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[Intervention Protocol]

Exercise training for adult kidney transplant recipients

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ABSTRACT

Objectives

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

This review aims:

1. To assess the benefits and harms of regular physical activity interventions in adult kidney transplant recipients when compared with any other or no intervention.
2. To determine whether benefits and harms vary in absolute or relative terms dependent on specific characteristics of the physical activity intervention (i.e. frequency, intensity, type, time, volume, progression and pattern of the intervention).
3. To determine whether benefits and harms vary in absolute or relative terms dependent on specific characteristics of the participants studied (i.e. the influence of age and underlying kidney disease).

BACKGROUND

Description of the condition

Chronic kidney disease (CKD) has a prevalence of around 10% in the general population (Jager 2017). Well before people reach kidney failure, the effects of CKD affect health, well-being and physical function (Platinga 2011). Physical function, measured as aerobic capacity, muscular strength, endurance and balance, gradually deteriorates as kidney function declines and reaches 50% to 60% of the expected norm in patients on maintenance dialysis (Clyne 1994; Painter 1986). Predominant causes for this deterioration are conditions inherent to uremia per se, such as renal anaemia, tiredness, lack of energy, metabolic acidosis and loss of appetite, which contribute to loss of skeletal muscle and myopathy as well as imbalances in calcium homeostasis which affect muscle and bone (Clyne 1994; Fahal 2014). Cardiovascular disease is common and accelerated in these patients contributing to the deconditioned state.

Kidney transplantation is the treatment of choice for kidney failure. A successful kidney transplant reverses some of these conditions, but not all, as the transplanted patient "inherits" many of the long-term effects of CKD, notably muscle wasting and dysfunction and cardiovascular morbidity (Jardine 2011; Nielens 2001). Moreover, kidney transplant recipients are treated with corticosteroids and other immune-modulating agents, such as calcineurin inhibitors (CNIs), which also have detrimental effects on skeletal muscle, bone, cardiovascular and metabolic health (Bouquegneau 2016; Halloran 2004). The fact that these key immunosuppressive agents aggravate the existing risk profile emphasizes the need for patients to remain physically active to counteract these effects.

Description of the intervention

Physical activity is defined as any type of bodily movement produced by skeletal muscles that increase energy expenditure above that at rest and includes structured exercise. It has the intention of improving physical health outcomes that contribute to optimal life participation opportunities and health-related quality of life (HRQoL) (Warburton 2019). Patients should be encouraged to spend less time sitting and take any opportunity to move throughout the day (Booth 2017; Bull 2020). Simple activities such as walking, climbing stairs, housework or gardening and stretching can make a difference by counterbalancing some of the risks of being sedentary (Fletcher 2018). By simply increasing the amount and intensity of physical activity gradually over time, patients can perform their daily tasks more easily, gain various physiological adaptations and improve their health status and QoL (Bull 2020).

Structured exercise is a subset of physical activity that is planned, structured and repetitive, done to improve or maintain one or more of the components of physical fitness definitions according to the American College of Sports Medicine (ACSM) position stand (ACSM 2011). Exercise training comprises a number of interventions, such as aerobic, strength, and flexibility exercises (Bull 2020).

How the intervention might work

In the general adult population, the health benefits of physical activity interventions include reductions in the lifetime risk of cardiovascular disease and cancer, as well as beneficial effects on metabolic, muscular, bone, digestive, reproductive, and mental health (Kerr 2017; McTiernan 2019; Sattelmair 2011; Warburton 2006). Both an acute bout of exercise and training interventions positively affect all organ systems in the body (McGee 2020). If relative benefits found in the general population can be extrapolated to those with a functioning kidney graft, then expected gains are likely to be high.

Exercise training might benefit kidney transplant recipients through various mechanisms. Physical activity modifies both traditional and non-traditional risk factors, such as chronic low-grade inflammation and oxidative stress, and causes shear-stress-induced adaptations of the cardiovascular system (Gielen 2010; Van Craenenbroeck 2014). In theory, such changes may translate into improved cardiac autonomic function, better blood pressure regulation and fewer cardiovascular events. Given the particularly high cardiovascular risk for kidney transplant recipients, any relative treatment effect in the general population may likely result in greater absolute risk reduction in this patient group.

From an immunological point of view, presently, little is known about the effects of exercise on a suppressed immune system, except for the fact that moderate- to high-intensity aerobic exercise training is considered to be safe in kidney transplantation as it does not cause aberrant immune cell activation (Highton 2020). Additionally, skeletal muscle dysfunction and wasting may be reversed or halted in response to exercise, possibly due to improvement in pathways involved in protein-energy wasting (Carrero 2013).

As many patients remain deconditioned after transplantation, regaining physical function after breaking the vicious circle of a sedentary lifestyle likely adds to a better HRQoL.

Why it is important to do this review

Kidney transplantation generally offers patients an improvement in survival and HRQoL compared with remaining on dialysis. Yet, life expectancy for kidney transplant recipients continues to be far below that of the general population, with cardiovascular disease being the predominant cause of premature death (Methven 2017; Saran 2018; Zelle 2011).

Levels of physical activity and physical function remain surprisingly low after kidney transplantation and may contribute to more deaths (Zelle 2017). During the past decade, several randomised controlled trials (RCTs) have indicated that exercise training not only increases physical function but also can improve cardiovascular fitness in kidney transplant recipients (Kouidi 2013). Effects on other outcomes have been less clear (Calella 2019, Chen 2019).

Patients themselves have identified physical activity and exercise training as a priority topic for research (Tong 2017). A previous Cochrane review (Heiwe 2011) identified three studies conducted in kidney transplant recipients. The publication of at least 10 new studies since that search in May 2010 justifies a separate review.

OBJECTIVES

This review aims:

1. To assess the benefits and harms of regular physical activity interventions in adult kidney transplant recipients when compared with any other or no intervention.

2. To determine whether benefits and harms vary in absolute or relative terms dependent on specific characteristics of the physical activity intervention (i.e. frequency, intensity, type, time, volume, progression and pattern of the intervention).
3. To determine whether benefits and harms vary in absolute or relative terms dependent on specific characteristics of the participants studied (i.e. the influence of age and underlying kidney disease).

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) looking at physical activity interventions in adult kidney transplant recipients will be included. The first period of randomised cross-over studies and outcomes recorded that first period will also be included.

Types of participants

Studies involving adult (male or female, 18 years of age or older) recipients of a donor kidney will be included. We will include participants who receive treatment at the time of transplantation and those who receive treatment at any time during the post-transplantation period. Graft function may be variable, but participants with a failed kidney transplant on maintenance dialysis (CKD5D) will be excluded. Recipients of any transplanted organ other than a kidney will be excluded (multi-organ transplant recipients).

Types of interventions

Physical activity interventions for health benefits, which include structured exercise interventions, are defined as any prescription of physical activity or exercise to be followed regularly. The included physical activity interventions will have to report on one or more of the following FITT criteria:

- **F**requency: defined as the number of sessions/week
- **I**ntensity: specific information relevant to the participant's fitness using any indices of the percentage of maximal heart rate (HR max) or HR reserve, or of measured or estimated VO_2 peak, or percentage of submaximal exercise tolerance indices such as lactate threshold or of stepping pace. Borg rate of perceived exertion (RPE) can also be used as a subjective but reliable scale to monitor and guide exercise intensity
- **T**ype: any aerobic, strength and flexibility exercises or regular physical activity prescriptions or any combination of these. Interventions will have to be monitored (either by participants or other defined personnel), supervised (either by participants or other defined personnel), and delivered either in the participants' lived environment or other specified research or community setting and can be individual or group based or both
- **T**ime: duration of the prescribed intervention.

All FITT components will be used to estimate a total volume of prescribed and achieved dose of intervention, expressed either as minutes of exercise/week or Kcal spent on physical activity/week or the number of steps/week. In addition, information regarding adherence (number of sessions completed versus prescribed) to the physical activity prescription will be recorded when available to assess the overall volume of the intervention delivered.

We will include studies comparing physical interventions with any other or no intervention.

Types of outcome measures

This review will not exclude studies based on non-reporting of outcomes of interest. The outcomes selected include the relevant SONG core outcome sets as specified by the Standardised Outcomes in Nephrology initiative (SONG 2017).

Primary outcomes

1. Death (any cause)
2. Cardiovascular death
3. Graft loss
4. HRQoL: as assessed by the SF-36 questionnaire or any other used by the investigator
5. Physical fitness:
   a. Aerobic capacity: measured or estimated VO_2 peak (expressed in mL/min/kg), but also VO_2 max or maximal metabolic equivalent of tasks (METs)
   b. Muscular strength: maximal isokinetic and isometric muscle strength, five repetition maximum or peak torque or one repetition maximum when five repetition maximum is not reported, handgrip strength
   c. Muscular endurance: peak power output (expressed in Watts) or maximal exercise duration, sit-to-stand in 60 seconds, 8-foot up-and-go test
6. Physical function
   a. Walking capacity: 6-minute walking test (6MWT), gait speed (m/sec)
   b. Activities of daily life capacity: physical component summary score (PCS) from all versions and variations of the SF-36 questionnaire (expressed in arbitrary units), but also leisure time physical activity participation (expressed in frequency/week, total time/week, kcal/week, MET-MIN/week) as well as functional dependency scores form ADL questionnaires if PCS is not available
7. Exercise-induced injury

Secondary outcomes

1. Graft function: measured glomerular filtration rate (mGFR), estimated GFR (eGFR), serum creatinine (SCr)
2. Nonfatal stroke
3. Nonfatal myocardial events
4. Hospital admission (any cause)
5. Cancer: any type of solid organ or blood cancer
6. Risk modifiers of cardiovascular disease: hyperlipidaemia, diabetes, obesity as estimated by body mass index (BMI) (kg/m^2) or waist circumference (in cm), hypertension, endothelial dysfunction, arterial stiffness, cardiac autonomic dysfunction or sympathetic overactivity
7. Nutritional status: body composition (measured using bioimpedance or DEXA), expressed as fat-free mass (in kg and as % of whole body mass), fat mass (kg and % of whole body

mass), muscle mass (in kg and as % of whole body mass), plasma albumin, subjective global assessment (SGA)
8. Any infection
9. Adherence to the described intervention

Search methods for identification of studies

Electronic searches

We will search the Cochrane Kidney and Transplant Register of Studies through contact with the Information Specialist using search terms relevant to this review. The 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. Searches of kidney and transplant journals and the proceedings and abstracts from major kidney and transplant conferences
4. Searching 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 Register are identified through searches of CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of search strategies, as well as a list of hand-searched journals, conference proceedings and current awareness alerts, are available on the Cochrane Kidney and Transplant website under CKT Register of Studies.

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. Contacting relevant individuals/organisations seeking information about unpublished or incomplete studies.
3. Grey literature sources (e.g. abstracts, dissertations and theses), in addition to those already included in the Cochrane Kidney and Transplant Register of Studies, will not be searched.

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 studies 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. Disagreements will be resolved in consultation with a third author.

Data extraction and management

Data extraction will be carried out independently by two authors using standard data extraction forms. Disagreements will be resolved in consultation with a third author. 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

The following items will be independently assessed by two authors using the risk of bias assessment tool (Higgins 2022) (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 risk of bias?

Measures of treatment effect

For dichotomous outcomes (e.g. death, cardiovascular death, graft loss, any infection, exercise-induced injury, nonfatal stroke, nonfatal myocardial event, hospital admission for any cause, cancer), results will be expressed as risk ratio (RR) with 95% confidence intervals (CI). Time-to-event data will be reduced to dichotomous data at specific time points unless all studies report the outcome as time-to-event data, in which case the outcome will be expressed as hazard ratio (HR) with 95% CI. Where continuous scales of measurement are used to assess the effects of treatment (e.g. HRQoL, physical function, graft function, nutritional status, risk modifiers of cardiovascular disease), the mean difference (MD) will be used, or the standardised mean difference (SMD) if different scales have been used. If outcomes are reported as a change from baseline, these data will be preferred over post-intervention values unless outcomes are reported on a different scale (Higgins 2022). Missing standard deviations will be imputed using the highest value available within the meta-analysis, with sensitivity analysis using the average value to assess the robustness of the results.

Unit of analysis issues

We will include studies with non-standard designs, including cross-over RCTs, studies with more than two interventions, and cluster RCTs.

Cross-over studies will be eligible for inclusion in the review and meta-analyses. However, as the carry-over of the exercise intervention given in the first period is likely to persist into subsequent treatment periods due to behaviour modification and extended treatment effects, we only will include data for endpoints reported during the first period of study in which the order of receiving treatments was randomly allocated.

Studies with multiple interventions will be included. If studies have multiple treatment groups, and at least two treatment groups

provide data for eligible interventions, the study will be included in the review. If there are adequate data from the study, then the treatment groups relevant to the treatment comparisons of interest will be included in applicable meta-analyses.

We plan to include information from cluster randomised studies. We plan to divide the effective sample size for each data point by the design effect calculated as 1 + (m - 1) ρ hat, where m is the average cluster size and ρ hat is the sample estimate of the intra-cluster correlation coefficient ρ. In this calculation, a common design effect is assumed across all intervention groups. The intra-cluster coefficient is seldom available in published reports. Hence, we plan to adopt a common approach using external estimates obtained from similar studies. For dichotomous outcomes, we plan to divide the number of participants and the number experiencing the event by the design effect. For continuous endpoints, we plan to only divide the sample size by the design effect with means, leaving standard deviations unchanged (Donner 2002).

Dealing with missing data

Any further information required from the original author will be requested by written correspondence (e.g. emailing the 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 2022).

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). A guide to the interpretation of I^2 values will be as follows:

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity

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 CI for I^2) (Higgins 2022).

Assessment of reporting biases

If possible, funnel plots will be used to assess for the potential existence of small study bias (Higgins 2022).

Data synthesis

Data will be pooled using the random-effects model; however, the fixed-effect model will also be used to ensure the robustness of the model chosen and its susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses when appropriate:

Related to participants

- Incident versus prevalent kidney transplant populations. Differential transplant vintage is likely to have an effect on accumulated cardiovascular risk, which may influence the expected relative effects of physical activity on outcomes such as death and cardiovascular death.
- Pre-existing versus no pre-existing cardiovascular disease. The extent of pre-existing disease may influence the expected relative effects of physical activity on outcomes such as death and cardiovascular death.
- Baseline physical fitness and function: people with lower fitness normally experience the largest relative gains overall, but it takes longer to adjust to the new stimulus and for adaptations to show.

Related to interventions

- Time (duration) of the intervention (3 months versus > 3 months). Short interventions are likely to have limited effect on outcomes such as death, cardiovascular events (unless as a harmful outcome), and physical function gains.
- Type of interventions: different types of interventions are expected to produce varied effects on outcomes such as physical function and physical fitness.
- The intensity of the prescribed physical activity programme is expected to result in varied gains in physical function outcomes, with greater intensities resulting in greater benefits.
- The overall dose of the intervention is expected to influence outcomes with larger volumes of physical activity overall, resulting in larger gains in the investigated outcomes.

Related to study design

- Allocation concealment (low risk versus high or unclear risk). Selection may bias effect size towards larger effect estimates.
- Duration of follow-up. Short-term follow-up may bias the effect size of long-term outcomes towards the null.

Adverse effects will be tabulated and assessed with descriptive techniques, as they are likely to be different for the different physical activity interventions. Where possible, the risk difference with 95% CI will be calculated for each adverse effect, either compared to no treatment or to another intervention.

Sensitivity analysis

We will perform sensitivity analyses in order to explore the influence of the following factors on effect size:

- Repeating the analysis, excluding unpublished studies
- Repeating the analysis taking account of the risk of bias, as specified
- 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, the language of publication, source of funding (industry versus other), and country.

Summary of findings and assessment of the certainty of the evidence

We will present the main results of the review in 'Summary of findings' tables. These tables present key information concerning the certainty of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schunemann 2022a). 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 certainty 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. This will be assessed by two authors. The certainty 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 (Schunemann 2022b). We plan to present the following outcomes in the 'Summary of findings' tables.

- Death (any cause)
- Cardiovascular death
- Graft loss
- HRQoL: total score from any questionnaire
- Physical fitness: VO_2 peak
- Physical function: 6MWT
- Exercise-induced injury

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APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor: [Exercise Therapy] explode all trees 2. MeSH descriptor: [Exercise] explode all trees 3. MeSH descriptor: [Physical Exertion] this term only 4. MeSH descriptor: [Exercise Test] this term only 5. MeSH descriptor: [Physical Fitness] this term only 6. MeSH descriptor: [Physical Endurance] explode all trees 7. (exercise* or lifestyle):ti,ab,kw (Word variations have been searched) 8. (physical near/2 (training or therapy or fitness)):ti,ab,kw 9. kinesiotherap*:ti,ab,kw 10.MeSH descriptor: [Exercise Movement Techniques] explode all trees 11.MeSH descriptor: [Physical Therapy Modalities] this term only 12.MeSH descriptor: [Rehabilitation] this term only 13.{or #1-#12} 14.((kidney or renal) near/1 (transplant* or graft* or allograft*)):ti,ab,kw 15.#13 and #14 in Trials
MEDLINE	1. exp Exercise Therapy/ 2. exp Exercise/ 3. Physical Exertion/ 4. Exercise Test/ 5. Physical Fitness/ 6. exp Physical Endurance/ 7. exp Exercise Movement Techniques/ 8. Physical Therapy Modalities/ 9. Rehabilitation/ 10.(exercise* or training or lifestyle).tw. 11.or/1-10 12.Kidney Transplantation/ 13.((kidney or renal) adj1 (transplant* or graft* or allograft*)).tw. 14.or/12-13 15.and/11,14
EMBASE	1. exp kinesiotherapy/ 2. exp "physical activity, capacity and performance"/ 3. (exercise* or training or lifestyle).tw. 4. or/1-3 5. exp kidney transplantation/

(Continued)

6. ((kidney or renal) adj1 (transplant* or graft* or allograft*)).tw.
7. or/5-6
8. and/4,7

Appendix 2. Risk of bias assessment tool

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.
	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

(Continued)

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, plausible 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.

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: AVC, PK, EN, ESO, EK, NC
2. Study selection: PK, EK
3. Extract data from studies: PK, AVC
4. Enter data into RevMan: PK, ESO
5. Carry out the analysis: EN, ESO, PK, AVC, EK
6. Interpret the analysis: EN, AVC, PK, ESO, EK, NC
7. Draft the final review: AVC, PK, EN, ESO, EK, NC
8. Disagreement resolution: AVC, EK
9. Update the review: AVC, PK, EN, ESO, EK, NC

DECLARATIONS OF INTEREST

- Amaryllis H Van Craenenbroeck: no relevant interests were disclosed
- Pelagia Koufaki: no relevant interests were disclosed
- Evi V Nagler: no relevant interests were disclosed
- Eva Segura-Orti: no relevant interests were disclosed
- Evangelia J Kouidi: no relevant interests were disclosed
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