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PROTOCOL

Changes in functional health status following open abdominal aortic aneurysm repair and the role of exercise-based rehabilitation: protocol for a systematic review and meta-analysis

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Plain English Summary

Why we are undertaking this work: The abdominal aorta is a major blood vessel which carries blood to the organs in the abdomen and measures 1.4–3 cm. An abdominal aortic aneurysm (AAA) is a balloon-like swelling of the aorta, which has a significant chance of rupturing if it grows beyond 5.5 cm. Consideration of AAA repair within 8 weeks is therefore recommended for all patients with aneurysms greater than 5.5 cm. Delayed recovery and complications are frequent following AAA repair. Complications include temporary or long-term damage to the lungs, kidneys and/or bowel. Reduction in functional status, likely due to bed rest and the demands of surgery, is also common. Currently, we do not know the extent of the decrease in functional status following AAA repair. In addition, exercise-based therapy following AAA repair could improve functional status, but we do not know if there is enough evidence to support this suggestion. We aim to identify how much functional status is reduced following AAA repair and whether it can be improved with exercise therapy.

What we will do: We plan to systematically review the evidence to improve our understanding of the reduction in functional status following AAA repair (component 1) and whether exercise can improve functional status (component 2) following AAA repair. We intend to search databases to identify trials that have explored the changes in physical function and the effect of exercise following AAA surgery.

What this means: This information will help us to understand just how much functional status is affected by surgery and whether exercise after surgery is helpful to improve it. If there is not enough information to find this out, this will help us to plan new studies.

Key words: abdominal aortic aneurysm, exercise therapy, postoperative care, rehabilitation, function recovery

Abstract

Background and objectives: The aim of this systematic review is to explore the current evidence surrounding the changes in functional status following open or endovascular abdominal aortic aneurysm (AAA) repair and the role of postoperative exercise-based rehabilitation programmes.

Methods: The proposed study will incorporate two separate systematic reviews within it, one to assess changes in functional status (component 1) and another to consider the role of exercise-based rehabilitation for improving functional status (component 2), both following AAA repair. The Medline, EMBASE and Cochrane CENTRAL databases will be searched using two separate search strategies including the terms “aortic aneurysm”, “functional capacity”, “functional decline” and” exercise therapy”. We plan to include all prospective randomised and non-randomised trials that have considered the impact of AAA repair on functional status and/or the effect of exercise-based rehabilitation following AAA repair. For component 1, the primary outcome will be changes in objective measures of functional capacity or physical function following AAA repair and, for component 2, it will be changes in physical function or functional capacity following exercise-based rehabilitation after AAA repair. The extracted data will include study characteristics – ie, sample size, a description of the intervention and control conditions (where applicable), outcome measures, length of follow-up and main findings related to outcome measures. For both components a narrative synthesis will be produced, supported by a summary table. We intend to

conduct quantitative meta-analyses for both components. For each selected outcome we plan to evaluate the certainty of evidence based on the GRADE approach and risk of bias of included studies will be assessed using the Cochrane tool.

Conclusions: Based on a lack of current evidence, we present a protocol for a systematic review to investigate the functional changes associated with open and endovascular AAA repair and the potential value of postoperative exercise rehabilitation.

Introduction

Abdominal aortic aneurysm (AAA) repair may be associated with significant perioperative respiratory, cardiac, distal arterial or renal complications, which might necessitate a prolonged intensive care or hospital stay.[1–3] In addition, patients with AAA are frequently elderly with widespread atherosclerosis, cardiovascular risk factors and comorbidities.[4–8] This, in combination with the fact that AAA repair is associated with significant perioperative metabolic and cardiopulmonary challenges,[9,10] may mean that the required recovery, both in and out of hospital, has a significant and immediate impact on functional capacity, physical function and quality of life (QoL).

Indeed, systematic review evidence suggests that there are initial declines in both mental and physical domains of QoL following AAA repair, with the mental domains recovering to preoperative levels by 4–6 weeks, whilst the physical domains may take more than a year to recover.[11,12] There is, however, no systematic review evidence considering the quantitative changes in functional capacity and physical function following AAA repair that are reflected in these reductions in physical QoL domains

Moreover, the evidence for postoperative exercise-based rehabilitation following AAA repair has not been synthesised, despite its potential to ameliorate some of these reductions in physical function and QoL. This is despite evidence to suggest that preoperative exercise programmes improve postoperative functional capacity and outcomes,[13,14] and recommendations to enroll patients in exercise-based cardiovascular rehabilitation following major cardiac surgery.[15]

Therefore, the aims of this study are (1) to review the evidence considering quantitative changes in functional capacity and physical function following AAA repair; and (2) to review the evidence for postoperative exercise-based rehabilitation following AAA repair.

Methods

Protocol development

This protocol has been developed using the Cochrane Handbook for Systematic Reviews of Interventions[16] and is written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol extension (PRISMA-P).[17] The PRISMA-P checklist is shown in Appendix 1 (online at www.jvsgbi.com). As we are encompassing two separate aims within this review, we plan to perform two separate systematic reviews which are outlined below.

Component 1: Considering quantitative changes in functional capacity and physical function following AAA repair

Search strategy and inclusion criteria

Searches will be performed using the MEDLINE, EMBASE and Cochrane CENTRAL databases with no date restrictions applied. In addition, trial registries such as clinicaltrials.gov and the Web of Science conference proceedings will be searched and authors of any identified ongoing studies or conference abstracts will be contacted to obtain study outcome reports where possible. Reference lists of any screened full texts or relevant systematic reviews will also be hand searched for other relevant papers. Only studies published in the English language will be included. Search terms will include “Aortic Aneurysm” [AND] “Functional Capacity” [OR] “Functional decline” [OR] “Functional capacity” [OR] “Aerobic endurance” [OR] “Functional Fitness”. A draft search is shown in Appendix 2 (online at www.jvsgbi.com).

We will include all prospective randomised and non-randomised trials that consider the impact of AAA surgery on quantitative measures of functional capacity and physical function. We plan to include participants aged 18 years and older, of either sex, who have undergone an elective open surgical repair or endovascular aneurysm repair, with results presented separately based on method of repair. We plan to include all types of AAA: infrarenal; juxtarenal; and suprarenal. To maximise available data, studies that include multiple surgical patient groups will be included if the data on the AAA subgroup can be obtained. Measures of physical function and functional capacity will include – but will not be limited to – cardiopulmonary exercise testing, the six-minute walk test, the short physical performance battery or its individual components and the timed up and go test.

Trial designs will include randomised controlled trials (RCTs) and observational cohort studies, but articles will only be included if measures are taken at baseline and following surgery to allow comparison. If studies include an intervention designed to reduce the impact of surgery on measures of physical function, these will only be included if data are available for a control group who did not receive an intervention.

Single-group, before-after studies will be included if the group did not receive an intervention designed to reduce the impact of AAA surgery on physical function. Studies that include other interventions, which are not likely to reduce the impact of AAA surgery on physical function, will be included.

Component 2: Considering the role of exercise-based rehabilitation following AAA repair

Search strategy and inclusion criteria

Searches will be performed using the same methods as those outlined above. However, search terms will include "Aortic Aneurysm" [AND] "Exercise therapy" [OR] "Physical Therapy" OR "rehabilitation". A draft search is shown in Appendix 3 (online at www.jvsgbi.com).

We plan to include all prospective RCTs and non-randomised trials that consider the effect of exercise-based rehabilitation following AAA repair. Again, we plan to include participants aged 18 years and older, of either sex, who have undergone an elective open surgical repair or endovascular aneurysm repair. To maximise available data, studies that include multiple surgical patient groups will be included if the data on the AAA subgroup can be obtained. Rehabilitation may include supervised or unsupervised programmes but will only be considered exercise-based if they include some form of structured exercise training with regard to frequency, intensity and/or duration during the postoperative period. We plan to consider all exercise-based interventions either delivered in isolation or as part of a more comprehensive multimodal rehabilitation programme.

Data management, selection and collection process

For both components, search results will be uploaded and deduplicated using the specialised online review tool Covidence.[18] Following this, titles and abstracts will be reviewed for eligibility by two independent reviewers (BR and RL). Full texts of these articles will be obtained and reviewed for inclusion. Any disagreement between reviewers will be resolved via discussion or by consensus with a third reviewer (SP). Information regarding search hits, number of duplicates removed, number of full texts reviewed, number of full texts excluded (with reasons) and number of studies included will be recorded for reporting in the PRISMA flow diagram. Where any full texts are not obtainable via conventional access methods, the authors will be approached to request the full article text.

Data extraction will then be performed by two independent reviewers using two separate bespoke designed spreadsheets, managed using a Microsoft Excel database (Microsoft, 2016, Redmond, WA, USA). The extracted data will include study characteristics including the sample size, a description of the intervention and control conditions (where applicable), outcome measures, length of follow-up and main findings related to outcome measures (a sample data extraction sheet is shown in Appendix 4, online at www.jvsgbi.com).

Outcome measures

For component 1, the primary outcome will be changes in objective measures of functional capacity and physical function following AAA repair. These measures will include – but will not be limited to – the ventilatory anaerobic threshold, peak oxygen consumption and ventilatory equivalents for carbon dioxide from cardiopulmonary exercise testing, the six-minute walk test, change in short physical performance battery scores and time taken for the timed up and go test. The changes in functional capacity and physical function at different time points following surgery will be collated and analysed as appropriate.

For component 2, the primary outcome will be changes in objective measures of functional capacity and physical function, including the measures outlined above, following exercise-based rehabilitation. For both components, secondary outcomes will include all-cause mortality, cardiovascular mortality, event-free survival, rate of rehospitalisation, changes in QoL and adverse events related to the intervention. We also plan to include measures of frailty such as the modified frailty index and components of comprehensive geriatric assessment such as nutritional status, cognition and falls risk, if available. However, all relevant secondary outcomes will be considered and reported including compliance with exercise interventions.

Risk of bias and rating the quality of evidence

For both components, the risk of bias for each of the included studies will be independently assessed by two review authors using the criteria outlined in the revised Cochrane tool (ROB 2.0)[19] (see Appendix 5, online at www.jvsgbi.com) or the ROBINS-I tool[20] for non-randomised studies (see Appendix 6, online at www.jvsgbi.com). The relevant information will be extracted as outlined in the guidelines and each study will be either classified as having a 'high risk', 'low risk' or 'some concerns' of bias. In the case of 'some concerns' of bias, study authors will be contacted for more information. We also plan to include the overall predicted direction of bias for each outcome as outlined in the guidelines.[16]

For each selected outcome we plan to evaluate the certainty of evidence based on the GRADE approach, which includes five main domains: study limitations, imprecision, indirectness, inconsistency and publication bias. These domains will be used to upgrade or downgrade evidence after initial assessment. Based on these, we plan to categorise the quality of evidence as high, moderate, low or very low.[21] We also plan to include a summary of the certainty of evidence and a quantitative synthesis of effects for each outcome.

Data analysis and synthesis

For component 1, the aim is to identify the impact of AAA repair on measures of functional capacity and physical function rather than to assess the impact of an intervention. Therefore, a narrative synthesis will be produced, outlining for each study the key characteristics and findings, supported by a summary of findings table.

For component 2, a similar narrative synthesis with a summary of findings table will be produced. In addition, if the included studies are sufficiently homogenous and include an intervention and control group, a meta-analysis will be carried out. This meta-analysis will

provide a pooled estimate of the effect of a postoperative rehabilitation programme on various outcomes of interest. A quantitative analysis will be generated using Review Manager (RevMan version 5.3),[22] which will allow for the creation of forest plots with an overall effect estimate and 95% confidence intervals. For this, we will use the reported post-intervention mean and standard deviation, unless only change scores are given. If the data reported are not suitable for entry into the meta-analyses, the authors will be contacted to obtain the required data.

The suitability of pooled analyses will be considered via interpretation of heterogeneity based on the I^2 statistic and p value for the χ^2 test. If significant heterogeneity is not present, data will be pooled using a fixed-effects model, with mean difference reported. If significant heterogeneity is present and the reason for it is not clear and explainable, then data will be pooled using a random-effects model, with standardised mean difference reported, which considers heterogeneity in the effect estimate. If the reason for significant heterogeneity is identifiable (ie, due to clear differences between interventions), data will not be pooled.

If meta-analyses are to be performed, sensitivity analyses will be carried out, removing trials of lower quality based on the risk of bias assessment and repeating the analyses. A minimal change in results would suggest that the analyses are robust.[23] In the case that studies report both post-intervention scores and change scores from baseline, a further sensitivity analysis will be performed by using change scores instead of post-intervention scores, as has been recommended.[24] If only post-intervention scores are reported in some studies, these will be used in conjunction with the change scores that are reported for the purpose of sensitivity analyses.

KEY MESSAGES

- This systematic review aims to explore the current evidence surrounding the changes in functional status following abdominal aortic aneurysm (AAA) repair and the role of exercise-based rehabilitation programmes.
- We plan to include all prospective randomised and non-randomised trials that have considered the impact of AAA repair on functional status (component 1) and/or the effect of exercise-based rehabilitation following AAA repair (component 2).
- For both components a narrative synthesis will be produced, supported by a summary of findings table. We intend to conduct quantitative meta-analyses for both components including a pre- and post-intervention meta-analysis, where possible. For each selected outcome we plan to evaluate the certainty of evidence based on the GRADE approach and risk of bias of included studies will be assessed using the Cochrane tool.

Discussion and conclusion

The possible complications and perioperative metabolic and cardiopulmonary challenges associated with AAA repair mean that the required recovery is likely to have a significant impact on physical function, functional capacity and QoL. Indeed, the former has been demonstrated in patients undergoing coronary artery bypass grafting,[25] but the evidence is yet to be evaluated in those undergoing AAA repair. QoL changes have been considered in those undergoing AAA repair, with significant reductions noted, which can take over a year to recover.[12] Exercise-based rehabilitation has the potential to ameliorate some of these reductions in physical function, functional capacity and QoL. In addition, the objective of any AAA treatment is to prolong patient survival and maintain a QoL comparable to that of the general population, which can arguably be assisted by postoperative rehabilitation. However, the evidence for such interventions following AAA repair has not been considered, despite evidence to suggest that preoperative exercise programmes are beneficial in this population and the recommendation that all patients undergo cardiovascular rehabilitation following major cardiac surgery. Even if adequate evidence is obtained in this review to support the efficacy of exercise-based rehabilitation, barriers to exercise rehabilitation such as lack of funding, patient motivation and paucity of specialised physical therapists providing standardised exercise programmes will be pertinent.[26,27] Given the limited evidence available, future research is urgently needed to explore ways to tackle these barriers in a patient cohort likely to achieve measurable benefit from exercise-based rehabilitation.

The anticipated limitation of this review is the possibility that there is little or limited evidence considering the areas of interest. Such a limitation has been identified in a recent review considering prehabilitation in a different vascular patient group.[28]

However, it is important to identify the current state of evidence on this topic to ensure that future research is accurately informed and appropriately designed to answer the intended question.

Conflict of Interest: None.

Funding: None.

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References

1. Kudo T. Surgical complications after open abdominal aortic aneurysm repair: intestinal ischemia, buttock claudication and sexual dysfunction. *Ann Vasc Dis* 2019;**12**(2):157–62. https://doi.org/10.3400/avd.ra.19-00038
2. Nayeemuddin M, Pherwani AD, Asquith JR. Imaging and management of complications of open surgical repair of abdominal aortic aneurysms. *Clin Radiol* 2022;**67**(8):802–14. https://doi.org/10.1016/j.crad.2011.12.005
3. Latz CA, Boitano L, Schwartz S, *et al*. Editor's Choice: Mortality is high following elective open repair of complex abdominal aortic aneurysms. *Eur J Vasc Endovasc Surg* 2022;**61**(1):90–7. https://doi.org/10.1016/j.ejvs.2020.09.002
4. Forsdahl SH, Singh K, Solberg S, Jacobsen BK. Risk factors for abdominal aortic aneurysms: a 7-year prospective study: the Tromsø Study, 1994-2001. *Circulation* 2009;**119**(16):2202–8. https://doi.org/10.1161/CIRCULATIONAHA.108.817619

5. Li X, Zhao G, Zhang J, Duan Z, Xin S. Prevalence and trends of the abdominal aortic aneurysms epidemic in general population - a meta-analysis. *PLoS One* 2013;**8**(12):e81260. https://doi.org/10.1371/journal.pone.0081260
6. Kent KC, Zwolak RM, Egorova NN, *et al*. Analysis of risk factors for abdominal aortic aneurysm in a cohort of more than 3 million individuals. *J Vasc Surg* 2010;**52**(3):539–48. https://doi.org/10.1016/j.jvs.2010.05.090
7. Jahangir E, Lipworth L, Edwards TL, *et al.* Smoking, sex, risk factors and abdominal aortic aneurysms: a prospective study of 18 782 persons aged above 65 years in the Southern Community Cohort Study. *J Epidemiol Community Health* 2015;**69**(5):481–8. https://doi.org/10.1136/jech-2014-204920
8. Salzler GG, Meltzer AJ, Mao J, *et al*. Characterizing the evolution of peri-operative outcomes and costs of endovascular abdominal aortic aneurysm repair. *J Vasc Surg* 2015;**62**(5):1134–9. https://doi.org/10.1016/j.jvs.2015.06.138
9. Moris DN, Kontos MI, Mantonakis EI, *et al*. Concept of the aortic aneurysm repair-related surgical stress: a review of the literature. *Int J Clin Exp Med* 2014;**7**(9):2402–12.
10. Pasin L, Nardelli P, Belletti A, *et al*. Pulmonary complications after open abdominal aortic surgery: a systematic review and meta-analysis. *J Cardiothorac Vasc Anesth* 2017;**31**(2):562–8. https://doi.org/10.1053/j.jvca.2016.09.034
11. Shan L, Saxena A, Goh D, Robinson D. A systematic review on the quality of life and functional status after abdominal aortic aneurysm repair in elderly patients with an average age older than 75 years. *J Vasc Surg* 2019;**69**(4): 1268–81. https://doi.org/10.1016/j.jvs.2018.09.032
12. Coughlin PA, Jackson D, White AD, *et a*l. Meta-analysis of prospective trials determining the short- and mid-term effect of elective open and endovascular repair of abdominal aortic aneurysms on quality of life. *Br J Surg* 2013;**100**(4): 448–55. https://doi.org/10.1002/bjs.9018
13. Barakat HM, Shahin Y, Barnes R, *et al*. Supervised exercise program improves aerobic fitness in patients awaiting abdominal aortic aneurysm repair. *Ann Vasc Surg* 2014;**28**(1):74–9. https://doi.org/10.1016/j.avsg.2013.09.001
14. Barakat HM, Shahin Y, Khan JA. Preoperative supervised exercise improves outcomes after elective abdominal aortic aneurysm repair: a randomized controlled trial. *J Vasc Surg* 2016;**64**(4):1171. https://doi.org/10.1016/j.jvs.2016.08.074
15. Lawton JS, Tamis-Holland JE, Bangalore S, *et al*. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022;**145**(3):E18–114. https://doi.org/10.1161/CIR.0000000000001038
16. Cochrane Training. Cochrane Handbook for Systematic Reviews of Interventions. 2022. Available from: https://training.cochrane.org/handbook/current
17. Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;**4**(1):1. https://doi.org/10.1186/2046-4053-4-1
18. Covidence. Better systematic review management. Available from: https://www.covidence.org/ [accessed 2 June 2022].
19. Cochrane Methods. Risk of Bias 2 (RoB 2) tool. Available from: https://methods.cochrane.org/risk-bias-2 [accessed 30 April 2022].
20. Sterne JA, Hernán MA, Reeves BC, *et al*. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;**355**:i4919. https://doi.org/10.1136/bmj.i4919
21. GRADE. GRADE Handbook. Available from: www.gradeworkinggroup.org [accessed 24 April 2022].
22. Cochrane Training. RevMan. Available from: https://training.cochrane.org/online-learning/core-software/revman [accessed 1 May 2022].
23. Bown MJ, Sutton AJ. Quality control in systematic reviews and meta-analyses. *Eur J Vasc Endovasc Surg* 2010;**40**(5):669–77. https://doi.org/10.1016/j.ejvs.2010.07.011
24. Fu R, Holmer HK. Change score or follow-up score? Choice of mean difference estimates could impact meta-analysis conclusions. *J Clin Epidemiol* 2016;**76**: 108–17. https://doi.org/10.1016/j.jclinepi.2016.01.034
25. Rengo JL, Savage PD, Hirashima F, Leavitt BJ, Ades PA, Toth MJ. Assessment of the early disabling effects of coronary artery bypass graft surgery using direct measures of physical function. *J Cardiopulm Rehabil Prev* 2022;**42**(1):28–33. https://doi.org/10.1097/HCR.0000000000000587
26. Popplewell MA, Bradbury AW. Why do health systems not fund supervised exercise programmes for intermittent claudication? *Eur J Vasc Endovasc Surg* 2014;**48**(6):608–10. https://doi.org/10.1016/j.ejvs.2014.07.008
27. Hageman D, Van Den Houten MML, Spruijt S, Gommans LNM, Scheltinga MRM, Teijink JAW. Supervised exercise therapy: it does work, but how to set up a program? *J Cardiovasc Surg (Torino)* 2017;**58**(2):305–12. https://doi.org/10.23736/S0021-9509.16.09825-6
28. Palmer J, Pymer S, Smith GE, *et al*. Presurgery exercise-based conditioning interventions (prehabilitation) in adults undergoing lower limb surgery for peripheral arterial disease. *Cochrane Database Syst Rev* 2020;**9**(9): CD013407. https://doi.org/10.1002/14651858.CD013407.pub2

Appendix 1 PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

Appendix 1 PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol* CONTINUED

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;**349**:g7647.

Appendix 2 Draft search strategy for Component 1: Quantitative changes in functional capacity and physical function following AAA repair

1. exp Aortic Aneurysm/
2. exp Aneurysm, Ruptured/
3. exp Aorta, Abdominal/
4. AAA*.ti,ab.
5. (aneurysm* adj4 abdom*).ti,ab.
6. (aneurysm* adj4 thoracoabdom*).ti,ab.
7. (aneurysm* adj4 thoracoabdom*).ti,ab.
8. (aneurysm* adj4 aort*).ti,ab.
9. (aneurism* adj4 abdom*).ti,ab.
10. (aneurism* adj4 thoracoabdom*).ti,ab.
11. (aneurism* adj4 thoracoabdom*).ti,ab.
12. (aneurism* adj4 aort*).ti,ab.
13. or/1-12
14. Quality of Life.ti,ab
15. Standard of living.ti,ab
16. Healthy Days Measures.ti,ab.
17. Functional capacity.ti,ab
18. Functional decline.ti,ab
19. Activity status.ti,ab
20. Cardiopulmonary exercise testing.ti,ab
21. Cardio-pulmonary exercise testing.ti,ab
22. CPET.ti,ab
23. CPEX.ti,ab
24. Short performance physical battery.ti,ab
25. SPBB.ti,ab
26. Physical performance test.ti,ab
27. Aerobic endurance.ti,ab
28. Functional fitness.ti,ab
29. Or/14-28
30. randomized controlled trial.pt.
31. controlled clinical trial.pt.
32. randomized.ab.
33. placebo.ab.
34. randomly.ab.
35. trial.ab.
36. groups.ab.
37. or/30-36
38. exp animals/ not humans.sh.
39. 37 NOT 38
40. 13 AND 29 AND 39

Appendix 3 Draft Search Strategy for Component 2: The role of exercise-based rehabilitation following AAA repair

1. exp Aortic Aneurysm/
2. exp Aneurysm, Ruptured/
3. exp Aorta, Abdominal/
4. AAA*.ti,ab.
5. (aneurysm* adj4 abdom*).ti,ab.
6. (aneurysm* adj4 thoracoabdom*).ti,ab.
7. (aneurysm* adj4 thoracoabdom*).ti,ab.
8. (aneurysm* adj4 aort*).ti,ab.
9. (aneurism* adj4 abdom*).ti,ab.
10. (aneurism* adj4 thoracoabdom*).ti,ab.
11. (aneurism* adj4 thoracoabdom*).ti,ab.
12. (aneurism* adj4 aort*).ti,ab.
13. or/1-12
14. Exp Exercise/
15. Exp Exercise therapy/
16. Exp Postoperative Care/
17. Exp Enhanced recovery after surgery/
18. Exp ERAS
19. Fast-track.ti,ab
20. "home based train*".ti,ab.
21. "Interval Train*".ti,ab.
22. physiotherap*.ti,ab.
23. "Physical train*".ti,ab.
24. "Physical Therap*".ti,ab.
25. recuperat*.ti,ab.
26. restorat*.ti,ab.
27. rehabilitat*.ti,ab.
28. recovery.ti,ab.
29. Or/14-28
30. randomized controlled trial.pt.
31. controlled clinical trial.pt.
32. randomized.ab.
33. placebo.ab.
34. randomly.ab.
35. trial.ab.
36. groups.ab.
37. or/30-36
38. exp animals/ not humans.sh.
39. 37 NOT 38
40. 13 AND 29 AND 39

Appendix 4 Sample data extraction sheet

STUDY ELIGIBILITY FORM

FACTORS	ASSESSMENT	COMMENTS
TYPE OF STUDY		
1. Is the study described as randomised? NB. Please answer "No" if the study is a crossover or quasi-randomised trial.	Yes Unclear No	
PARTICIPANTS		
2. Were participants diagnosed as patients with disease of interest?	Yes Unclear No	
3. Were participants of the prespecified age? NB: Please answer "Yes" if mix age participants i.e. both >18 years and <18 years are included and state it as comments. No: If only <18 years.	Yes Unclear No	Subgroups available?
INTERVENTIONS		
4. Were comparison groups treated with prespecified intervention in one group and control intervention in other group? NB: study can have 3 arms e.g. CT arm, CT+RT (CMT) arm or RT arm, if so please cross "Yes" and state it as comments.	Yes Unclear No	
OUTCOMES		
5. Did the study report prespecified outcomes?	Yes Unclear No	
FINAL DECISION		

Appendix 4 Data extraction sheet CONTINUED

ORGANISATIONAL ASPECTS				**EX**		**IN**	
REF ID		Reviewer, Date		Checked by			
Author, Year							
Journal/Source				Study ID		NR /	
Country of origin							
Publication type	Full text / Abstract / Book chapter / Internal progress report other (please specify)						
Other relevant publications in DE-form							
Outcome	Decision pending / Check references / Use for discussion / EX without listing / EX with listing / Other (please specify)						
Notes / Short description							

Appendix 4 Data extraction sheet CONTINUED

REASONS FOR EXCLUSION OF STUDY FROM REVIEW	
Methods	No RCT / Inadequate concealment of allocation / Other
Patients	Subgroups available?
Outcomes	No clinically relevant outcomes assessed No data for relevant subgroup extractable
Other	Duplicate publication / Other
NONE	Included

STUDY BASICS	
Domain of study	
Inclusion criteria	
Exclusion criteria	
Additional treatment	
Compliance	Evaluated? Y / N
Outcomes assessed	
Subgroup evaluated	
Confounders	

Appendix 4 Data extraction sheet CONTINUED

STUDY CHARACTERISTICS	
Sample size	Randomised / recruited
Number of excluded patients	
Recruitment method	
Setting of Exercise	in-patient / out-patient / unclear / NR
HRQOL instrument	
Functional capacity evaluation?	
Length of follow-up	
Number of groups	
Flow diagram?	
Method of randomisation	Adequate?
Method of concealment of allocation	Adequate?
Blinding	
Primary study aims	
Secondary study aims	

Power calculation?	No / Yes (expected effect:_____) Expected difference on primary outcome: Alpha (α) pre-specified: Beta error (β) pre-specified: Calculated sample size Sample size achieved?

Appendix 4 Data extraction sheet CONTINUED

Statistical methods	
Analysis	ITT as treated per protocol unclear

BASELINE CHARACTERISTICS OF THE COHORT				
	Arm 1	**Arm 2**	Others	
Overall comment				
Number of patients				
Age	--	--		
mean/±	±	±		
median/±	±	±		
Ethnicity No. %	NR	NR		
Gender No. %	Male: Female:	Male: Female:		
Exercise therapy?				
QoL data				
Follow-up				
Hb				
Albumin				
CPET				
Functional assessment				
Performance status				

Appendix 5 Cochrane risk-of-bias tool for randomized trials

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)
TEMPLATE FOR COMPLETION

Edited by Julian PT Higgins, Jelena Savović, Matthew J Page, Jonathan AC Sterne
on behalf of the RoB2 Development Group

Version of 22 August 2019

The development of the RoB 2 tool was supported by the MRC Network of Hubs for Trials Methodology Research (MR/L004933/2- N61), with the support of the host MRC ConDuCT-II Hub (Collaboration and innovation for Difficult and Complex randomised controlled Trials In Invasive procedures - MR/K025643/1), by MRC research grant MR/M025209/1, and by a grant from The Cochrane Collaboration.

Study details

Reference	

Study design

X Individually-randomized parallel-group trial

☐ Cluster-randomized parallel-group trial

☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: | Comparator:

Specify which outcome is being assessed for risk of bias

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Is the review team's aim for this result…?

☐ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)

☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

☐ Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?		Y / PY / PN / N / NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y / PY / PN / N / NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		NA / Y / PY / PN / N / NI
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA / Y / PY / PN / N / NI
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y / PY / PN / N / NI
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA / Y / PY / PN / N / NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?		NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y / PY / PN / N / NI
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA / Y / PY / PN / N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		Y / PY / PN / N / NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		Y / PY / PN / N / NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		NA / Y / PY / PN / N / NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		Y / PY / PN / N / NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		Y / PY / PN / N / NI
5.3 ... multiple eligible analyses of the data?		Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Table A. The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

The ROBINS-I tool is reproduced from riskofbias.info with the permission of the authors. The tool should not be modified for use.

ROBINS-I tool (Stage I): At protocol stage

Specify the review question

Participants	
Experimental intervention	
Comparator	
Outcomes	

List the confounding domains relevant to all or most studies

List co-interventions that could be different between intervention groups and that could impact on outcomes

ROBINS-I tool (Stage II): For each study

Specify a target randomized trial specific to the study

Design	Individually randomized / Cluster randomized / Matched (e.g. cross-over)
Participants	
Experimental intervention	
Comparator	

Is your aim for this study…?

☐ to assess the effect of *assignment to* intervention

☐ to assess the effect of *starting and adhering to* intervention

Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Preliminary consideration of confounders

Complete a row for each important confounding domain (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.

"Important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).

(i) Confounding domains listed in the review protocol				
Confounding domain	Measured variable(s)	Is there evidence that controlling for this variable was unnecessary?*	Is the confounding domain measured validly and reliably by this variable (or these variables)?	OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator?
			Yes / No / No information	Favour experimental / Favour comparator / No information

(ii) Additional confounding domains relevant to the setting of this particular study, or which the study authors identified as important				
Confounding domain	Measured variable(s)	Is there evidence that controlling for this variable was unnecessary?*	Is the confounding domain measured validly and reliably by this variable (or these variables)?	OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator?
			Yes / No / No information	Favour experimental / Favour comparator / No information

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that "no statistically significant association" is not the same as "not predictive".

Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.

"Important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.

(i) Co-interventions listed in the review protocol		
Co-intervention	Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)?	Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information

(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important		
Co-intervention	Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)?	Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Bias domain	Signalling questions	Elaboration	Response options
Bias due to confounding			
	1.1 Is there potential for confounding of the effect of intervention in this study? **If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered	In rare situations, such as when studying harms that are very unlikely to be related to factors that influence treatment decisions, no confounding is expected and the study can be considered to be at low risk of bias due to confounding, equivalent to a fully randomized trial. There is no NI (No information) option for this signalling question.	Y / PY / PN / N
	If Y/PY to 1.1: determine whether there is a need to assess time-varying confounding:		
	1.2. Was the analysis based on splitting participants' follow up time according to intervention received? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, go to question 1.3.	If participants could switch between intervention groups then associations between intervention and outcome may be biased by time-varying confounding. This occurs when prognostic factors influence switches between intended interventions.	NA / Y / PY / PN / N / NI
	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)	If intervention switches are unrelated to the outcome, for example when the outcome is an unexpected harm, then time-varying confounding will not be present and only control for baseline confounding is required.	NA / Y / PY / PN / N / NI

	Questions relating to baseline confounding only		
	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Appropriate methods to control for measured confounders include stratification, regression, matching, standardization, and inverse probability weighting. They may control for individual variables or for the estimated propensity score. Inverse probability weighting is based on a function of the propensity score. Each method depends on the assumption that there is no unmeasured or residual confounding.	NA / Y / PY / PN / N / NI
	1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Appropriate control of confounding requires that the variables adjusted for are valid and reliable measures of the confounding domains. For some topics, a list of valid and reliable measures of confounding domains will be specified in the review protocol but for others such a list may not be available. Study authors may cite references to support the use of a particular measure. If authors control for confounding variables with no indication of their validity or reliability pay attention to the subjectivity of the measure. Subjective measures (e.g. based on self-report) may have lower validity and reliability than objective measures such as lab findings.	NA / Y / PY / PN / N / NI
	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Controlling for post-intervention variables that are affected by intervention is not appropriate. Controlling for mediating variables estimates the direct effect of intervention and may introduce bias. Controlling for common effects of intervention and outcome introduces bias.	NA / Y / PY / PN / N / NI
	Questions relating to baseline and time-varying confounding		
	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Adjustment for time-varying confounding is necessary to estimate the effect of starting and adhering to intervention, in both randomized trials and NRSI. Appropriate methods include those based on inverse probability weighting. Standard regression models that include time-updated confounders may be problematic if time-varying confounding is present.	NA / Y / PY / PN / N / NI
	1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	See 1.5 above.	NA / Y / PY / PN / N / NI

	Risk of bias judgement	See Table B	Low / Moderate / Serious / Critical / NI
	Optional: What is the predicted direction of bias due to confounding?	Can the true effect estimate be predicted to be greater or less than the estimated effect in the study because one or more of the important confounding domains was not controlled for? Answering this question will be based on expert knowledge and results in other studies and therefore can only be completed after all of the studies in the body of evidence have been reviewed. Consider the potential effect of each of the unmeasured domains and whether all important confounding domains not controlled for in the analysis would be likely to change the estimate in the same direction, or if one important confounding domain that was not controlled for in the analysis is likely to have a dominant impact.	Favours experimental / Favours comparator / Unpredictable

Bias in selection of participants into the study			
	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? **If N/PN to 2.1:** go to 2.4	This domain is concerned only with selection into the study based on participant characteristics observed *after* the start of intervention. Selection based on characteristics observed *before* the start of intervention can be addressed by controlling for imbalances between experimental intervention and comparator groups in baseline characteristics that are prognostic for the outcome (baseline confounding).	Y / PY / PN / N / NI
	2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Selection bias occurs when selection is related to an effect of either intervention or a cause of intervention **and** an effect of either the outcome or a cause of the outcome. Therefore, the result is at risk of selection bias if selection into the study is related to both the intervention and the outcome.	NA / Y / PY / PN / N / NI
	2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?		NA / Y / PY / PN / N / NI
	2.4. Do start of follow-up and start of intervention coincide for most participants?	If participants are not followed from the start of the intervention then a period of follow up has been excluded, and individuals who experienced the outcome soon after intervention will be missing from analyses. This problem may occur when prevalent, rather than new (incident), users of the intervention are included in analyses.	Y / PY / PN / N / NI
	2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases?	It is in principle possible to correct for selection biases, for example by using inverse probability weights to create a pseudo-population in which the selection bias has been removed, or by modelling the distributions of the missing participants or follow up times and outcome events and including them using missing data methodology. However such methods are rarely used and the answer to this question will usually be "No".	NA / Y / PY / PN / N / NI
	Risk of bias judgement	See Table B	Low / Moderate / Serious / Critical / NI
	Optional: What is the predicted direction of bias due to selection of participants into the study?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions.	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Bias in classification of interventions			
	3.1 Were intervention groups clearly defined?	A pre-requisite for an appropriate comparison of interventions is that the interventions are well defined. Ambiguity in the definition may lead to bias in the classification of participants. For individual-level interventions, criteria for considering individuals to have received each intervention should be clear and explicit, covering issues such as type, setting, dose, frequency, intensity and/or timing of intervention. For population-level interventions (e.g. measures to control air pollution), the question relates to whether the population is clearly defined, and the answer is likely to be 'Yes'.	Y / PY / PN / N / NI
	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	In general, if information about interventions received is available from sources that could not have been affected by subsequent outcomes, then differential misclassification of intervention status is unlikely. Collection of the information at the time of the intervention makes it easier to avoid such misclassification. For population-level interventions (e.g. measures to control air pollution), the answer to this question is likely to be 'Yes'.	Y / PY / PN / N / NI
	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Collection of the information at the time of the intervention may not be sufficient to avoid bias. The way in which the data are collected for the purposes of the NRSI should also avoid misclassification.	Y / PY / PN / N / NI
	Risk of bias judgement	See Table B	Low / Moderate / Serious / Critical / NI
	Optional: What is the predicted direction of bias due to measurement of outcomes or interventions?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions.	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Bias due to deviations from intended interventions			
	If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2		
	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Deviations that happen in usual practice following the intervention (for example, cessation of a drug intervention because of acute toxicity) are part of the intended intervention and therefore do not lead to bias in the effect of assignment to intervention. Deviations may arise due to expectations of a difference between intervention and comparator (for example because participants feel unlucky to have been assigned to the comparator group and therefore seek the active intervention, or components of it, or other interventions). Such deviations are not part of usual practice, so may lead to biased effect estimates. However these are not expected in observational studies of individuals in routine care.	Y / PY / PN / N / NI
	4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome?	Deviations from intended interventions that do not reflect usual practice will be important if they affect the outcome, but not otherwise. Furthermore, bias will arise only if there is imbalance in the deviations across the two groups.	NA / Y / PY / PN / N / NI
	If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6		
	4.3. Were important co-interventions balanced across intervention groups?	Risk of bias will be higher if unplanned co-interventions were implemented in a way that would bias the estimated effect of intervention. Co-interventions will be important if they affect the outcome, but not otherwise. Bias will arise only if there is imbalance in such co-interventions between the intervention groups. Consider the co-interventions, including any pre-specified co-interventions, that are likely to affect the outcome and to have been administered in this study. Consider whether these co-interventions are balanced between intervention groups.	Y / PY / PN / N / NI
	4.4. Was the intervention implemented successfully for most participants?	Risk of bias will be higher if the intervention was not implemented as intended by, for example, the health care professionals delivering care during the trial. Consider whether implementation of the intervention was successful for most participants.	Y / PY / PN / N / NI

	4.5. Did study participants adhere to the assigned intervention regimen?	Risk of bias will be higher if participants did not adhere to the intervention as intended. Lack of adherence includes imperfect compliance, cessation of intervention, crossovers to the comparator intervention and switches to another active intervention. Consider available information on the proportion of study participants who continued with their assigned intervention throughout follow up, and answer 'No' or 'Probably No' if this proportion is high enough to raise concerns. Answer 'Yes' for studies of interventions that are administered once, so that imperfect adherence is not possible. We distinguish between analyses where follow-up time after interventions switches (including cessation of intervention) is assigned to (1) the new intervention or (2) the original intervention. (1) is addressed under time-varying confounding, and should not be considered further here.	Y / PY / PN / N / NI
	4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	It is possible to conduct an analysis that corrects for some types of deviation from the intended intervention. Examples of appropriate analysis strategies include inverse probability weighting or instrumental variable estimation. It is possible that a paper reports such an analysis without reporting information on the deviations from intended intervention, but it would be hard to judge such an analysis to be appropriate in the absence of such information. Specialist advice may be needed to assess studies that used these approaches. If everyone in one group received a co-intervention, adjustments cannot be made to overcome this.	NA / Y / PY / PN / N / NI
	Risk of bias judgement	See Table	
	Optional: What is the predicted direction of bias due to deviations from the intended interventions?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions.	

Bias due to missing data			
	5.1 Were outcome data available for all, or nearly all, participants?	"Nearly all" should be interpreted as "enough to be confident of the findings", and a suitable proportion depends on the context. In some situations, availability of data from 95% (or possibly 90%) of the participants may be sufficient, providing that events of interest are reasonably common in both intervention groups. One aspect of this is that review authors would ideally try and locate an analysis plan for the study.	Y / PY / PN / N / NI
	5.2 Were participants excluded due to missing data on intervention status?	Missing intervention status may be a problem. This requires that the *intended* study sample is clear, which it may not be in practice.	Y / PY / PN / N / NI
	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	This question relates particularly to participants excluded from the analysis because of missing information on confounders that were controlled for in the analysis.	Y / PY / PN / N / NI
	5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions?	This aims to elicit whether either (i) differential proportion of missing observations or (ii) differences in reasons for missing observations could substantially impact on our ability to answer the question being addressed. "Similar" includes some minor degree of discrepancy across intervention groups as expected by chance.	NA / Y / PY / PN / N / NI
	5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data?	Evidence for robustness may come from how missing data were handled in the analysis and whether sensitivity analyses were performed by the investigators, or occasionally from additional analyses performed by the systematic reviewers. It is important to assess whether assumptions employed in analyses are clear and plausible. Both content knowledge and statistical expertise will often be required for this. For instance, use of a statistical method such as multiple imputation does not guarantee an appropriate answer. Review authors should seek naïve (complete-case) analyses for comparison, and clear differences between complete-case and multiple imputation-based findings should lead to careful assessment of the validity of the methods used.	NA / Y / PY / PN / N / NI
	Risk of bias judgement	See Table	Low / Moderate / Serious / Critical / NI

	Optional: What is the predicted direction of bias due to missing data?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions.	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Bias in measurement of outcomes			
	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Some outcome measures involve negligible assessor judgment, e.g. all-cause mortality or non-repeatable automated laboratory assessments. Risk of bias due to measurement of these outcomes would be expected to be low.	Y / PY / PN / N / NI
	6.2 Were outcome assessors aware of the intervention received by study participants?	If outcome assessors were blinded to intervention status, the answer to this question would be 'No'. In other situations, outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators; the answer this question would then also be 'No'. In studies where participants report their outcomes themselves, for example in a questionnaire, the outcome assessor is the study participant. In an observational study, the answer to this question will usually be 'Yes' when the participants report their outcomes themselves.	Y / PY / PN / N / NI
	6.3 Were the methods of outcome assessment comparable across intervention groups?	Comparable assessment methods (i.e. data collection) would involve the same outcome detection methods and thresholds, same time point, same definition, and same measurements.	Y / PY / PN / N / NI
	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	This question refers to differential misclassification of outcomes. Systematic errors in measuring the outcome, if present, could cause bias if they are related to intervention or to a confounder of the intervention-outcome relationship. This will usually be due either to outcome assessors being aware of the intervention received or to non-comparability of outcome assessment methods, but there are examples of differential misclassification arising despite these controls being in place.	Y / PY / PN / N / NI
	Risk of bias judgement	See Table	Low / Moderate / Serious / Critical / NI
	Optional: What is the predicted direction of bias due to measurement of outcomes?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions.	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Bias in selection of the reported result			
	Is the reported effect estimate likely to be selected, on the basis of the results, from...		
	7.1. ... multiple outcome *measurements* within the outcome domain?	For a specified outcome domain, it is possible to generate multiple effect estimates for different measurements. If multiple measurements were made, but only one or a subset is reported, there is a risk of selective reporting on the basis of results.	Y / PY / PN / N / NI
	7.2 ... multiple *analyses* of the intervention-outcome relationship?	Because of the limitations of using data from non-randomized studies for analyses of effectiveness (need to control confounding, substantial missing data, etc), analysts may implement different analytic methods to address these limitations. Examples include unadjusted and adjusted models; use of final value vs change from baseline vs analysis of covariance; different transformations of variables; a continuously scaled outcome converted to categorical data with different cut-points; different sets of covariates used for adjustment; and different analytic strategies for dealing with missing data. Application of such methods generates multiple estimates of the effect of the intervention versus the comparator on the outcome. If the analyst does not pre-specify the methods to be applied, and multiple estimates are generated but only one or a subset is reported, there is a risk of selective reporting on the basis of results.	Y / PY / PN / N / NI
	7.3 ... different *subgroups*?	Particularly with large cohorts often available from routine data sources, it is possible to generate multiple effect estimates for different subgroups or simply to omit varying proportions of the original cohort. If multiple estimates are generated but only one or a subset is reported, there is a risk of selective reporting on the basis of results.	Y / PY / PN / N / NI
	Risk of bias judgement	See Table	Low / Moderate / Serious / Critical / NI
	Optional: What is the predicted direction of bias due to selection of the reported result?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions.	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall bias			
	Risk of bias judgement	See **Table** D	Low / Moderate / Serious / Critical / NI
	Optional: What is the overall predicted direction of bias for this outcome?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Table B. Reaching risk of bias judgements in ROBINS-I: pre-intervention and at-intervention domains

Judgement	Bias due to confounding	Bias in selection of participants into study	Bias in classification of interventions
Low risk of bias (the study is comparable to a well-performed randomized trial with regard to this domain)	No confounding expected.	(i) All participants who would have been eligible for the target trial were included in the study; *and* (ii) For each participant, start of follow up and start of intervention coincided.	(i) Intervention status is well defined; *and* (ii) Intervention definition is based solely on information collected at the time of intervention.
Moderate risk of bias (the study is sound for a non-randomized study with regard to this domain but cannot be considered comparable to a well-performed randomized trial)	(i) Confounding expected, all known important confounding domains appropriately measured and controlled for; *and* (ii) Reliability and validity of measurement of important domains were sufficient, such that we do not expect serious residual confounding.	(i) Selection into the study may have been related to intervention and outcome; *and* The authors used appropriate methods to adjust for the selection bias; *or* (ii) Start of follow-up and start of intervention do not coincide for all participants; *and* (a) the proportion of participants for which this was the case was too low to induce important bias; *or* (b) the authors used appropriate methods to adjust for the selection bias; *or* (c) the review authors are confident that the rate (hazard) ratio for the effect of intervention remains constant over time.	(i) Intervention status is well defined; *and* (ii) Some aspects of the assignments of intervention status were determined retrospectively.

Serious risk of bias (the study has some important problems)	(i) At least one known important domain was not appropriately measured, or not controlled for; *or* (ii) Reliability or validity of measurement of an important domain was low enough that we expect serious residual confounding.	(i) Selection into the study was related (but not very strongly) to intervention and outcome; *and* This could not be adjusted for in analyses; *or* (ii) Start of follow up and start of intervention do not coincide; *and* A potentially important amount of follow-up time is missing from analyses; *and* The rate ratio is not constant over time.	(i) Intervention status is not well defined; *or* (ii) Major aspects of the assignments of intervention status were determined in a way that could have been affected by knowledge of the outcome.
Critical risk of bias (the study is too problematic to provide any useful evidence on the effects of intervention)	(i) Confounding inherently not controllable *or* (ii) The use of negative controls strongly suggests unmeasured confounding.	(i) Selection into the study was very strongly related to intervention and outcome; *and* This could not be adjusted for in analyses; *or* (ii) A substantial amount of follow-up time is likely to be missing from analyses; *and* The rate ratio is not constant over time.	(Unusual) An extremely high amount of misclassification of intervention status, e.g. because of unusually strong recall biases.
No information on which to base a judgement about risk of bias for this domain	No information on whether confounding might be present.	No information is reported about selection of participants into the study or whether start of follow up and start of intervention coincide.	No definition of the intervention or no explanation of the source of information about intervention status is reported.

Table C. Reaching risk of bias judgements in ROBINS-I: post-intervention domains

Judgement	**Bias due to deviations from intended intervention**	**Bias due to missing data**	**Bias in measurement of outcomes**	**Bias in selection of the reported result**
Low risk of bias (the study is comparable to a well-performed randomized trial with regard to this domain)	**Effect of assignment to intervention:** (i) Any deviations from intended intervention reflected usual practice; *or* (ii) Any deviations from usual practice were unlikely to impact on the outcome. **Effect of starting and adhering to intervention:** The important **co-interventions** were balanced across intervention groups, and there were no deviations from the intended interventions (in terms of **implementation or adherence**) that were likely to impact on the outcome.	(i) Data were reasonably complete; *or* (ii) Proportions of and reasons for missing participants were similar across intervention groups; *or* (iii) The analysis addressed missing data and is likely to have removed any risk of bias.	(i) The methods of outcome assessment were comparable across intervention groups; *and* (ii) The outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants (i.e. is objective) or the outcome assessors were unaware of the intervention received by study participants; *and* (iii) Any error in measuring the outcome is unrelated to intervention status.	There is clear evidence (usually through examination of a pre-registered protocol or statistical analysis plan) that all reported results correspond to all intended outcomes, analyses and sub-cohorts.

Moderate risk of bias (the study is sound for a non-randomized study with regard to this domain but cannot be considered comparable to a well-performed randomized trial)	**Effect of assignment to intervention:** There were deviations from usual practice, but their impact on the outcome is expected to be slight. **Effect of starting and adhering to intervention:** (i) There were deviations from intended intervention, but their impact on the outcome is expected to be slight. *or* (ii) The important co-interventions were not balanced across intervention groups, or there were deviations from the intended interventions (in terms of implementation and/or adherence) that were likely to impact on the outcome; *and* The analysis was appropriate to estimate the effect of starting and adhering to intervention, allowing for deviations (in terms of implementation, adherence and co-intervention) that were likely to impact on the outcome.	(i) Proportions of and reasons for missing participants differ slightly across intervention groups; *and* (ii) The analysis is unlikely to have removed the risk of bias arising from the missing data.	(i) The methods of outcome assessment were comparable across intervention groups; *and* (ii) The outcome measure is only minimally influenced by knowledge of the intervention received by study participants; *and* (iii) Any error in measuring the outcome is only minimally related to intervention status.	(i) The outcome measurements and analyses are consistent with an *a priori* plan; or are clearly defined and both internally and externally consistent; *and* (ii) There is no indication of selection of the reported analysis from among multiple analyses; *and* (iii) There is no indication of selection of the cohort or subgroups for analysis and reporting on the basis of the results.

Serious risk of bias (the study has some important problems)	**Effect of assignment to intervention:** There were deviations from usual practice that were unbalanced between the intervention groups and likely to have affected the outcome. **Effect of starting and adhering to intervention:** (i) The important co-interventions were not balanced across intervention groups, or there were deviations from the intended interventions (in terms of implementation and/or adherence) that were likely to impact on the outcome; *and* (ii) The analysis was not appropriate to estimate the effect of starting and adhering to intervention, allowing for deviations (in terms of implementation, adherence and co-intervention) that were likely to impact on the outcome.	(i) Proportions of missing participants differ substantially across interventions; *or* Reasons for missingness differ substantially across interventions; *and* (ii) The analysis is unlikely to have removed the risk of bias arising from the missing data; *or* Missing data were addressed inappropriately in the analysis; *or* The nature of the missing data means that the risk of bias cannot be removed through appropriate analysis.	(i) The methods of outcome assessment were not comparable across intervention groups; *or* (ii) The outcome measure was subjective (i.e. vulnerable to influence by knowledge of the intervention received by study participants); *and* The outcome was assessed by assessors aware of the intervention received by study participants; *or* (iii) Error in measuring the outcome was related to intervention status.	(i) Outcomes are defined in different ways in the methods and results sections, or in different publications of the study; *or* (ii) There is a high risk of selective reporting from among multiple analyses; *or* (iii) The cohort or subgroup is selected from a larger study for analysis and appears to be reported on the basis of the results.

Critical risk of bias (the study is too problematic to provide any useful evidence on the effects of intervention)	**Effect of assignment to intervention:** There were substantial deviations from usual practice that were unbalanced between the intervention groups and likely to have affected the outcome. **Effect of starting and adhering to intervention:** (i) There were substantial imbalances in important co-interventions across intervention groups, or there were substantial deviations from the intended interventions (in terms of implementation and/or adherence) that were likely to impact on the outcome; *and* (ii) The analysis was not appropriate to estimate the effect of starting and adhering to intervention, allowing for deviations (in terms of implementation, adherence and co-intervention) that were likely to impact on the outcome.	(i) (Unusual) There were critical differences between interventions in participants with missing data; *and* (ii) Missing data were not, or could not, be addressed through appropriate analysis.	The methods of outcome assessment were so different that they cannot reasonably be compared across intervention groups.	(i) There is evidence or strong suspicion of selective reporting of results; *and* (ii) The unreported results are likely to be substantially different from the reported results.
No information on which to base a judgement about risk of bias for this domain	No information is reported on whether there is deviation from the intended intervention.	No information is reported about missing data or the potential for data to be missing.	No information is reported about the methods of outcome assessment.	There is too little information to make a judgement (for example, if only an abstract is available for the study).

Table D. Interpretation of domain-level and overall risk of bias judgements in ROBINS-I*

Judgement	Within each domain	Across domains	Criterion
Low risk of bias	The study is comparable to a well-performed randomized trial with regard to this domain	The study is comparable to a well-performed randomized trial	The study is judged to be at **low risk of bias for all domains**.
Moderate risk of bias	The study is sound for a non-randomized study with regard to this domain but cannot be considered comparable to a well-performed randomized trial	The study provides sound evidence for a non-randomized study but cannot be considered comparable to a well-performed randomized trial	The study is judged to be at **low or moderate risk of bias for all domains**.
Serious risk of bias	the study has some important problems in this domain	The study has some important problems	The study is judged to be at **serious risk of bias** in at least one domain, but not at critical risk of bias in any domain.
Critical risk of bias	the study is too problematic in this domain to provide any useful evidence on the effects of intervention	The study is too problematic to provide any useful evidence and should not be included in any synthesis	The study is judged to be at **critical risk of bias in at least one domain.**
No information	No information on which to base a judgement about risk of bias for this domain	No information on which to base a judgement about risk of bias	There is no clear indication that the study is at serious or critical risk of bias *and* there is a lack of information in one or more key domains of bias (*a judgement is required for this*).

*Also saved as table 2 in main article.