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[Intervention Protocol]

Pre-emptive versus non pre-emptive kidney transplantation for end-stage kidney disease

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

This review aims to look at the benefits and harms of pre-emptive kidney transplantation compared with kidney transplantation after dialysis for patients with ESKD.

BACKGROUND

Description of the condition

People with end-stage kidney disease (ESKD) require renal replacement therapy (RRT), either as dialysis or kidney transplantation. Most people prefer kidney transplantation over dialysis, because it is seen as generally prolonging their life and substantially improving its quality.

It is estimated that each year 80,000 kidney transplants are performed around the world (Tong 2017). Despite the possibility of living donor kidney transplantation, organ demand far exceeds organ availability worldwide, and the number of patients listed for kidney transplantation continues to rise (ANZDATA 2016; Branger 2015; ERA-EDTA 2017; OPTN/SRTR 2012). In 2016, close to 100,000 people were waiting for a donor kidney in the USA alone.

Description of the intervention

Most transplant physicians consider pre-emptive transplantation - before dialysis initiation - the best option for the individual patient. First, it avoids the reduction in quality of life associated with dialysis (Howell 2012; Tong 2017). Second, several registry-based studies have suggested that indeed those receiving a donor kidney pre-emptively have better patient and graft survival than those being transplanted after having started dialysis (Abramowicz 2016). However, such observational data carry an important risk of bias.

In addition, the optimal timing of pre-emptive transplantation remains controversial and increased pre-emptive listing may increase the waiting time for those patients already established on dialysis. The rates of pre-emptive transplantation reported in these registry-based studies vary depending on the country and on the population. In studies of adults, the reported rates ranged between 2.3% in a US-based study (including both deceased and living donors) (Pradel 2008) to 22% in a study of transplantation in Australia and New Zealand (all from living donors) (Milton 2008). In paediatric populations, the frequency of pre-emptive transplantation ranged between 14% for the Eurotransplant area (8% for cadaveric donors and 39% for living donors; The Eurotransplant area covers Austria, Belgium, Germany, Luxembourg, The Netherlands and Slovenia) (Cransberg 2006) to 28% in the USA (18% for cadaveric donors and 35% for living donors) (Butani 2011).

How the intervention might work

Chronic dialysis patients generally consider their quality of life to be substantially better after transplantation. Many are able to resume their professional activities, family and social lives improve, and energy levels increase (Howell 2012; Malone 2017; Tong 2017). In addition, dialysis requires creation of a vascular access, and often repeated interventions to maintain its function (Abramowicz 2016; Pradel 2008).

The average survival after kidney transplantation is better than on dialysis. More than half the deaths among adults treated with dialysis are caused by cardiovascular disease; dialysis is often implicated as the main contributor (Foley 2005; Goodman 2000; Kutner 2012). Hence, avoiding dialysis altogether may explain why pre-emptive kidney transplant recipients live longer and possibly have better graft outcome too. For children, dialysis is associated with poor growth and impaired neurocognitive development (Butani 2011; Cransberg 2006).

Yet, one could think of mechanisms causing a decrease rather than improvement in outcome. Patients who have experienced the hardships of dialysis may value transplantation more and adhere more closely to anti-rejection therapy (Cransberg 2000; Dobbels 2005; Pradel 2008). In addition, the earlier the transplant, the longer the exposure to immunosuppressive medications, with subsequent increased risk of infection and cancer (Butani 2011; Vajdic 2006; Webster 2007).

Why it is important to do this review

The ERA-EDTA Descartes working group and European Renal Best Practice (ERBP) conducted a systematic review in 2016 to assess whether pre-emptive kidney transplantation versus transplantation after having started dialysis improves outcomes for recipients of kidneys from living donors (Abramowicz 2016). The working group recommended that programmes for pre-emptive transplantation with living donor kidneys should be encouraged. Although they classified this recommendation as strong, they considered that the certainty of the evidence to be very low (Abramowicz 2016).

Their review process identified only cohort studies, all registry-based and frequently relying on transplant registries. With transplant registries, the follow-up starts at transplantation and the period under dialysis is not accounted for. Consequently, there is differential follow-up between the group being transplanted pre-emptively, where start of treatment matches the start of follow-up, and the group being transplanted after having started dialysis, where follow-up starts after treatment onset. This results in lead-time bias (Hernan 2016). Moreover, people who receive a kidney pre-emptively tend to be healthier, less anaemic, and better fed; they have better residual kidney function, and fewer cardiovascular co-morbidities, resulting in selection bias, possibly explaining the seemingly improved results after transplantation (Abramowicz 2016; Cransberg 2000; Goldfarb-Rumyantzev 2005; Kutner 2012). Therefore, the current review aims to identify and assess the methods used to address the potential benefit of pre-emptive kidney transplantation and the quality of evidence provided for decision making to highlight limitations in the approaches currently used.

The ultimate aim of our review is to determine whether the individual patient with ESKD set to undergo transplantation benefits from being transplanted before dialysis is initiated. It will expand the scope of the review conducted by the ERA-EDTA Descartes working group and ERBP in order to include both living and deceased donors, as both scenarios are encountered in daily practice. Even if the individual benefits from pre-emptive kidney transplantation, we acknowledge there may be barriers for implementation of this strategy within the societal context of organ shortage; further research will be needed to assess the effect that such a change may have for the waiting list and how to optimise current allocation algorithms to safeguard equity. This is beyond the scope of this review.

OBJECTIVES

This review aims to look at the benefits and harms of pre-emptive kidney transplantation compared with kidney transplantation after dialysis for patients with ESKD.

METHODS

Criteria for considering studies for this review

Types of studies

Eligible for the review are all randomised controlled trials (RCTs), quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) and cohort studies that compared pre-emptive kidney transplantation with transplantation after having started dialysis in people eligible for transplantation.

Although we are aiming to include RCTs, we do not expect them to exist. The choice between pre-emptive transplantation and transplantation after having started dialysis is mainly driven by the local allocation algorithm, in case of deceased donation, which considers factors such as time on the waiting list. For living donation, scheduling of the procedure depends on the time required to assess suitability of potential living donors. A recipient with a suitable donor already identified would probably prefer to undergo transplantation instead of giving consent for a trial that could delay the procedure. This makes it unlikely that RCTs will have been performed. In addition, the systematic review by the ERA-EDTA Descartes working group and ERBP only identified observational studies.

We will only include studies published after 1990, as we consider earlier studies to be outdated in terms of current practice in surgical techniques and immunosuppressive therapy (Abramowicz 2016). There will be no restrictions regarding the language of the study.

Types of participants

Inclusion criteria

All people of any age (both children and adults) eligible for kidney transplantation, regardless of underlying kidney disease, of type of dialysis received, if any, or whether they have history of previous kidney transplantation. We anticipate a wide variation of patients considered suitable for transplant depending on local centre policy.

Exclusion criteria

Patients eligible for, or with a history of, organ transplantation other than kidney.

Types of interventions

Intervention

Pre-emptive kidney transplantation: transplantation before having started chronic haemodialysis (HD) or peritoneal dialysis (PD), as defined by the authors. No restriction will be made regarding the baseline GFR at transplantation.

Comparator

Transplantation after having started chronic HD or PD. There will be no restrictions on dialysis modality (home HD, in-centre HD, night-time, daily) or duration of dialysis (dialysis vintage). Even though both living and deceased donors will be included, the comparison will be performed separately for each donor type. No restriction will be made for donors with brain death or circulatory death.

Types of outcome measures

The domain and outcomes selected follow the core outcome set for kidney transplantation as specified by the Standardised Outcomes in Nephrology for transplantation (SONG-Tx) (SONG 2017).

Primary outcomes

Death (all causes) for the follow-up available in the study and point estimates at one, five and 10 years after transplant.

Secondary outcomes

Table 1. Secondary outcomes

Domain	Dimension	Dimension	Type	Time point
Graft health	Graft survival	Graft loss (death, requiring RRT)	Dichotomous	1, 5 and 10 years after transplant
	Death-censored graft survival	Graft loss (requiring RRT)	Dichotomous	1, 5 and 10 years after transplant
	Kidney function	eGFR	Continuous	1, 5 and 10 years after transplant

(*Continued*)

		CrCl	Continuous	1, 5 and 10 years after transplant
Life participation	Quality of life	Any scale reported by authors (e.g. SF-36, EQ-5D)	Continuous	1, 5 and 10 years after transplant
Cardiovascular disease	Cardiovascular disease incidence	Incidence	Dichotomous	1, 5 and 10 years after transplant
Cancer	Cancer incidence	Incidence	Dichotomous	1, 5 and 10 years after transplant
Infection	Infection incidence	Incidence	Dichotomous	1, 5 and 10 years after transplant

eGFR - estimated glomerular filtration rate; CrCl - creatinine clearance; RRT - renal replacement therapy

Table 1 shows the secondary outcomes. There are likely to be some studies in which graft failure is defined as return to dialysis or re-transplantation and others that consider it to be a composite outcome that includes both these events and death. For those studies that do not consider death as graft failure, graft failure and death are competing risks. Whenever possible both death-censored graft survival and graft failure including death will be provided.

Search methods for identification of studies

Electronic searches

We will search the Cochrane Kidney and Transplant Specialised Register through contact with the Information Specialist using search terms relevant to this review. The Specialised Register contains studies identified from the following sources:

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about Cochrane Kidney and Transplant.

For non-randomised studies, MEDLINE (OVID) and EMBASE (OVID) will be searched.

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete trials to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The search strategy described will be used to obtain titles and abstracts of studies that may be relevant to the review. The titles and abstracts will be screened independently by two authors, who will discard studies that are not applicable; however studies and reviews that might include relevant data or information on trials will be retained initially. Two authors will independently assess retrieved abstracts and, if necessary the full text, of these studies to determine which studies satisfy the inclusion criteria.

Data extraction and management

Data extraction will be carried out independently by two authors using standardized data extraction forms. Studies reported in non-English language journals will be translated before assessment. Where more than one publication of one study exists, reports will be grouped together and the publication with the most complete data will be used in the analyses. Where relevant outcomes are only published in earlier versions these data will be used. Any discrepancy between published versions will be highlighted.

Assessment of risk of bias in included studies

Randomised studies

The following items will be independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
    - Participants and personnel (performance bias)
    - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Non-randomised studies

Non-randomised studies will be assessed using the Risk of Bias in Non-Randomised Studies of Interventions (ROBINS-I) tool (Sterne 2016a). The tool assesses risk of bias in 7 domains (confounding, selection into the study, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result) according to signalling questions that encompass issues before, during and after the intervention (Sterne 2016a) (see Appendix 3).

To apply the tool, a target hypothetical trial is specified against which the non-randomised study is compared. An ideal hypothetical RCT for this review is a clinical trial that randomises patients eligible for kidney transplantation to either pre-emptive transplantation or to a period of dialysis (haemodialysis or peritoneal dialysis at the discretion of the treating clinician) followed by transplantation; and then follows patients from randomisation. Periodic data regarding kidney function, graft failure and death would be recorded. Data analysis would be conducted according to intention-to-treat principles.

Two of the domains of ROBINS-I require pre-specification of important confounders and co-interventions. The confounders and co-interventions that we consider to be both potentially related to the intervention and are prognostic for mortality are listed in Table 2 (Foley 2005; KDIGO 2013; Kutner 2012).

Table 2. Confounders and co-interventions considered prognostic for death

Confounders	Co-interventions
• Age • Gender • Race • Cause of kidney disease • Baseline kidney function • Diabetes • Hypertension • Socio-economic status • Level of HLA sensitisation	Immunosuppression therapy

HLA - human leukocyte antigen

To apply the ROBINS-I tool, two authors will independently answer the signalling questions to grade each of the seven domains and give an overall risk of bias for each study (Sterne 2016a) (see Appendix 3). Any disagreements will be discussed to reach a consensus and a third author will be consulted if necessary. The bias assessment for each study, including their specific target trial, risk of bias for each separate domain and the overall risk of bias, will be presented in the final report of the review.

Measures of treatment effect

For dichotomous outcomes (e.g. death and graft failure after one, five and 10 years of transplantation) results will be expressed as risk ratios (RR) with 95% confidence intervals (CI). Where continuous scales of measurement are used to assess the effects of treatment (e.g. kidney function and quality of life after one, five and 10 years of transplantation), the mean difference (MD) will be used, or the standardised mean difference (SMD) if different scales have been used.

For time-to-event outcomes (e.g. time to death and/or graft failure for the available follow-up in the study) results will be expressed as a hazard ratio (HR) with 95% CI. In case that HR and/or CI are not reported, the methods developed by Parmar 1998 and Williamson 1998 will be used to extract the relevant information for estimating them whenever possible.

It is worth noting that these methods were developed for RCTs, where confounding is not a major concern given that the treatment is assigned randomly. As this is not the case for observational studies, adjusting for confounding factors becomes crucial for the causal effect estimate. When the study provides both crude and adjusted treatment effect estimates, both will be included, as they will shed light on any confounder bias.

Differences in the causal effect estimate can arise when assessing different populations, as the joint distribution of their covariates may vary. Moreover, differences can be seen when adjusting for different subsets of confounders and/or using different adjusting methods. Therefore the marginal effect measured is expected to differ if the covariates adjusted for differ or different approaches of dealing with confounding are used, for instance when dealing with time-varying confounding. If and when possible, we would aim to generate directly standardized risks referring to a common underlying confounder distribution at baseline, following the list of the minimum set of confounders previously presented (Table 2). In any case, the adjusted estimate will be preferred over the crude estimate and we will have to rely on the choice of covariates and methods for adjustment chosen by the authors and aim to be explicit what the adjusted effect is exactly measuring.

When HR change over time, it is inappropriate to report an average HR, as the estimate would depend on the time of follow-up (Hernan 2010). Therefore, if the proportional hazards assumption is violated, the follow-up will be divided into epochs to make an average estimate of the HR within epochs.

Unit of analysis issues

Non-standard designs are not expected for this review.

Dealing with missing data

Any further information required from the original author will be requested by written correspondence (e.g. emailing corresponding author) and any relevant information obtained in this manner will be included in the review. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat, as-treated and per-protocol population will be carefully performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals will be investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward) will be critically appraised (Higgins 2011).

Assessment of heterogeneity

We will first assess the heterogeneity by visual inspection of the forest plot. We will quantify statistical heterogeneity using the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than sampling error (Higgins 2003).

The importance of the observed value of I^2 depends on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (e.g. P-value from the Chi^2 test, or a confidence interval for I^2) (Higgins 2011).

Assessment of reporting biases

If possible, funnel plots will be used to assess for the potential existence of small study bias (Higgins 2011).

Data synthesis

We will report our findings separately by donor source (living versus cadaveric). If we consider that the studies are similar in terms of participants, interventions, comparators and outcomes then a meta-analysis will be performed. Data will be combined across studies using the random-effects model considering that the intervention effect is not the same for all studies but rather follows a distribution across the studies. However, the fixed-effect model will also be used to ensure robustness of results to the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses will be performed to explore possible sources of heterogeneity (e.g. RCT versus non-RCT, adult versus children). Crude versus adjusted estimates and the nature of covariates adjusted for will also be compared, given that they could vary from study to study. Heterogeneity in treatment effects could be related to previous type of dialysis (for those in the transplantation after dialysis arm) and duration of dialysis (for both groups, as there could be differences in definitions of pre-emptive kidney transplantation between studies, allowing for short-term dialysis versus no time in dialysis at all). Differences may also arise from different starting points of follow-up (date of transplantation in both groups versus onset of dialysis in the dialysis followed by transplantation arm), the duration of the follow-up (particularly if there are

time-varying hazards), inclusion criteria for transplant recipients, quality of the study and adjusting for different confounding factors. Additional sources of heterogeneity include differences in the population in terms of covariates (e.g. age and underlying kidney disease) and organ availability in the setting where the study was carried out.

Sensitivity analysis

We will perform sensitivity analyses to explore the robustness of the findings to the following factors:

- Repeating the analysis excluding unpublished studies
- Repeating the analysis taking account of risk of bias, excluding RCTs with high risk of bias or non-randomised studies with serious or critical risk of bias
- Repeating the analysis excluding any very long or large studies to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), and country
- Repeating the analysis excluding studies that differ in the choice of covariates on which they adjusted for, taking into account the most frequent covariates that studies include as confounders as the minimum required.

'Summary of findings' tables

We will present the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schünemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008; GRADE 2011). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schünemann 2011b).
A 'Summary of findings' table will be presented for each of the outcomes assessed (death (all causes), graft survival, death-censored graft survival, kidney function and quality of life), separating by type of donor (deceased versus living donor).

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor: [Kidney Transplantation] this term only 2. kidney transplant*:ti,ab,kw (Word variations have been searched) 3. {or #1-#2} 4. preemptive:ti,ab,kw (Word variations have been searched) 5. pre-emptive:ti,ab,kw (Word variations have been searched) 6. {or #4-#5} 7. {and #3, #6}
MEDLINE	1. exp Kidney Transplantation/ 2. (pre-emptive or preemptive).tw. 3. "prior to dialysis".tw. 4. (prior adj3 dialysis).tw. 5. (before adj4 dialysis).tw. 6. "transplant$ before dialysis".tw. 7. (post adj start adj2 dialysis).tw. 8. or/2-7

(*Continued*)

	9. and/1,8
EMBASE	1. exp kidney transplantation/ 2. (pre-emptive or preemptive).tw. 3. "prior to dialysis".tw. 4. (prior adj3 dialysis).tw. 5. (before adj4 dialysis).tw. 6. "transplant$ before dialysis".tw. 7. (post adj start adj2 dialysis).tw. 8. or/2-7 9. and/1,8

Appendix 2. Risk of bias assessment tool for RCT

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation (minimisation may be implemented without a random element, and this is considered to be equivalent to being random)
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention
	Unclear: Insufficient information about the sequence generation process to permit judgement
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes)
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure

(*Continued*)

	Unclear: Randomisation stated but no information on method used is available
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plau-

(*Continued*)

	sible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. sub-scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias

Appendix 3. Risk of bias assessment tool for non-randomised studies

Overall risk of bias assessment using ROBINS-I tool (Sterne 2016b)

Bias assessment	Criteria
Low risk of bias	The study is comparable to a well-performed randomised trial
Moderate risk of bias	The study provides sound evidence for a non-randomised study but cannot be considered comparable to a well-performed randomised trial
Serious risk of bias	The study has some important problems
Critical risk of bias	The study is too problematic to provide any useful evidence and should not be included in any synthesis
No information	No information on which to base a judgement about risk of bias

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: COP, EN, AM, RE, JH, EG
2. Study selection: COP, CVdB, EN
3. Extract data from studies: COP, CVdB, LW
4. Enter data into RevMan: COP
5. Carry out the analysis: COP, AM, RE
6. Interpret the analysis: COP, EN, AM, RE, JH, EG
7. Draft the final review: COP, CVdB, LW, EN, AM, RE, JH, EG
8. Disagreement resolution: EN, JH
9. Update the review: COP

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External sources

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