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Title: The content of prehabilitative interventions for patients undergoing repair of abdominal aortic aneurysms and their effect on post-operative outcomes; a systematic review

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What this paper adds

This study provides a review of current evidence investigating prehabilitation in patients undergoing abdominal aorta aneurysm (AAA) repair and its effects on post-operative outcomes. Whilst prehabilitation has potential to improve clinical and health-related quality of life outcomes, the limited and heterogenous state of current literature precludes conclusive recommendations for future practice. The contents of included interventions were analysed and found to be generally inadequately described according to existing reporting standards. More high-quality trials, conforming to an urgently needed set of core outcomes and reporting standards, are required to best inform the clinical and cost-effectiveness of prehabilitation for AAA repair.

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Keywords

Abdominal aortic aneurysm

Surgery

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Abstract

Objectives: Patients requiring abdominal aortic aneurysm (AAA) repair are at risk of post-operative complications due to poor pre-operative state. Prehabilitation describes the enhancement of functional capacity and tolerance to an upcoming physiologic stressor, intended to reduce these complications. The ability to provide such an intervention (physical, pharmacological, nutritional, or psychosocial) between diagnosis and surgery is a growing interest, but its role in AAA repair is unclear. This paper aims to systematically review existing literature to better describe the effect of prehabilitative interventions on post-operative outcomes of patients undergoing AAA repair.

Data Sources: EMBASE and Medline were searched from inception to October 2020. Retrieved papers, systematic reviews, and trial registries were citation-tracked.

Review Methods: Randomised controlled trials (RCTs) comparing post-operative outcomes for adult patients undergoing a period of prehabilitation prior to AAA repair (open or endovascular) were eligible for inclusion. Two authors screened titles for inclusion, assessed risk of bias, and extracted data. Primary outcomes were post-operative 30-day mortality, composite endpoint of 30-day post-operative complications, hospital length of stay (LOS), and health-related quality of life (HRQL) outcomes. The content of interventions was extracted and a narrative analysis of results undertaken.

Results: Seven RCTs with 901 patients were included (3 exercise-based, 2 pharmacological-based, and 2 nutritional-based). Risk of bias was mostly unclear or high and the clinical heterogeneity between the trials precluded data pooling for meta-analyses. The quality of intervention descriptions was highly variable. One exercise-based RCT reported significantly reduced hospital LOS and another improved HRQL outcomes. Pharmacological nor nutritional-based RCTs reported significant differences in primary outcomes.

Conclusions: There is limited evidence to draw clinically robust conclusions about the effect of prehabilitation on post-operative outcomes following AAA repair. Well-designed RCTs, adhering to reporting standards for intervention content and trial methods, are urgently needed to establish the clinical-effectiveness and cost-effectiveness of prehabilitation interventions.

Introduction

Abdominal Aortic Aneurysm (AAA) is a permanent, focal, full-thickness dilatation of the abdominal aorta (luminal diameter ≥3.0cm) with the risk of AAA rupture increasing with diameter. An anteroposterior diameter of 5.5cm is typically the threshold at which open or endovascular (EVAR) repair is offered.

The risk factors predisposing AAA development are also those predicting morbidity and mortality post-surgery, with an estimated 17% of people with AAA referred deemed unsuitable for surgery[1]. Attitudes towards the use of EVAR for patients deemed unfit for open repair are changing due to potentially worse long-term morbidity and mortality[2,3]. As such, there is an increasing need to improve this cohort's pre-operative health.

The period between AAA diagnosis and repair is a potential window for patient optimisation. Prehabilitation describes the process of enhancing a patient's functional capacity to improve their tolerance for an upcoming physiologic stressor, aiming to improve peri-operative and post-operative outcomes[4]. A systematic review by Kato et al[5] in 2019 investigated the safety of exercise training compared with usual care for patients with AAA (≥3cm). This review of 7 trials (489 patients) concluded that exercise training was safe (adverse cardiac event rate during exercise training 0.8%, 95% confidence intervals [CI] 0.2% to 3.1%), with no reports of AAA rupture. Significant improvements in recognised predictors of short- and long-term survival after elective AAA (pre-operative peak oxygen consumption and anaerobic threshold) in favour of exercise were also observed.

Prehabilitation can also be a complex intervention, including pharmacological, nutritional, and psychosocial modalities. Cancer management pathways encourage this multi-modal approach for pre-operative optimisation[6], but recent systematic reviews[7,8] of randomised controlled trials (RCTs) conclude that more high-quality studies are needed to confirm their benefits amongst various patient groups (e.g. level of risk and cancer type). Furthermore, a recent mixed-methods analysis[9] suggests that RCTs with poor rehabilitative intervention development are less likely to report treatment success. To our knowledge, the quality and effects of such interventions prior to elective AAA repair have not been reviewed.

Current national and international guidelines[2,10,11] highlight a lack of literature examining AAA pre-operative optimisation. This study aims to systematically review the content of prehabilitative interventions for patients undergoing AAA repair and their effect on

postoperative outcomes to inform future studies and the preoperative management in this population.

Methods

This systematic review was prospectively registered on PROSPERO (CRD42019157759) and was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[12].

Data searches and sources

A literature search was performed using EMBASE (1947 to October 2020) and Medline (1946 to October 2020) *(see Supplementary information)*. PROSPERO, the ClinicalTrials.gov registry, Cochrane database, and the WHO International Clinical Trials Registry Platform were searched for active and unpublished trials. References from relevant papers were reviewed to identify other relevant trials and papers describing study protocols. Further searches were run in Google scholar to identify any trials, or companion papers, missing from the original searches. The search was limited to English language.

Study selection

RCTs investigating the effect of one or more prehabilitative interventions compared with usual care or placebo, on the postoperative outcomes of patients undergoing elective AAA repair (open or EVAR) were included. Studies including participants at least 18 years old, diagnosed with an AAA requiring repair, with any level of risk of post-operative mortality were eligible for inclusion. Eligible interventions included physical exercise, psychosocial, nutritional, or pharmacological interventions designed to improve an individual's physical or mental health in the period between identifying the need for repair and the operation. Since an objective of this study was to assess the content of these prehabilitative interventions no further selection criteria, such as minimum intervention duration, were set. Interventions restricted to the peri-operative period, including those administered as part of the direct work-up to surgery (24 hours prior to operation), were excluded. Studies could include one of the pre-operative interventions listed above within the standard care as long as both intervention and control groups were in receipt of usual care, and the intervention tested the direct effect of another intervention of interest provided in addition to usual care.

Trials reporting at least one of the post-operative clinical outcomes (Table 1) were eligible for inclusion. Similarly to intervention selection, no minimum follow-up time or further criteria were set.

Duplicate studies were removed and the titles and abstracts were screened for potential inclusion by two independent reviewers (RJB and ADJ). The full text reports of the remaining studies were subjected to the inclusion criteria by two independent researchers (RJB and ADJ); any disagreements were settled by a third reviewer (SHR).

Outcomes

The primary and secondary clinical outcomes of interest (Table 1) are based on the Society for Vascular Surgery Reporting Standards for EVAR[13] and expert opinion (Professor, DJS, and Consultant, TW, Vascular Surgeons). Participant reported health-related quality of life (HRQL) outcomes are also considered primary outcomes as they are important indicators of treatment success.

Data extraction and management

Data from the selected studies were independently extracted by one author (RJB) and checked by another (SHR) using a standardised pro forma; any disagreements were resolved by discussion. Authors of included papers were contacted in the event of missing data in relation to primary outcomes of interest.

Participant baseline characteristics (mean age, proportion of females, mean AAA diameter, proportion of ethnicities) and mortality risk factors based on expert opinion (derived from European Society for Vascular Surgery guidelines[10]) were extracted using a standardised data extraction tool. The Template for Intervention Description and Replication (TIDieR) checklist[14] and an extension based on Goodwin et al[9] were used to guide intervention appraisal. The interventions' theories, designs, and procedures were extracted onto a standardised pro forma, referring to both the trial report, and any linked publications, supplemental materials and/or protocols describing intervention delivery. Event rate data were extracted for the clinical outcomes (mortality, post-operative composite complications). Means and standard deviations were extracted for the continuous outcomes (e.g. HRQL, hospital length of stay (LOS), health economic data); standard deviation was calculated if only standard error of the mean was provided.

Assessment of risk of bias and overall quality of evidence

The Cochrane Collaboration's tool for assessing risk of bias[15] was applied. Each category was scored as "low", "high", or "unclear" risk of bias depending on the information reported. All included papers were assessed for risk of bias by two independent researchers (RJB and ADJ) to ensure accuracy, with any disputes settled by a third reviewer (SHR).

Data synthesis and analysis

A narrative synthesis was undertaken as the clinical and methodological heterogeneity between prehabilitation interventions/trials precluded the pooling of data across studies. The results were grouped by prehabilitation type and the outcomes described for each group of interventions. The results of any sub-group analyses performed, comparing outcomes between open repair and EVAR, are stated within the narrative analysis. Any adjustments made for confounding factors by the authors is specified within the results.

Results

Study selection and inclusion

The PRISMA flow chart is summarised in Figure 1. After removing duplicate titles, 1639 papers were identified from electronic searches. Following the review of titles and abstracts, 1586 studies were excluded, and a full-text review was conducted for the remaining 53 papers. After final eligibility checks, 8 studies[16–23] were included (901 participants; study samples ranged from 14 to 624). No further studies were identified from citation tracking or manual online searches.

Intervention, study, and participant characteristics

The prehabilitation interventions all tested single component interventions including: exercise (3 studies[20–22]), pharmacological (3 studies[16,17,19]), and nutritional (2 studies[18,23]); no study investigated the effects of a psychosocial intervention. Table 2 summarises the intervention characteristics and Table 3 further summarises the reporting of the content of the comparators and prehabilitation interventions. Overall, both the intervention and comparator were inadequately described in each included study. Additionally, regarding materials and resources used, no study described the participant information provided. The Barry et al[16] and Mealy et al[17] papers reported results from the same study population and are regarded as the same cohort in analysis.

The procedures performed in each study (open or EVAR), the types of prehabilitative interventions tested, and baseline characteristics of the patients are presented in Table 4. The studies were published in Europe[16,17,19–22] and North America[18,23] from 1998 to 2018. The baseline characteristics and co-morbidities reported varied between studies. Similarly, duration of intervention and length of follow-up were inconsistent between prehabilitation types. Supplementary Table 2 lists the mortality risk factors and outcomes of interest reported by each study.

Risk of bias assessment

The risk of bias scores for each study were variable (Figure 2): one study[23] was deemed low risk in all domains, one study[22] had unclear risk for ITT analysis methods, and six studies[16–21] were either at high risk in at least one domain or unclear risk in more than one domain. Specifically, five papers[16,17,19–21] had unclear or high risk for blinding of assessors to outcomes and five papers[16–19,22] did not adequately describe ITT analysis methods.

Adherence to prehabilitation interventions

Four studies[18,21–23] assessed the adherence to their interventions. Of the exercised-based interventions, 32/62 (51.6%)[21] and 17/27 (63% [95% CI, 45 to 81])[22] attended at least 75% of classes. The two nutrition-based interventions reported pill counts to assess adherence, reporting at least 90% compliance in one study[18] and a median of 32/32 pills consumed in the other[23].

Neither of the pharmacological-based studies[16,17,19] measured compliance.

Exercise-based interventions

Primary outcomes

Two studies[21,22] reported post-operative 30-day mortality and neither found significant differences between groups. Barakat et al[21] reported a significant reduction in the median hospital LOS in the exercise group (7.0 days, IQR 5.0 to 9.0) compared to usual care (8.0 days, IQR 6.0 to 12.3) (p = .025). Sub-group analysis revealed significant reduction in hospital LOS following EVAR only, not open repair. Tew et al[22] found the median hospital LOS to be 7 days (IQR 4.5 to 8.5) in the intervention group compared to 6 days (IQR 4 to 8) in the control. Two studies[21,22] reported HRQL between the exercise and usual care groups at 3 months after discharge. Tew et al[22] reported significant improvements in the EuroQol five-dimension questionnaire (EQ-5D) [95% CI, 0.005 to 0.148] and 36-item Short Form Survey (SF-36) physical function (PF) subscale [95% CI, 0.4 to 5.4] following pre-operative exercise, but no difference in the EuroQol visual analogue scale (EQ-VAS) and SF-36 mental health (MH) subscale (analysis adjusted for baseline scores). In contrast, Barakat et al[21] reported no differences in mobility impairment using an undefined measure. Dronkers et al[20] circulated a patient satisfaction questionnaire to the intervention group only.

No exercise-based study reported composite endpoint of 30-day post-operative complications.

Secondary outcomes

Two studies[21,22] reported the composite endpoint of total post-operative complications. Barakat et al[21] found significant reductions in combined cardiac, pulmonary, and renal complications at 3 months after discharge with exercise (14/62, 22.6%) compared to usual care (26/62, 41.9%) (p = .021). When the authors individually analysed systemic complications, cardiac and renal complications were significantly reduced but pulmonary were not. Additionally, sub-group analysis within the exercise group showed that cardiac and renal complications were significantly reduced following open repair only, not EVAR. Tew et al[22] reported Post-Operative Morbidity Survey scores and did not find significant differences between intervention and control until discharge date. Dronkers et al[20] did not find a significant reduction in the incidence of atelectasis – the follow-up period was not defined. Barakat et al[21] also reported rates of re-operation and post-operative bleeding or transfusion of more than 4 units but found no significant differences between groups. No other rates of surgical complications were described in the 3 studies.

Tew et al[22] reported 3 adverse events (2 withdrawals and referral to cardiology, 1 cessation of exercise with angina) in the exercise group but no comparison was made with usual care. The other 2 studies[21,22] reported "no adverse events" but did not define what constituted an adverse event.

No exercise-based study compared total post-operative mortality at follow-up or the rates of discharge to independent living between groups. Dronkers et al[20] reported the death of one participant in the intervention group but did not report if deaths occurred in the control.

Pharmacological-based interventions

Primary outcomes

Barry and Mealy et al[16,17] reported 1 post-operative death (in the control group) within 30 days and a mean hospital LOS of 13 days (SEM 2) in the intervention group compared to 17 (SEM 3) in the control. Decker et al[19] found no significant difference in mean hospital LOS between the human recombinant growth hormone (HrGH) and placebo groups.

No pharmacological-based study reported composite endpoint of 30-day post-operative complications or HRQL outcomes at follow-up.

Secondary outcomes

Barry and Mealy et al[16,17] reported post-operative mortality and systemic complications at 50 days following surgery: 1 patient in the control group suffered a brain stem infarct which subsequently led to respiratory failure and death. Decker et al[19] stated "no complications occurred" but did not define their criteria. Neither study reported significant differences in intensive care unit (ICU) / high dependency unit (HDU) LOS. Barry and Mealy et al[16,17] reported adverse events and described 1 patient who experienced hyperglycaemia requiring treatment due to the HrGH therapy.

No pharmacological-based study reported rates of post-operative surgical complications or discharge to independent living.

Nutrition-based interventions

Primary outcomes

Both studies[18,23] reported post-operative 30-day mortality and median[23] or mean[18] hospital LOS, no significant differences were found. Garg et al[23] found no significant reduction in composite endpoint of 30-day post-operative complications (including 14 clinical events) following curcumin supplementation. Watters et al[18] examined HRQL outcomes and found significant improvements in the physical function ($p < .05$) and general health ($p < .05$) components of SF-36 in the micronutrient supplementation group at 4 weeks following surgery. No significant differences were reported in the EQ-VAS at 7 days, Karnofsky performance status[24] at 4 weeks, or other SF-36 components at 4 weeks following surgery.

Secondary outcomes

Garg et al[23] reported total post-operative mortality (at 90 days after surgery) and found no significant difference. The same paper also compared the rate of acute kidney injury (AKI) in the first 48 post-operative hours and reported a significant decrease with curcumin supplementation (51/301, 16.9%) versus placebo (30/302, 9.9%) ($p = .01$). Watters et al[18] measured ICU/HDU LOS and found no significant differences between groups. Garg et al[23] reported no significant differences in rates of clinically important bleeding or adverse events between groups.

No nutrition-based study reported composite endpoint of total post-operative complications or rates of discharge to independent living.

No difference in outcomes between open and EVAR procedures were reported by Garg et al following sub-group analysis.

Health economic data analysis

One study[22] performed an economic evaluation of their prehabilitation intervention against the comparator. Tew et al[22], who conducted a feasibility study, found no significant comparison in the bootstrapped mean differences of the total costs between their exercise therapy and usual care.

Discussion

Main Findings

Research into the effectiveness of prehabilitation between diagnosis and elective surgery is increasing. Whilst commonly regarded as exercise-based, there are other strategies to optimise a patient's physical and mental health. This review summarised the content of prehabilitation interventions and explored their effect on post-operative outcomes for patients undergoing AAA repair. Seven trials[16–23] were identified evaluating single-component prehabilitation interventions testing the effectiveness of exercise (n=3), pharmacological interventions (HrGH therapy; n=2), or nutritional supplementation (n=2, micronutrient, curcumin); no trials tested interventions targeting psychosocial factors; only one included assessment of the health economic impact[22]. When assessed relative to standardised reporting guidelines[9,14], while all studies reported the rationale of their intervention, none satisfied all the criteria regarding the content of intervention and/or comparator groups.

Over half the trials were of unknown or high risk of bias, and the clinical and methodological heterogeneity observed ruled out meta-analysis. The outcomes reported varied considerably, in part reflecting the different interventions evaluated. Notwithstanding this, the measures likely to be of importance to patients (e.g. HRQL and functioning) were sparsely reported. Important sub-group analysis and adjustments for confounding factors were also limited. Regarding the three exercise-based trials, it should be noted only one[21] was sufficiently powered to identify clinically important differences; the other two were pilot[20] or feasibility[22] trials.

Overall, hospital LOS was significantly improved in one study[21] and HRQL outcomes in another[22] following different pre-operative exercise regimes. One study[23] reported reduced rates of AKI following curcumin supplementation. There was no evidence of differences in clinical outcomes in the pharmacological-based studies[16,17,19].

Findings in context

A recent meta-analysis[25] investigating the effects of exercise therapies prior to abdominal surgeries (cancer resection, AAA repair, bariatric surgery) observed a reduction in overall morbidity (n=9 trials; odds ratio [OR] 0.63, 95% CI 0.46 to 0.87) and pulmonary morbidity (n=9 trials; OR 0.40, 95% CI 0.23 to 0.68) following exercise intervention compared with controls. However, our review demonstrates that there is insufficient evidence to make recommendations regarding the most effective types of exercise when limiting to people

undergoing AAA repair. Furthermore, prehabilitation may provide varied benefit depending on surgical approach (EVAR or open) as shown by the differences seen in the exercise study by Barakat et al[21].

Although a small trial[16,17] investigated the effects of HrGH on cardiorespiratory function and the acute inflammatory response; more than 20 years later HrGH is not widely used for pre- or post-surgical optimisation. As ischaemic heart disease, congestive heart failure, diabetes mellitus, renal insufficiency, peripheral arterial disease, and chronic obstructive pulmonary disease are recognised predictors of post-operative complications[10], all remain plausible targets for pre-operative optimisation. European guidelines[10] recommend blood pressure control, statins, and antiplatelet therapy for all patients with AAA, but no drug has been found to slow the rate of AAA growth.

Interestingly, smoking is the strongest associated modifiable risk factor of AAA[26]. There is evidence that psychological intervention with behavioural support have been shown to improve the rates of smoking cessation and reduce anxiety levels in patients awaiting surgery[27,28]. Most AAA guidelines[2,10,11] recommend smoking cessation, often at least 2 weeks before surgery, however the value of incorporating this support into prehabilitation for patients with AAA is untested.

Pre-operative nutrition is increasingly recommended for surgical management. Malnutrition results in poor patient outcomes due to the high metabolic demands of the surgical stress response[29]. An observational study[30] of 15,002 patients reported significantly increased 30-day mortality, re-operation rates, and pulmonary complications in patients undergoing AAA repair with hypoalbuminaemia (a marker of malnutrition). While recent guidelines[10,11] advise the assessment and optimisation of nutritional status in the pre-operative period, it is unclear whether it is changing clinical practice, or could be effectively included as part of prehabilitation.

Studies seeking to combine different treatments into a multi-modal prehabilitation package are limited. Bolshinsky et al[31] systematically reviewed RCTs and observational evidence to investigate the effect of multi-modal prehabilitation in gastrointestinal cancer surgery. Like our review, they were unable to draw conclusions about its effectiveness and its integration into normal care due to lack of studies. An RCT[32] comparing multi-modal prehabilitation (personalised programmes to promote healthy living, exercise, and motivational interviewing) in patients undergoing major abdominal surgery showed reduced post-operative

complications compared to standard care. While there remains considerable potential to undertake sufficiently powered prehabilitation trials in AAA repair, evaluating both single and multi-modal interventions, the lack of evidence means it is too early to make evidence-based recommendations for clinical practice.

Study strengths and limitations

Despite adopting a broad definition of prehabilitation, only seven trials were deemed eligible for inclusion. By applying standardised checklists[9,14], we were able to systematically describe the contents of interventions and identify important gaps in the reporting of treatment protocols. However, the small number of studies, combined with poor reporting of pre-operative risk factors and heterogeneity of intervention components, limited the ability to evaluate the effect of prehabilitation on AAA repair. Importantly, two studies[21,22] testing exercise regimes reported low intervention adherence (51% and 63%) and this has potential to dilute treatment effects in an intention-to-treat analysis. It remains possible that treatment effects could be improved by incorporating strategies to increase adherence to exercise interventions, but this is currently untested. Furthermore, all interventions were uni-modal thus any potential synergistic effects of combining treatments were not measurable.

Implications for practice

Whilst a prehabilitation care bundle could provide an answer to the poor fitness levels in pre-operative AAA patients, it is important to consider the challenges of implementing it in practice. An editorial[33], responding to the new Macmillan Cancer Support prehabilitation guidance, raises concerns about the potential burden on patients. Prehabilitation aims to empower the patient by giving them control, but this new responsibility, amongst the high volume of information that is delivered alongside, could be overwhelming. This further supports the inclusion of psychological interventions in prehabilitation, as well as adherence support strategies to enhance patient compliance[14].

The optimum timeframe to deliver prehabilitation care also needs further investigation. The trial by Barakat et al[21] showed improved post-operative outcomes with their 6-week exercise programme whilst current UK guidance[1] advices AAA repair to occur within 8 weeks of diagnosis. Therefore, there is an evident window of time which should be used productively to improve the pre-operative fitness of patients with AAA. Clearly, the perceived benefit of any prehabilitative intervention would need to be weighed against the individual's risk of rupture by delaying the definitive repair. Several weeks of exercise-based prehabilitation may

not be appropriate in those with very large aneurysms, who tend to be admitted and repaired on an urgent basis. Cardiopulmonary testing is already being used to assess patients' pre-operative fitness and it could provide an opportunity to recognise individual needs prior to the invasive procedure[5,10,34]. Moreover, Tew et al[22] reported no surgeries were delayed due to their exercise programme. It is also possible that initiating prehabilitative modalities at different times, even before the patient has reached the threshold for surgery, results in beneficial effects. Twelve studies were excluded as the interventions were only administered in the peri-operative period (Figure 1) and there might be some value to these as part of an expanded multi-modal programme.

Implications for research

There is a paucity of high-quality research into the acceptability, and clinical and cost effectiveness of different types of prehabilitation intervention, and on how to combine them to achieve the best outcomes for patients waiting for AAA repair. The use of reporting standards (e.g. TIDIER checklist[14] including the Goodwin et al[9] extension for physical interventions), can guide the design of future prehabilitation interventions thus improving study quality and generalisability. Authors should carefully consider the issues surrounding compliance to prehabilitative interventions during the design phase to better establish its feasibility and effect. There is an urgent need to agree a core outcome measurement set for such trials, including outcomes of importance to both clinicians and patients, to allow direct comparisons between studies and to aid meta-analysis in the future. Together with consistent reporting of important baseline characteristics, such as AAA diameter and the presence of co-morbidities, adherence rates, and the procedures performed (with sub-group analysis), care providers will be more informed to decide which populations should receive certain treatments.

Conclusions

The time between diagnosis and repair for AAA presents an opportunistic period to implement prehabilitative interventions and optimise pre-operative state to improve post-operative outcomes. RCTs investigating prehabilitation in patients undergoing AAA repair are limited in availability and quality, limiting the ability to draw robust conclusions to inform practice. More high-quality trials investigating and comparing the various prehabilitative modalities are required to inform the clinical and cost-effectiveness, and to guide best practice for patients undergoing AAA repair.

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Conflict of interest statement

No authors of this study have any conflicting interests.

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Table 1: Primary and secondary outcomes.

Primary Outcomes	Secondary Outcomes
Post-operative 30-day mortality	Adherence to the intervention
Composite endpoint of 30-day post-operative complications	Post-operative mortality at follow-up (if longer than 30 days)
Hospital LOS	Composite endpoint of total post-operative complications (if longer than 30 days)
HRQL outcomes at follow-up (EQ-5D[24]; **EQ-VAS**[26]; **SF-36 PF and MH subscales**[25])	Post-operative systemic complications for the following areas: cardiac, pulmonary, renal, neurological, delirium
	Post-operative surgical complications: haemorrhage, transfusion, limb ischaemia, limb loss, sepsis, complications requiring endovascular or open surgical re-intervention, readmission within 30 days
	ICU / HDU LOS
	Adverse outcomes that: are life-threatening, result in death, cause significant morbidity, require hospitalisation or a prolonged hospital admission, require additional intervention to treat it, or lead to the participant needing to withdraw from the trial
	Discharge to independent living
	Health economic data

Table 1 legend: EQ-5D, EuroQol five-dimension questionnaire; EQ-VAS, EuroQol visual analogue scale; SF-36, 36-item Short Form Survey; PF, physical function; MH, mental health; ICU, intensive care unit; HDU, high dependency unit

Table 2: Intervention characteristics of included studies.

Trial	Type ǂ	Intervention (I) and control (C) ǂ,¶	Duration ǂ	Mode, Setting ǂ	Staff level of training ǂ	Pilot study / Piloted §
Dronkers et al 2008[20]	Exercise (unimodal)	I: "Inspiratory muscle training" C: Usual care	At least 2 weeks pre-operative	Single-centre 1 session per week was supervised, 5 sessions were unsupervised *Location of intervention provision/ administration NR*	Experienced physical therapist	Pilot
Barakat et al 2016[21]	Exercise (unimodal)	I: "Hospital-based exercise class" C: Usual care	6 weeks pre-operative	Single-centre Supervised Hospital-based, physiotherapy gym	*NR*	Piloted
Tew et al 2017[22]	Exercise (unimodal)	I: "HIT programme" C: Usual care	At least 4 weeks pre-operative	Multi-centre (3) Each session supervised Hospital-based *(no further information)*	Research nurse and physio-therapist, trained in ILS	Pilot
Barry and Mealy et al 1998[16,17]	Pharmacological (unimodal)	I: HrGH C: Placebo	6 days pre-operative until 6 days post-operative	Single-centre *Location of intervention provision/ administration NR*	*NR*	–
Decker et al 2005[19]	Pharmacological (unimodal)	I: HrGH C: Placebo	2 days pre-operative until 7 days post-operative	Single-centre *Location of intervention provision/ administration NR*	*NR*	–
Watters et al 2002[18]	Nutrition (unimodal)	I: Micronutrient supplement C: Placebo	2 to 3 weeks pre-operative until 7 days post-operative	Single-centre *Location of intervention provision/ administration NR*	*NR*	–
Garg et al 2018[23]	Nutrition (unimodal)	I: Curcumin supplement C: Placebo	2 days pre-operative until 1-day post-operative	Multi-centre (10) *Location of intervention provision/ administration NR*	*NR*	–

Table 2 legend: ǂ, Criteria definition from TIDieR guidelines[14]; §, Additional criteria definition from Goodwin et al guidelines[9] – only applicable to exercise-based interventions. ¶, *See Supplementary Table 1* for full details of procedures and doses reported.
HIT, high-intensity interval training; HrGH, human recombinant growth hormone; ILS, immediate life support
NR, not reported.

Table 3: Study intervention and comparator descriptions.

Trial	Rationale ǂ	Comparator ǂ	Materials and sources ǂ	Tailoring ǂ	Modification ǂ	Fidelity assessment ǂ	Co-design §	Context considered §	Adherence support §
Dronkers et al 2008[20]	Full	Partial	I: Partial C: Partial	Full	*NR*	*NR*	*NR*	*Pilot study*	*NR*
Barakat et al 2016[21]	Full	Partial	I: Partial C: *NR*	*NR*	*NR*	Partial	*NR*	Full	Partial
Tew et al 2017[22]	Full	Partial	I: Partial C: NR	Full	*NR*	Full	*NR*	*Feasibility study*	Full
Barry and Mealy et al 1998[16,17]	Full	Partial	I: Partial C: *NR*	*NR*	*NR*	*NR*	–	–	–
Decker et al 2005[19]	Full	Partial	I: Partial C: *NR*	*NR*	*NR*	*NR*	–	–	–
Watters et al 2002[18]	Full	Partial	I: Partial C: *NR*	*NR*	*NR*	*NR*	–	–	–
Garg et al 2018[23]	Full	Partial	I: Partial C: Partial	Partial	*NR*	*NR*	–	–	–

Table 3 legend: ǂ, Criteria definition from TIDieR guidelines[14]; §, Additional criteria definition from Goodwin et al guidelines[9] – only applicable to exercise-based interventions.
Rating system: Full, describes criteria to standard of guidelines; Partial, describes criteria but not to standard of guidelines; *NR*, not reported.

Table 4: General study and participant characteristics.

Trial (Country)	Procedure	Type ¶	Longest follow-up time	AAA pathology, [mean diameter (SD)]	Participants allocated to group (I/C)	Age, mean (SD)	Female sex, n (%) §	Ethnicity (white), n (%)
Dronkers et al 2008[20] (Netherlands)	*NR*	Exercise	2 weeks post-discharge	*NR [NR]*	10/10 ǀ	I: 70 (6) C: 59 (6)*	I: 8 (80) C: 7 (70)	*NR*
Barakat et al 2016[21] (UK)	Open or EVAR	Exercise	3 months post-discharge	*NR* [AAA ≥5.5cm in maximum diameter, I: 6.0 (0.7) C: 6.3 (0.9)]	68/68	I: 73.8 (6.5) C: 72.9 (7.9)	I: 6 (9.7) C: 7 (11.3)	*NR*
Tew et al 2017[22] (UK)	Open or EVAR	Exercise	12 weeks post-discharge	Infra-renal AAA [5.5 to 7cm diameter, I: 6.0 (0.4) C: 5.8 (0.4)]	27/26	I: 74.6 (5.5) C: 74.9 (6.4)	I: 2 (7.4) C: 1 (3.8)	*NR*
Barry and Mealy et al 1998[16,17] (Ireland)	*NR*	Pharmacological	50 days post-op	*NR [NR]*	8/10 ǀ	I: 71.1 (6.2) C: 72.7 (4.7)	I: 2 (25) C: 0 (0)	*NR*
Decker et al 2005[19] (Germany)	Open	Pharmacological	7 days post-op	Infra-renal AAA *[NR]*	7/7 ǀ	I: 67 (57-78) † C: 69.8 (51-77) †	I: 2 (28.6) C: 3 (42.9)	*NR*
Watters et al 2002[18] (Canada)	*NR*	Nutrition	30 days post-op	Infra-renal AAA *[NR]*	18/18 ǀ	I: 70 (1) C: 72 (5)	I: 14 (77.8) C: 14 (77.8)	*NR*
Garg et al 2018[23] (Canada)	Open or EVAR	Nutrition	30 days post-op	*NR* [I: 57 (54 to 61) C: 57 (55 to 60)] ǂ	313/311	I: 76 (71 to 80) ǂ C: 76 (70 to 81) ǂ	I: 58 (19.1) C: 47 (15.6)	I: 298 (98) C: 293 (97)

Table 4 legend: ¶, *See Supplementary Table 1* for full details of procedures.

I, intervention; C, control; *NR*, not reported; EVAR, endovascular aneurysm repair; HIT, high-intensity interval training; post-op, post-operatively; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise testing; IHD, ischaemic heart disease; CVD, cerebrovascular disease; DM, Diabetes mellitus; PAD, peripheral arterial disease; CHF, congestive heart failure; HTN, hypertension; HRQL, health-related quality of life; LOS, length of stay; ICU, intensive care unit; HDU, high dependency unit

§**,** Females from the participants analysed (not allocated) by trials; ǀ, Unclear if trial is reporting N of allocated or analysed participants; *, Groups reported by study as statistically significant (p = .001); †, Unclear measure of dispersion reported by trial; ǂ, Median and IQR reported.

Figure 1: PRISMA flow diagram[12] for literature search to identify RCTs on prehabilitation in AAA repair and surgical outcomes.

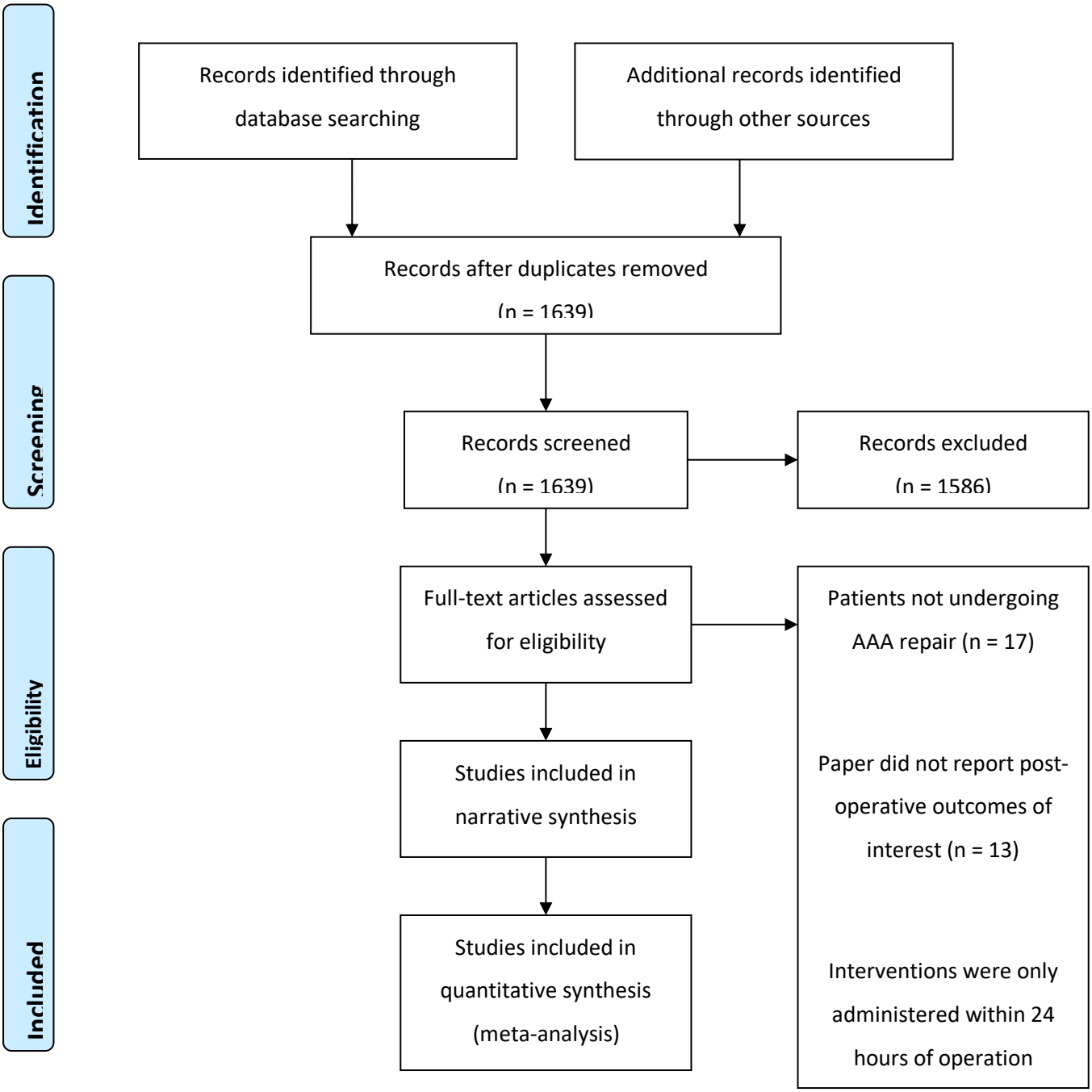

Figure 2: Risk of bias summary (colourised).

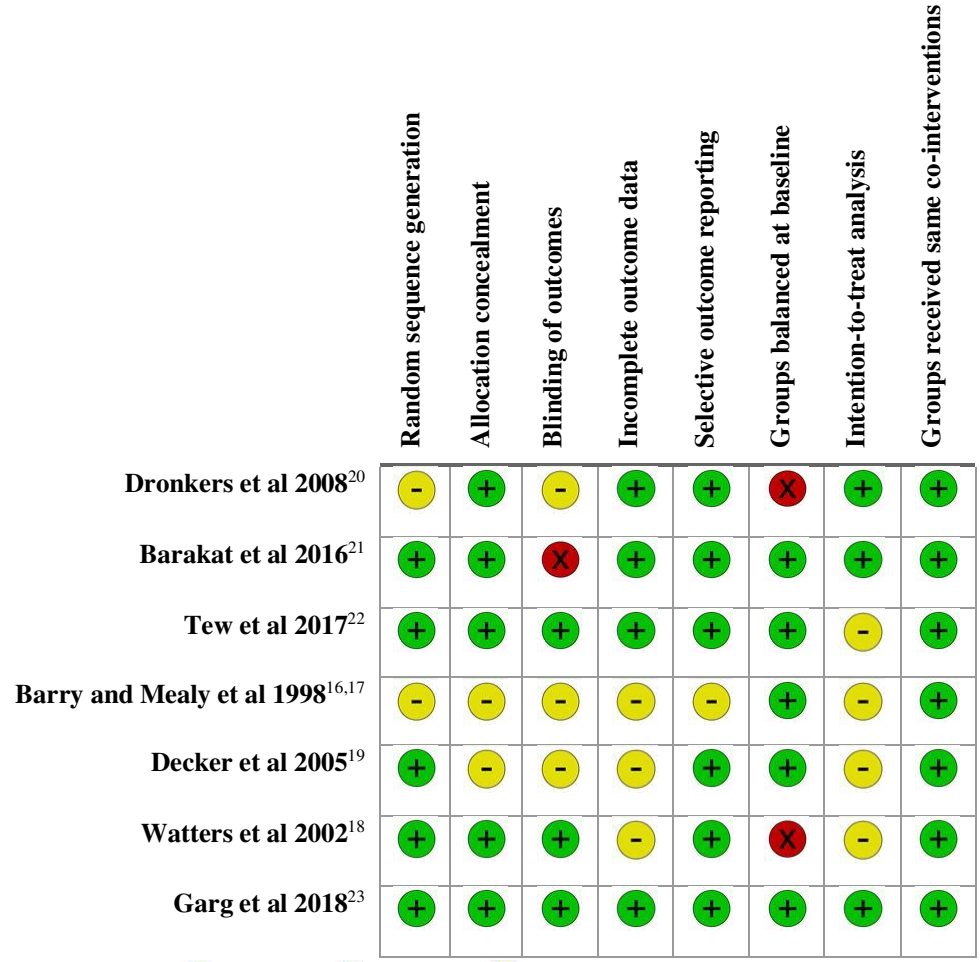

Figure 2 legend: **+**, Low risk; **x**, High risk; **-**, Unclear risk

Supplementary Information

EMBASE search strategy

1. (aneurysm* adj4 abdom*).mp.
2. (aneurysm* adj4 aort*).mp.
3. (aneurysm* adj4 thoraco?abdom*).mp.
4. AAA*.mp.
5. exp abdominal aorta aneurysm/ or exp aortic aneurysm/ or exp aorta aneurysm/ or exp aorta rupture/
6. 1 or 2 or 3 or 4 or 5
7. exp psychotherapy/
8. exp cognitive therapy/
9. exp patient education/
10. psycholog* therap*.mp.
11. psycholog* treat*.mp.
12. psycholog* interven*.mp.
13. behavio?r*.mp.
14. (patient* adj4 educat*).mp.
15. psychotherap*.mp.
16. cognitive therap*.mp.
17. cognitive behavio?r& therap*.mp.
18. CBT*.mp.
19. counsel*.mp.
20. mind therap*.mp.
21. psychoeducat*.mp.
22. motivat*.mp.

23. meditat*.mp.

24. (smok* adj4 cessat*).mp.

25. (smok* adj4 stop*).mp.

26. (behavio?r* adj2 chang*).mp.

27. health behavio?r.mp.

28. exp preoperative care/

29. exp Exercise Therapy/ or exp Physical Therapy Modalities/

30. Pre?operat* care.mp.

31. pre?operat* optim*.mp.

32. Exercis* therap*.mp.

33. physiotherap*.mp.

34. physical* exercis*.mp.

35. (breath* adj4 exercis*).mp.

36. (Breath* adj4 technique*).mp.

37. (Exercis* adj4 train*).mp.

38. (breath* adj4 train*).mp.

39. kinesiotherap*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

40. exp nutritional support/

41. exp diet therapy/

42. exp nutritional assessment/

43. diet* therap*.mp.

44. food intake*.mp.

45. (weight adj2 los*).mp.

46. (weight adj2 reduc*).mp.

47. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46

48. exp Platelet Aggregation/de, pd [Drug Effects, Pharmacology]

49. exp Phosphodiesterase Inhibitors/

50. exp Tetrazoles/

51. exp Antihypertensive Agents/

52. exp Adrenergic beta-Antagonists/

53. exp Angiotensin-Converting Enzyme Inhibitors/

54. exp Diuretics/

55. exp Calcium Channel Blockers/

56. exp Anticholesteremic Agents/

57. exp Fish Oils/

58. exp Fatty Acids, Omega-3/

59. exp Antioxidants/

60. 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59

61. 47 or 60

62. indobufen.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

63. (antiplatelet* or anti-platelet* or antiaggreg* or anti-aggreg*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

64. ((platelet or thromboxane or thrombocyte or cyclooxygenase or cyclo-oxygenase or phosphodiesterase or fibrinogen or PAR-1) adj3 (antagonist or inhibitor)).mp.

[mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

65. ((gp* or glycoprotein* or protease or P2Y12 or TXA2) adj3 inhibit*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

66. thienopyridine.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

67. (clopidogrel or Plavix).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

68. (Prasugrel or Effient or Efient or Prasita).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

69. (ticagrelor or AZD6140 or Brilinta).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

70. (elinogrel or PRT060128 or PRT-060128).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

71. (ticlopidine or Ticlid).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

72. (cangrelor or AR-C6993* or ARC6993*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

73. (SCH530348 or SCH-530348).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

74. E5555.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

75. (terutroban or Triplion).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

76. (aspirin* or nitroaspirin or ASA).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

77. acetylsalicylic acid.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

78. acetyl salicylic acid*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

79. (triflusal or disgren).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

80. (Cilostazol or Pletal or Pletaal).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

81. (dipyridamol* or Persantine).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

82. (OPC-13013 or OPC13013).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

83. (picotamide or picotinamide).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

84. satigrel.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

85. vorapaxar.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

86. (antihypertensi* or anti-hypertensi*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

87. (calcium adj3 (antag* or block*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

88. (amlodipin* or diltiazem or diltiazam or felodipin*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

89. (nicardipin* or nifedipin* or nimodipin*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

90. (nisoldipin* or nitrendipin* or verapamil).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

91. diureti*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

92. (angiotensin adj3 inhibitor*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

93. (alacepril or altiopril or benazepril or captopril or ceronapril or cilazapril or delapril or de- rapril).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

94. (enalapril or fosinopril or idapril or imidapril or lisinopril).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

95. (moexipril or moveltipril or pentopril).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

96. (perindopril or quinapril).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

97. (ramipril or spirapril or temocapril or trandolapril or zofenopril).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

98. ACE inhibitor*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

99. (adrenergic adj3 (antagonist* or block*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

100. (betablocker* or beta-blocker*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

101. (acebutolol or atenolol or Tenormin).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

102. (alprenolol or betaxolol or bisoprolol or bupranolol).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

103. (carvedilol or Coreg or carteolol or celiprolol).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

104. (esmolol or labetalol).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

105. (metoprolol or nadolol or nebivolol).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

106. (oxprenolol or penbutolol or pindolol).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

107. (practolol or propranolol or timolol).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

108. (bumetanide or ethacrynic acid or furosemide or torsemide).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

109. thiazide.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

110. epitizide.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

111. (indapamide or chlorthalidone or metolazone).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

112. (amiloride or triamterene or spironolactone).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

113. statin.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

114. meglutol.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

115. mevacor.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

116. pravachol.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

117. escol.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

118. ipitor*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

119. cholestyramine.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

120. (cholesterol adj lowering).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

121. (lipid adj lowering).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

122. colestipol.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

123. gemfibrozil.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

124. clofibrate.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

125. (nicotinic adj acid).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

126. ezetimibe.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

127. (fatty adj acid*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

128. (omega adj2 acid*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

129. (eicosapentanoic or docosahexanoic or docosapentanoic or alpha-linolenic).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

130. (eicosapentaen* or icosapentaenoic or docosahexaeno*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug

manufacturer, device trade name, keyword, floating subheading word, candidate term word]

131. (fish adj2 oil*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

132. (cod adj2 oil).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

133. (antioxidant* or anti-oxidant*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

134. 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133

135. 47 or 60 or 134

136. (Medic* adj4 optim*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

137. (Pharmac* adj4 manag*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

138. (Pharmac* adj4 treat*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

139. (Pharmac* adj4 intervention*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

140. (Pharmac* adj4 optim*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

141. (Medic* adj4 manag*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

142. (Medic* adj4 treat*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

143. (Cardio* adj4 optim*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

144. (Cardio* adj4 manag*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

145. (Cardio* adj4 treat*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

146. (Vasc* adj4 optim*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

147. (Vasc* adj4 manag*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

148. (Vasc* adj4 treat*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

149. (Diabet* adj4 optim*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

150. (Diabet* adj4 manag*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

151. (Diabet* adj4 treat*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

152. (Respirat* adj4 optim*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

153. (Respirat* adj4 manag*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

154. (Respirat* adj4 treat*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

155. (Co?morbid* adj4 optim*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

156. (Co?morbid* adj4 manag*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

157. (Co?morbid* adj4 treat*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

158. saba.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

159. bronchodilator*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

160. Salbutamol.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

161. Ipratropium.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

162. LABA.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

163. Salmeterol.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

164. (Indacaterol or Arformaterol or Olodaterol or Tiotropium or Umeclidinium or Aclidinium or Glycopyrronium).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

165. (Oxygen therap* or Systematic corticosteroid* or steroid therap* or Prednisolone or Methylprednisolone or Hydrocortisone or Inhaled corticosteroid* or Beclomethasone or Budesonide or Flunisolide or Fluticasone proprionate or Mometasone).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

166. (Antibiotic* or anti?micro* or Doxycycline or Tetracycline or Roxithromycin or Amoxicillin or Co?amoxiclav or (amoxicillin and clavu*) or Cefaclor or Azithromycin or Clarithromycin or Telithromycin or Levofloxacin or Moxifloxacin or Ciprofloxacin or Theophylline or Aminophylline).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

167. exp Anti-Bacterial Agents/

168. exp Steroids/

169. exp Bronchodilator Agents/

170. exp Drug Combinations/

171. (drug therap$ or drug combination$).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

172. ((combination$ or oral or multiple) adj (therap$ or agent$ or drug$ or treatment$)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

173. monotherap*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

174. exp SULFONYLUREA COMPOUNDS/

175. exp BIGUANIDES/

176. exp ACARBOSE/

177. (biguanid$ or sulfonylurea$ or sulphonylurea$ or acarbose).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

178. (gliglacid$ or glibornurid$ or gliguidon$ or glisoxepid$ or glipizid$ or gliburid$ or glyburid$ or tolazamid$).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

179. (tolbutamid$ or carbutamid$ or chlorpropamid$ or acetohexamid$ or glibenclamid$ or glimepirid$).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

180. (metformin$ or buformin$ or chlorhexidin$ or chlorguanid$ or phenformin$).mp. [mp=title, abstract, heading word, drug trade name, original title,

device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

181. keyword, floating subheading word, candidate term word]

182. (troglitazon$ or rosiglitazon$ or pioglitazon$ or thioazolidinedion$ or glitazon$).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

183. repaglinid*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

184. exp INSULIN/

185. nsulin$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

186. ((antidiabet$ or anti diabet$) adj (drug$ or herb$ or agent$ or compound$)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

187. (hypoglyc?emic adj (drug$ or herb$ or agent$ or compound$)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

188. exp cardiovascular disease/

189. exp diabetes mellitus/

190. exp respiratory tract disease/

191. 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or

171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190

192. (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.

193. RETRACTED ARTICLE/

194. or/192-193

195. (animal$ not human$).sh,hw.

196. (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/

197. (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomized controlled trial/

198. 194 not (195 or 196 or 197)

199. 135 or 191

200. 6 and 198 and 199

Supplementary Table 1: Description of intervention procedures and doses

Trial	Intervention description	Comparator description
Dronkers et al 2008[20]	"The intervention group took part in a training programme (six sessions, six days a week for at least two weeks before surgery) designed to increase the strength and endurance of the inspiratory muscles. Each session consisted of 15 minutes of inspiratory muscle training…The subjects were instructed to keep a daily diary during the study… The subjects started breathing at a resistance equal to 20% of their maximal inspiratory pressure, measured at baseline, for 15 minutes a day. The resistance was increased incrementally, based on the rate of perceived exertion (RPE) scored by the patient on the Borg Scale. If the RPE was <5, the resistance of the inspiratory threshold trainer was increased incrementally by 2cmH2O."	"In the preoperative period the control and the experimental groups received care as usual, consisting of instruction in (a) diaphragmatic breathing, (b) deep inspirations with the aid of incentive spirometer, and (c) coughing and 'forced expiration techniques'. The control group received this usual care one day before surgery, and the intervention group 2–3 weeks before surgery during the intervention."
Barakat et al 2016[21]	"Patients allocated to the intervention arm, that is, exercise, were provided with instructions and a timetable to join hospital- based exercise classes, carried out 3 times a week, for 1-hour duration, in the physiotherapy gym... Each exercise class consisted of the following: 5-minute warm up and stretching, cycle ergometer against moderate resistance for 2 minutes, heel-raise repetitions for 2 minutes, knee extensions against resistance repetitions for 2 minutes, dumbbells' biceps/arm curls repetitions for 2 minutes, step-up lunges repetitions for 2 minutes, knee bends (bodyweight) repetitions for 2 minutes, and 5 minutes for cool down and stretching. Between each of the exercise stations, patients either walked around the gym or on a treadmill, or rested for 2 minutes before moving on to the next exercise."	"Patients allocated to the control group were clearly instructed to continue with their normal lifestyle, and avoid any additional, unsupervised exercises."
Tew et al 2017[22]	"Participants allocated to the exercise group were also invited to complete three hospital-based exercise sessions per week… All exercise was undertaken on a cycle ergometer... Each of the first three sessions comprised a 10-min warm-up of unloaded cycling, eight 2-min intervals of high-intensity cycling interspersed with 2-min rest periods of unloaded cycling, and then a 5-min cool-down of unloaded cycling. In all subsequent sessions, participants had the choice of performing eight 2-min or four 4-min 'work'	"All participants received usual care, which comprised evidence-based medical optimization."

	intervals for the main body of the workout. In the first exercise session, the 2-min work intervals were performed at the power output corresponding to anaerobic threshold on a baseline cardiopulmonary exercise test (CPET). The power output in all subsequent sessions was guided by participants' ratings of perceived exertion (RPE), which were assessed separately for legs (RPE-L) and breathless- ness/chest (RPE-C) at the end of each interval using Borg's CR-10 scale. The aim was for all work intervals to be undertaken at a hard to very hard level of exertion (RPE-L or RPE-C of 5 and 7 respectively)."	
Barry and Mealy et al 1998[16,17]	"The dose of GH was 0.3 IU/kg/day administered subcutaneously at 08 00 daily."	"Placebo vials contained the same vehicle as the GH and were visually indistinguishable." *Dose and timing NR*
Decker et al 2005[19]	"…daily dosage of 16 IU HrGH (5.3 mg/d…)." *Route NR*	"…received placebo at the same time points." *Dose and route NR*
Watters et al 2002[18]	"MN supplementation consisted of beta-carotene (10 000 IU/d), vitamins C (1000 mg/d), and E (400 IU/ d), selenium (50 mg/d) and zinc (24 mg/d) (16). The MN supplement and placebo were prepared in identical capsules with contents matched for color and texture. They were taken orally..." *Frequency NR*	"The MN supplement and placebo were prepared in identical capsules with contents matched for color and texture… Patients were instructed to maintain their routine diets before surgery." *Frequency NR*
Garg et al 2018[23]	"… 4000 mg of curcumin per day in 2 divided doses for 2 days before the repair, followed by 2000 mg the morning of the repair, 2000 mg on call to the operating room, 2000 mg 6 hours after surgery and 2000 mg the next morning."	"The placebo capsules looked, smelled and tasted the same as the curcumin capsules, and were made of yellow food colouring, gelatin and cellulose… Patients were assigned to take curcumin or placebo according to the trial regimen."

Supplementary Table 1 legend: *NR,* not reported; HrGH, human recombinant growth hormone; GH, growth hormone; MN, micronutrient

Supplementary Table 2: Mortality risk factors and outcomes of interest reported by included studies

Trial	Mortality risk factors of interest reported	Outcomes of interest, primary and *secondary*
Dronkers et al 2008[20]	COPD, CPET measures	HRQL outcomes at follow-up, *post-op systemic comp.*
Barakat et al 2016[21]	IHD, CVD, Diabetes, COPD, CPET measures	Post-op 30-day mortality, hospital LOS, HRQL outcomes at follow-up, *adherence, composite endpoint of total post-op comp., post-op systemic comp., post-op surgical comp., discharge to independent living*
Tew et al 2017[22]	IHD, CVD, Diabetes, COPD, CPET measures, PAD	Post-op 30-day mortality, hospital LOS, HRQL outcomes at follow-up, *adherence, composite endpoint of total post-op comp., adverse outcomes, health economic data*
Barry and Mealy et al 1998[16,17]	*NR*	Post-op 30-day mortality, hospital LOS, *post-op mortality at follow-up, post-op systemic comp., ICU/HDU LOS, adverse outcomes*
Decker et al 2005[19]	*NR*	Hospital LOS, *ICU/HDU LOS*
Watters et al 2002[18]	CPET measures	Post-op 30-day mortality, hospital LOS, HRQL outcomes at follow-up, *adherence*, *ICU/HDU LOS*
Garg et al 2018[23]	IHD, CHF, CVD, Diabetes, COPD, HTN	Post-op 30-day mortality, composite endpoint of 30-day post-op mortality, hospital LOS, *adherence, post-op mortality at follow-up, post-op systemic comp., post-op surgical comp., adverse outcomes*

Supplementary Table 2 legend: COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise testing; IHD, ischaemic heart disease; CVD, cerebrovascular disease; DM, Diabetes mellitus; PAD, peripheral arterial disease; CHF, congestive heart failure; HTN, hypertension; HRQL, health-related quality of life; Post-op, post-operatively; comp., complications; LOS, length of stay; ICU, intensive care unit; HDU, high dependency unit