Interval, d = Cohen's d and g = Hedges' g = standardised mean differences (see below for interpretation of effect size), I² = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), IC = integrated care, IPT = Integrated psychosocial treatment, MD = mean difference, 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, Q_w = test for within group differences (heterogeneity in study results within a group of studies – measure of study consistency), Q_B = test for between group differences (heterogeneity between groups of studies for an outcome of interest), RCT = randomised controlled trial, RR = risk ratio, TAU = treatment as usual, 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 small¹¹.

† 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 randomized trial there is an assumption that both groups are comparable on this measure Standardised mean prior to treatment. 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. 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

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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 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 а 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 Standardised variables. regression coefficients represent the change being in units of standard deviations to comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) which is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I² can calculated from Q (chi-square) for the test of heterogeneity with the following formula¹¹;

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

Imprecision refers to wide confidence intervals indicating a lack of confidence in the estimate. effect Based **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 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 B. Indirectness versus of population, comparator and/or outcome can also occur when the available evidence regarding a population, particular 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-tohead comparisons of A and B.





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