Table D-1. Characteristics of all included studies

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| --- | --- | --- | --- | --- |
| Study Identification | Goal of Study/Approach to Controlling for Biases in Study Conduct | Conditions Evaluated/  Outcomes Reported | Inclusion/Exclusion Criteria | Unit of Analysis and Number Included  Sources Searched for Studies or MA |
| Schulz et al., 19951 | Goal: To determine if selected biases are associated with estimates of treatment effect.  Control for bias:  Allocation concealment,  Generation of allocation schedule (randomization),  Exclusions after randomization,  Double-blinding | Conditions: care during pregnancy, preterm labor and delivery, induction of labor, labor and delivery, prophylactic antibiotics for cesarean delivery, puerperium, early neonatal period  Outcomes: Binary, specific outcomes: NR | Include: RCTs of pregnancy and childbirth; MAs of 5+ RCTs with at least 25 outcome events among control group and at least one trial with adequate concealment and one without; duplicative trials dropped by including most homogeneous MA.  Exclude: Unpublished and non-English language studies | MA level  33 MA (250 trials)  Search: Cochrane database of SRs published by the Pregnancy and Childbirth group (1955-1992); Based on Oxford database of perinatal trials; dates of trials dk |
| Juni et al.,19992 | Goal: To determine if the type of quality assessment scale affects the conclusions of MA.  Control for bias:  Concealment of randomization  Blinding of outcome assessor  Handling of drop-outs and withdrawals (ITT performed) | Condition: Prevention of postoperative thrombosis comparing low molecular-weight heparin to regular heparin in general surgery trials  Outcomes: thromboembolitic events (bleeding and deep vein thrombosis) | Inclusion/exclusion: NR in this article; heterogeneity in surgical procedures not described | RCT level  Data from 17 RCTs included in 1 MA  Search: MA by Nurmohamed et al., 19923 |

Table D-1. Characteristics of all included studies (continued)

| Study Identification | Goal of Study/Approach to Controlling for Biases in Study Conduct | Conditions Evaluated/  Outcomes Reported | Inclusion/Exclusion Criteria | Unit of Analysis and Number Included  Sources Searched for Studies or MA |
| --- | --- | --- | --- | --- |
| Linde et al., 19994 | Goal: To compare three different approaches to investigating the impact of quality aspects on outcomes in a published MA of placebo-controlled trials: (1) the influence of single-quality components on the outcome, (2) using cut-off points in quality scores as inclusion criterion, and (3) entering trials into MAs consecutively according to quality scores (cumulative MA).  Control for bias:  Randomization (explicitly stated)  Double blinding (patients and evaluators, txs indistinguishable)  Full description of handling of drop-outs and withdrawals | Condition: homeopathic intervention for tx or prevention  Outcomes: NR | From 186 trials evaluated, 119 selected for original MA (Linde et al., 1997)5. Of these, 89 selected for sensitivity analysis of quality  Include: controlled trials on tx or prevention; parallel control group receiving placebo; explicit statement of random assignment to tx and placebo groups, or that the trial involved double-blind conditions for participants, therapists, and outcome evaluators, making unbiased tx allocation likely; presented in a written report, published or unpublished; abstract, full report, or book section; sufficient information after data extraction to have outcome rates calculated for both groups.  Exclude: homoeopathic “provings” in which remedies are given to healthy volunteers to assess effects; studies of healthy participants not aimed at tx or prevention; single-case reports; a reasonable outcome measure for data synthesis could not be determined. | Trial level  Data from 89 trials included within a single MA on homeopathic interventions compared with placebo  Search: Medline, Embase and CAM registries for trials evaluating homeopathy, contacts with researchers, bibliographies of identified articles. |

Table D-1. Characteristics of all included studies (continued)

| Study Identification | Goal of Study/Approach to Controlling for Biases in Study Conduct | Conditions Evaluated/  Outcomes Reported | Inclusion/Exclusion Criteria | Unit of Analysis and Number Included  Sources Searched for Studies or MA |
| --- | --- | --- | --- | --- |
| Moher et al., 1999,6  Moher et al., 19987 | Goal: To determine the effect that the quality of RCTs included in a MA has on estimates of intervention effectiveness  Control for bias:   * Randomization sequence * Allocation concealment * Double blinding * Adequate follow-up | Conditions: 3 MAs each from the areas of digestive diseases, circulatory diseases, and mental health; 3 MA randomly chosen on stroke, 2 on pregnancy and childbirth.  Outcomes: varied across studies | Random selection of 12 MAs (1 excluded post hoc) from larger database of 491 MAs of RCTs.  Inclusion: published in English; no formal incorporation of quality scores in quantitative analysis; binary outcomes reported using an overall quantitative summary result.  Exclusion: MAs that did not provide references for included trials. | MA level  11 MA: data from 127 trials  Search: Cochrane Database of Systematic Reviews |
| Kjaergard, Villumsen and Gluud, 20018 | Goal: To explore whether methodologic quality affects estimated intervention effects in RCTs and contributes to differences between large and small RCTs in MA.  Control for bias:   * Allocation sequence * Allocation concealment * Double blinding * Adequate follow-up | Conditions: NR  Outcomes: mortality, neonatal mortality, cesarean section, deep vein thrombosis, dropouts, endocervical cells, resumed smoking, | Inclusion (SRs): MAs that included at least one large trial (≥ 1000 subjects)  Exclusion (SRs): MA with RCTs that were also included in larger eligible MA, lacking references to the primary trials, or low-quality  Exclusion (RCTs): unpublished, quasi-randomized, published as abstracts, language (not English or German) | MA level  14 MA: data from 190 RCTs (23 large, 167 small)  Search: Medline and Cochrane library |
| Balk et al., 20029 | Goal: To determine if quality measures are associated with tx effect sizes in RCTs  24 controls for biases, including:   * allocation concealment, * randomization, * attrition & loss to follow-up, * blinding (double & component) * valid statistical methods * confounding | Conditions: Cardiovascular diseases, infectious diseases, pediatrics, surgery  Outcomes: mortality in cardiovascular disease studies; varied in other clinical areas. If multiple outcomes, included those examined by the largest number of studies or those most clearly defined. | Inclusion: MA with at least 6 RCTs, dichotomous outcomes; sig between-study heterogeneity within MA.  Exclusion: abstracts, letters, unavailable articles, detailed outcome data not available. | MA level  26 MAs, data from 276 trials (included "85%" of the 325 trials from the MAs)  Cardiovascular: 8 MA (93 trials)  Infectious disease: 6 MA (56 trials)  Pediatrics: 5 MA (60 trials)  Surgery: 7 MA (67 trials)  Search: Medline and Cochrane databases |

Table D-1. Characteristics of all included studies (continued)

| Study Identification | | Goal of Study/Approach to Controlling for Biases in Study Conduct | | Conditions Evaluated/  Outcomes Reported | | Inclusion/Exclusion Criteria | Unit of Analysis and Number Included  Sources Searched for Studies or MA |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Clifford et al., 200210 | | Goal: To examine the relationships between funding source, trial outcome and reporting quality--particularly allocation concealment.  Controls for biases:   * allocation concealment | | Conditions: pharmaceutical intervention  Outcomes: primary outcome as defined by authors or if not defined, most clinically relevant | Inclusion: RCT published as full report; pharmaceutical intervention. | RCT level  100 RCTs (convenience sample)  Search: Hand search of 1/99-10/00 issues of 5 high-impact medical journals (Annals; BMJ; JAMA, Lancet; NEJM) until 20 articles found in a journal. | |
| Sterne et al., 200211 | | Goal: To compare methods for assessing the influence of trial characteristics on estimated tx effects in data sets containing collections of MAs: (1) fixed effects logistic regression, (2) a meta-analytic approach that combines separate logistic regressions, and  (3) meta-regression approach  Controls for biases:   * Allocation concealment, * Double-blinding | | Conditions and Outcomes: See Schulz et al., 19951 description | Re-analysis of Schulz et al. (1995)1 database | MA level  33 MA, data from 250 trials  Search: As per Schulz et al. (1995).1 | |
| Als-Nielsen et al., 200312 | | Goal: To examine whether an association between funding and conclusions in randomized drug trials. Also, to explore the impact of methodological quality, type of control intervention, trial size, year of publication, or publication in high-impact journals on this association.  Bias examined:   * Double blinding | | Conditions: intensive care, smoking cessation, respiratory disease, ob/gyn, gastroenterology, neurology, psychiatry, infectious disease, rheumatology, nephrology, dermatology | Include: all RCTs in eligible meta-analyses from a random sample of Cochrane reviews obtained in May 2001 | RCT level  370 RCTs in 25 MA  Source: Cochrane reviews obtained in May 2001 | |

Table D-1. Characteristics of all included studies (continued)

| Study Identification | | Goal of Study/Approach to Controlling for Biases in Study Conduct | | Conditions Evaluated/  Outcomes Reported | | Inclusion/Exclusion Criteria | Unit of Analysis and Number Included  Sources Searched for Studies or MA |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Egger et al.,200313 | | Goal: To compare within MAs the characteristics of trials that are difficult to locate (unpublished, published in languages other than English, published in journals not indexed in MEDLINE database), and of lower quality and to assess the impact of excluding trials from pooled effect estimates, based on these characteristics.  Controls for biases:   * Allocation concealment * Double blinding | | Conditions: therapeutic or preventive interventions.  Outcomes: binary, specifics: NR | Exclude: MAs that did not have quality information or showed no differences in quality between included RCTs; unpublished, and non-English RCTs. | MA level  Allocation concealment: 39 MA, (304 trials) Blinding: 22 MA (399 trials)  Search: Issue 1 of Cochrane Database of SRs (1998), SRs included in Database of Abstracts of Reviews of Effectiveness (1994-1998), handsearch: *Health Technology Assessment* and 8 medical journals that regularly publish SRs (1994-1998). | |
| Chan et al., 200414 | | Goal: To study empirically the extent and nature of outcome reporting bias in a cohort of RCTs. The odds of having statistically sig results if the results were fully or partially reported compared with results that were qualitatively reported or unreported.  Bias examined:   * Selective outcome reporting | | Condition: NR  Outcomes: N=2175 for efficacy and N=605 for harms | Include: Completed RCTs with at least 1 published result; outcomes compared between protocol and publication and statistical sig for missing outcome sought from trialists by survey  Exclude: if entire rows or columns for trial were empty in a 2x2 table of statistical sig (N of outcomes with p<0.5 vs. p>=0.05) with reporting (fully or partially/qualitatively or unreported) | RCT level  (based on comparisons of individual trials and protocols)  35 trials for efficacy  15 trials for harms  Sources:  PubMed, EMBASE and Cochrane Controlled Trials Register using investigator names and keywords (final search January 2003) protocols for RCTs that were approved for funding (1990-1998) by the Canadian Institutes of Health or the Medical Research Council of Canada | |

Table D-1. Characteristics of all included studies (continued)

| Study Identification | | Goal of Study/Approach to Controlling for Biases in Study Conduct | Conditions Evaluated/  Outcomes Reported | Inclusion/Exclusion Criteria | Unit of Analysis and Number Included  Sources Searched for Studies or MA | |
| --- | --- | --- | --- | --- | --- | --- |
| Chan et al., 200415 | | Goal: To study empirically the extent and nature of outcome reporting bias in a cohort of RCTs  Bias examined:   * Selective outcome reporting | Condition: NR  Outcome: N=1039 efficacy and N=145 for harms. | Include: Completed RCTs with available protocol and at least 1 published result  Exclude: if entire rows or columns for trial were empty in a 2x2 table of statistical sig (N of outcomes with p<0.5 vs. p>=0.05) with reporting (fully or partially/qualitatively or unreported) | RCT level (comparisons of published studies and protocols)  30 trials for efficacy,  4 trials for harms  Sources: PubMed, EMBASE and Cochrane Trials Register using investigator names and keywords (final search in January 2003) for protocols | |
| Kyzas et al., 200516 | Goal: To assemble empirical evidence on the importance of selective reporting biases for prognostic evidence in malignant diseases  Biases examined:   * Outcome reporting * Blinding | | Condition: Association between the tumor suppressor protein TP53 and head and neck squamous cell cancer (HNSCC),  Outcome: all cause mortality and lymph node status | Inclusion: All English language MAs that examined potential prognostic factors for any malignancy and their association with mortality. | Trial level  42 trials  Sources:  PubMed and EMBASE |
| Tierney et al., 200417 | Goal: To investigate how excluding patients from RCTs can affect the results of trials and MAs  Bias examined:   * Attrition (ITT vs. not) | | Condition: Cancer (bladder, brain, lung, esophagus, ovary, lung, and soft tissue sarcoma)  Outcome: survival | Inclusion/Exclusion: No other details reported | MA and trial level  14 MA  92 RCTs with at least one patient exclusion (21905 patients)    Sources: SRs and MAs of patient-level data from RCTs that addressed cancer therapies |

Table D-1. Characteristics of all included studies (continued)

| Study Identification | | Goal of Study/Approach to Controlling for Biases in Study Conduct | Conditions Evaluated/  Outcomes Reported | Inclusion/Exclusion Criteria | Unit of Analysis and Number Included  Sources Searched for Studies or MA | |
| --- | --- | --- | --- | --- | --- | --- |
| Derry et al., 200618 | Goal: To review the efficacy of SRs to accurately assess the evidence for acupuncture.  Biases examined:   * Randomization * Blinding | | Condition: those treated with acupuncture including various painful conditions (18 SRs), stroke (2 SRs), nausea and vomiting (2SRs), depression (2 SRs) and other including insomnia, smoking cessation, weight loss, and asthma (11 SRs)  Outcomes: those relevant to topic area (e.g. patient pain scoring, number of headache-free days, long-term outcomes for chronic conditions) | Inclusion: English, examining the efficacy of traditional Chinese or mechanical acupuncture, electro-acupuncture, laser acupuncture or acupressure, electrical nerve stimulation.  Exclusion: Transcutaneous or dry needling, reviews of adverse event from acupuncture.  Where one SR clearly updated a previous review, only the most recent was used. If more than one SR covered same trials for the same outcome and indication, the most recent was included. | SR level  35 SRs  Sources: PubMed, AMED, Cochrane library of SRs of acupuncture for any conditions in humans, published 1/1996-8/2005 using terms 'acupuncture' and 'systematic review OR meta-analysis'. |
| Furukawa et al., 2007 19 | Goal: To evaluate the extent Cochrane MAs include only a proportion of identified RCTs when estimating tx effect and whether the proportion of RCTs included in a MA is associated with its pooled effect size | | Conditions: NS  Outcomes: Primary but NS | Inclusion: SRs with 10 or more RCTs from a set of 500 SRs selected by random-number generator from Issue 4 of the Cochrane Library 2005. | RCT level  156 trials  Source: Cochrane Library, Issue 4 (2005) |

Table D-1. Characteristics of all included studies (continued)

| Study Identification | | Goal of Study/Approach to Controlling for Biases in Study Conduct | Conditions Evaluated/  Outcomes Reported | Inclusion/Exclusion Criteria | Unit of Analysis and Number Included  Sources Searched for Studies or MA | |
| --- | --- | --- | --- | --- | --- | --- |
| Pildal et al., 200720 | Goal: To estimate the fraction of conclusions based on statistically significant results in MAs that would no longer be supported if only trials with reported adequate allocation concealment were included, and to assess the impact of absence vs. presence of reported adequate allocation concealment on the effect estimates of trials.  Biases examined:   * Allocation concealment * Double blinding | | Conditions: NS  Outcomes: NS | Inclusion: SRs where authors concluded that one of assessed interventions was superior to the other and if this preference was supported by first statistically sig result of a MA reported in the abstract.  Exclusion: The first statistically sig result of a MA reported in the abstract was not for a binary outcome; substantial uncertainty concerning what authors of the SR perceived as experimental and conventional tx, more than 40 trials in the first statistically sig MA reported in the abstract, genuine MA not performed; abstract of the SR stated that it was partly based on non-randomized trials; a mix of adequate and inadequate concealment | MA level  MA level  34 MA for allocation concealment (283 trials), 20 MA for blinding (182 trials)  Sources: Cochrane Library, PubMed |
| Siersma et al., 200721 | Goal: To investigate the properties of multivariable meta-epidemiological analyses based on logistic regression and weighted regression models.  Biases examined:   * Sequence generation, * allocation concealment, * double blinding, * intention-to-treat | | Conditions: NS  Outcomes: Primary binary but NS | Inclusion: 167 SRs from the 1081 SRs published in The Cochrane Library selected by a computer-generated list of random numbers | Trial level  523 RCTs included in 48 MA  Source: Cochrane Library |

Table D-1. Characteristics of all included studies (continued)

| Study Identification | | Goal of Study/Approach to Controlling for Biases in Study Conduct | Conditions Evaluated/  Outcomes Reported | Inclusion/Exclusion Criteria | Unit of Analysis and Number Included  Sources Searched for Studies or MA | |
| --- | --- | --- | --- | --- | --- | --- |
| Fenwick et al., 200822 | Goal: To examine the impact of allocation concealment and assessor blinding on the size of clinical outcomes in periodontology  Biases examined:   * Allocation concealment * Assessor blinding | | Condition: periodontology  Outcomes: probing depth, and clinical or probing attachment level | Inclusion: RCTs published up to 1/2007, SRs with RCTs with outcomes of probing depth or clinical or probing attachment level, English language | RCT level  5 SRs (50 RCTs), 34 RCTs allocation concealment, 33 RCTs blinding  Sources: Cochrane library |
| Wood et al., 200823 | Goal: To examine whether the association of inadequate or unclear allocation concealment and lack of blinding with biased estimates of intervention effects varies with the nature of the intervention or outcome (objective vs. subjective measures)  Biases examined:   * Allocation concealment * Blinding * Combination of the two | | Condition: varied  Outcomes: Objectively assessed: All cause mortality, Laboratory measurement including surgical/instrumental (caesarean, instrumental delivery, epidural analgesia, manual removal of placenta), Other (birth weight, timing of delivery, hemorrhage or blood loss, non-cephalic birth, continuing lactation one week after birth, deep venous thrombosis, live birth, failed delivery, episiotomy, retention in school grade) Subjectively assessed: patient reported outcomes, physician reported | Data from 3 meta-epi studies:  Schulz et al, 1995:24 33 MA from Pregnancy and Childbirth Group of Cochrane. Each MA included at least 5 trials with a combined total of at least 25 outcome events  Kjaergard et al, 2001:8 14 MA from 11 SRs, including at least 1 trial of at least 1000 participants  Egger et al., 2003:25 122 MA from Cochrane Database of SRs that contained at least 5 randomized trials  Removed duplicate MA, retained trials that contributed to >1 MA because had >1 intervention arm or outcome. | RCT level  MA included: 146 of 169 eligible (1346 trials of 1615 eligible)  Allocation concealment: 102 MA (804 trials); Blinding: 76 MA (746 trials)  Sources: Authors of previously published meta-epidemiological studies: Schulz et al (1995):24, Kjaergard et al (2001):8, Egger et al (2003):25 |
| Hartling et al., 2009 26 | Goal: To evaluate the reliability and concurrent validity of the Cochrane risk of bias tool compared with the Jadad and Schulz approach to risk of bias assessment.  Biases examined:   * Allocation concealment * Sequence generation * Randomization * Blinding | | Condition: related to pediatric health  Outcomes: Primary but NS | Inclusion: Convenience sample of RCTs in child health. | RCT level  163 RCTs  Source: Manuscripts resulting from abstracts presented at the annual scientific meetings of the Society for Pediatric Research between 1992-1995 |

Table D-1. Characteristics of all included studies (continued)

| Study Identification | | Goal of Study/Approach to Controlling for Biases in Study Conduct | Conditions Evaluated/  Outcomes Reported | Inclusion/Exclusion Criteria | Unit of Analysis and Number Included  Sources Searched for Studies or MA | |
| --- | --- | --- | --- | --- | --- | --- |
| Inaba et al., 200927 | Goal: To evaluate differences in study design between single and multicenter trials on study outcomes. Specifically, the impact of adequate randomization and blinding of the outcome assessors.  Biases examined:   * Randomization * Blinding of outcome assessor * Disclosure of withdrawals | | Condition: heart procedures  Outcomes: mortality/ survival, impaired myocardial blush grade, incomplete ST resolution | Inclusion: RCTs, all languages, had to examine the use of adjunctive mechanical devices compared with percutaneous coronary intervention in patients with acute myocardial infarction.  Exclusion: if adjunctive mechanical devices were used in saphenous vein grafts, duplicate data from other studies, or insufficient data for MA. | Study-level without accounting for MA.  25 trials, two subgroup analyses (or MA) but the number of trials into these groups was not specified. The subgroups were based on different outcomes  Sources: Searched 9 bibliographic databases, slide and oral presentations. |
| Nuesch et al., 200928  Nuesch et al., 200929 | Goal: To evaluate the association of adequate allocation concealment and patient blinding with estimates of tx benefits in osteoarthritis trials (whether excluding patients from the analysis was associated with biased estimates of tx effects and with increased heterogeneity between trials in MAs)  Biases examined:   * Allocation concealment * Patient blinding * Attrition | | Condition: Pain in osteoarthritis of the knee or hip  Outcomes: non-binary subjective outcomes from interventions (Patient reported pain) | Inclusion: MAs of randomized or quasi-randomized trials. Trials using an unpredictable allocation sequence considered randomized, potentially predictable allocation mechanisms, such as alternation or the allocation of patients according to their date of birth considered quasi-randomized. MAs eligible if assessed patient reported pain, comparing any intervention with placebo, sham, or a non-intervention control. No language restrictions applied. | MA  Concealment: 14 MA (158 trials and 40,437 patients)  Blinding: 10 MA (122 trials and 27,452 patients)  Sources: Cochrane, PubMed, Embase and CINAHL (Within specified databases, combinations of keywords and text words related to osteoarthritis were combined with validated filters for SRs and MAs (Last update: 11/20/2007). |

Table D-1. Characteristics of all included studies (continued)

| Study Identification | | Goal of Study/Approach to Controlling for Biases in Study Conduct | Conditions Evaluated/  Outcomes Reported | Inclusion/Exclusion Criteria | Unit of Analysis and Number Included  Sources Searched for Studies or MA | |
| --- | --- | --- | --- | --- | --- | --- |
| Van Tulder et al. 2009 30 | Goal: To assess the validity of the criteria list recommended for evaluating internal validity by the Cochrane Back Review Group Editorial Board by evaluating whether individual items and a total score are associated with effect sizes in RCTs of back pain interventions.  Biases evaluated:   * method of randomization * allocation concealment * groups similar at baseline * patient, care provider, assessor blinding * effect of co-intervention * differential compliance * drop-out rate * timing of outcome assessment across groups * ITT | | Condition: Low-back pain  Outcomes: Pain, function, or similar improvement measure | Inclusion: RCT, comparison between tx and either placebo, usual care, no tx or another tx.  All Cochrane Back Review Group (CBRG) reviews of nonsurgical tx for nonspecific low back pain in the Cochrane library 2005, issue 3.  Exclusion: Data presented in such a way that effect size could not be calculated | RCT  N = 216  Comparison to placebo/tx/usual care: N = 122  Comparison to active intervention: N = 128  Some studies included both types of comparisons  Sources: Cochrane Library 2005, issue 3: all Cochrane Back Review Group reviews of a nonsurgical treatment for nonspecific low back pain. |
| Dwan et al., 201031 | Goal: To assess a SR for outcome reporting bias  Bias evaluated:   * Outcome reporting | | Condition: Acute asthma  Outcomes: Pulmonary function tests, including peak expiratory flow rate (PEFR) and forced expiratory volume in one second (FEV1), and hospital admission | Inclusion: Trials that were eligible for inclusion in the SR because they reported a measure of pulmonary function or hospital admission | RCT-level  24 trials  Sources: All studies included in the a SR concerning intravenous and nebulized magnesium sulfate for acute asthma' |

Table D-1. Characteristics of all included studies (continued)

| Study Identification | | Goal of Study/Approach to Controlling for Biases in Study Conduct | Conditions Evaluated/  Outcomes Reported | Inclusion/Exclusion Criteria | Unit of Analysis and Number Included  Sources Searched for Studies or MA | |
| --- | --- | --- | --- | --- | --- | --- |
| Hamm et al., 2010 32 | Goal: To review a sample of RCTs in the Cochrane pediatric registry and assess the validity of the results.  Biases evaluated:   * sequence generation, * allocation concealment, * blinding, * incomplete outcomes, * selective outcome reporting | | Conditions: Unspecified  Outcomes: Unspecified (primary RCT outcome) | Inclusion: Random selection of pediatric trials published in Cochrane Registry in 2007 | RCT-level  300 trials (236 analyzed)  Source: See inclusion criteria |
| Kirkham et al., 201033 | Goal: To examine the prevalence of outcome reporting bias and its impact on Cochrane reviews  Bias evaluated:   * Outcome reporting | | Condition: not specified;  Outcomes: Primary outcomes of SRs. If SR did not specify a single primary outcome, authors were contacted to select one. When no contact could be established, two investigators independently selected and agreed upon one from the outcomes listed in the SR. | Excluded: conducted by Cochrane methodology group; ill-defined primary outcome; no RCTs identified; fully reported review with primary outcomes from all included trials; multiple MAs of primary outcome; non-English; no MA; primary outcome measured in different ways; longitudinal study; studies not combined due to clinical heterogeneity  Inclusion: single MA of primary outcome; primary outcome of interest not fully reported in MA or tabulated form in at least one trial  Trial exclusion: non-English; primary outcome fully reported; primary outcome clearly not reported; unclear whether primary outcome was measured, but no suspicion of reporting bias or likely to have not been reported because of zero events | SR level  81 SRs for assessment of impact (RCTs: NR)  25 SRs for sensitivity analysis (RCTs: NR)  Sources: SRs in 3 issues of the Cochrane Library representing 50 of the 51 Cochrane Collaboration review groups: Issue 4, (2006); Issues 1 & 2 (2007). |

Table D-1. Characteristics of all included studies (continued)

| Study Identification | | Goal of Study/Approach to Controlling for Biases in Study Conduct | Conditions Evaluated/  Outcomes Reported | Inclusion/Exclusion Criteria | Unit of Analysis and Included  Sources Searched for Studies or MA | |
| --- | --- | --- | --- | --- | --- | --- |
| Hartling et al., 201134 | Goal: To evaluate the relationship between risk of bias and effect estimates in RCTs and to examine differences when unclear RoB is grouped with low RoB and when it is grouped with high RoB  Biases examined:   * Sequence generation * Allocation concealment * Blinding * Incomplete data * Selective reporting | | Conditions: Adults with persistent asthma  Outcomes: Forced expiratory volume in 1 second (FEV1) | Inclusion: RCTs included in a SR of combination long-acting beta-agonists and inhaled corticosteroids for maintenance therapy in persistent asthma. | RCT level  107 RCTs  Sources: electronic databases and grey literature |

Table D-1. Characteristics of all included studies (continued)

| Study Identification | | Goal of Study/Approach to Controlling for Biases in Study Conduct | Conditions Evaluated/  Outcomes Reported | Inclusion/Exclusion Criteria | Unit of Analysis and Included  Sources Searched for Studies or MA | |
| --- | --- | --- | --- | --- | --- | --- |
| Hempel et al., 2012 35, 2011 36 | Goal: to examine the empirical evidence for associations between a set of proposed quality criteria and estimates of effect sizes in RCTs using multiple datasets representing a variety of clinical fields and to explore variables potentially influencing the association (effect moderators or confounders); specifically, whether (1) the overall size of the observed treatment effect, (2) the condition being treated, (3) the type of outcome, and (4) the variance in effect sizes across studies moderates or confounds the association between quality and effect sizes.  Biases examined   * Randomization (sequence generation and allocation concealment) * Assessor blinding * Patient blinding * Care provider blinding * Similar co-interventions/ compliance/timing * Drop-out rate | | Conditions: Various including back pain, complementary and alternative medicine, mental health (Alzheimer’s, obsessive compulsive-disorder), diabetes, digestive diseases, pregnancy and childbirth, and infectious diseases.  Outcomes: Mostly continuous but some categorical such as death, pregnancy | Include: RCTs from four different data sets that contained MA.  Exclude: SRs that did not contain MA | RCT level  481 studies |
| Herbison 201137 Herbison 200638 | Goal: To determine how much bias is associated with different methods of tx allocation concealment (grouped into 6 categories).  Bias examined:   * Allocation concealment | | Condition: Not limited by condition  Outcome: Any binary outcome | Inclusion: SRs with binary outcomes, at least 10 included trials, and at least one trial with more than 500 people randomized to each arm. | Meta-analysis  65 MAs from 18 SRs; 389 studies  Source: Issue 1 (2001) of Cochrane Library |

Table D-1. Characteristics of all included studies (continued)

| Study Identification | | Goal of Study/Approach to Controlling for Biases in Study Conduct | Conditions Evaluated/  Outcomes Reported | Inclusion/Exclusion Criteria | Unit of Analysis and Included  Sources Searched for Studies or MA | |
| --- | --- | --- | --- | --- | --- | --- |
| Liu, LaValley & Latham, 201139 | Goal: To determine the differential effects of progressive resistance strength training on lower limb muscle strength in older adults between RCTs that used blinded outcome assessors and those that did not. As a further step, to determine the influence of ITT analysis while estimating the effect of blinding  Bias examined:   * Blinding | | Condition: Not limited by condition;  Outcome: Continuous outcome measuring lower limb muscle strength | Include: Must measure lower limb muscle strength, participants ≥60 years of age, progressive resistance training was main intervention | RCT level  73 studies |
| Hartling et al., 2012 3 | Goal: To assess the reliability of the Cochrane ROB tool for RCTs and the Newcastle-Ottawa Scale (NOS) for cohort studies between individual raters, and between consensus agreements of individual raters for the ROB tool; assess the validity of the Cochrane ROB tool and NOS by examining the association between study quality and treatment effect size; examine the impact of study-level factors (e.g., outcomes, interventions and conditions) on scale reliability and validity.  Bias examined:   * randomization * allocation concealment * double blinding * Selective outcome reporting * Attrition | | Conditions: Varied across studies. The most frequently represented categories were circulatory and respiratory health (18 percent), nutrition, metabolism, and diabetes (17 percent), and musculoskeletal health and arthritis (15 percent). The primary outcomes were objective in 48 percent of trials and subjective in 52 percent. Source of outcome assessment was primarily by clinician (35 percent), laboratory measure (23 percent), or self-report (23 percent).  Outcomes: 1) Objective include all cause mortality, measures based on a recognized laboratory procedure, surgical or instrumental outcomes and other objective measures.  2) Subjective include patient reported, physician assessed disease outcomes, measures combined from several outcomes, and withdrawals or study dropouts. | Inclusion: RCTs elected from previous study by Hopewell 2010 and selected random sample (154/ 616) representing approximately 25% of the original trials. | RCT level  154 studies  Source: previous study by Hopewell 2010 |

Table D-1. Characteristics of all included studies (continued)

| Study Identification | | Goal of Study/Approach to Controlling for Biases in Study Conduct | Conditions Evaluated/  Outcomes Reported | Inclusion/Exclusion Criteria | Unit of Analysis and Included  Sources Searched for Studies or MA | |
| --- | --- | --- | --- | --- | --- | --- |
| Hrobjartsson et al., 2012 40 | Goal: To review RCTs with blinded and non-blinded assessors of binary outcomes to evaluate the impact of non-blinded outcome assessment on estimated treatment effects and to examine reasons for the variation.  Bias examined:   * Assessor blinding | | Condition: Not searched in relation to specific conditions but included general surgery, orthopedic surgery, plastic surgery, cardiology, gynecology, anesthesiology, neurology, psychiatry, dermatology, otolaryngology, infectious diseases, and ophthalmology.  Outcome: One, primary, binary outcome from each RCT. | Inclusion: RCT, blinded and non-blinded assessment of the same binary outcome, if more than one outcome met criteria, the primary outcome was chosen.  Exclude: 1) Unclear which group was experimental and which control, 2) only a subgroup of patients evaluated by blinded and non-blinded assessors, unless they were selected at random, 3) blinded and non-blinded assessors had access to each other's results (e.g., blinded assessments were provided to non-blinded assessors as a quality enhancement procedure), 4) initially blinded assessors clearly had become unblinded, 5) blinded end point committees adjudicating the assessments made by non-blinded clinicians because such adjudication often involved previous knowledge of the non-blinded assessment or is restricted to adjudication of events only. | RCT level  25 RCTs included and of these, 21 RCTs analyzed  Searched: PubMed, Embase, PsycINFO, CINAHL, Cochrane Register of Controlled Trials, full text databases (High Wire Press and Google Scholar). Last search: January 26, 2010 |

Table D-1. Characteristics of all included studies (continued)

| Study Identification | | Goal of Study/Approach to Controlling for Biases in Study Conduct | Conditions Evaluated/  Outcomes Reported | Inclusion/Exclusion Criteria | Unit of Analysis and Included  Sources Searched for Studies or MA | |
| --- | --- | --- | --- | --- | --- | --- |
| Mhaskar et al., 2012 41 | Goal: To assess whether the reported methodological quality of RCTs reflects the actual methodological quality and to evaluate the association of effect size and sample size with methodological quality  Biases examined:   * Selective outcome reporting: * generation of randomization sequence * allocation concealment * intention-to-treat and description of dropouts * description of blinding procedures and appropriate statistical methods | | Conditions: Cancer trials  Outcomes: Survival | Inclusion: All National Cancer Institute sponsored Cooperative Group trials between 1968 and 2006 with protocols and publications available with unique RCTs. | RCT level  429 RCTs  Search: eight National Cancer Institute (NCI) sponsored Cooperative Groups (COG) |
| Savovic et al., 2012 42; Savovic et al., 43 | Goal: To combine trials and MAs across databases from previous meta-epidemiological studies and assess the impact of 3 different types of biases.  Bias examined:   * sequence generation, * allocation concealment, * double blinding | | Conditions: 8 clinical areas based on the ICD-10-CM coding: Pregnancy and Childbirth, Mental and Behavioral Health, Circulatory System, Digestive System, Other factors (factors influencing health status and contact with health services), Respiratory System, Other ICD-10, Unclassified  Outcomes: All cause mortality; Other objective; Objective but influenced by clinician judgment; Subjective; Mixture of objective and subjective | Data from 10 earlier meta-epidemiological studies combined into one database:  1) Als-Nielson et al., 2004,44 Siersma et al., 200745  2) Balk et al., 20029  3) Contopoulos-Ionnidis et al., 200546  4) Egger et al., 200313  5) Kjaergard, Villumsen, and Gluud; 20018  6) McAuley et al., 2000  7) Pildal et al., 200720  8) Royle, 2003  9) Sampson et al., 2003  10) Schulz et al., 19951 | MA level  234 MA, including 1793 trials (not all MA or RCTs used for all analyses)  Sources: see inclusion criteria |

Abbreviations: BMJ = British Medical Journal; CAM = complementary and alternative medicine; ITT = intent to treat; MA = meta-analysis; N = number; NEJM=New England Journal of Medicine; NR = not reported; ob/gyn: obstetrics and gynecology; RCT = randomized controlled trial; ROB = risk of bias; SR = systematic review; tx = treatment