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Original Article

A randomised controlled trial of prehabilitation in patients undergoing elective cardiac surgery

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Summary

The feasibility, safety and efficacy of prehabilitation in adult patients awaiting elective cardiac surgery are unknown. A total of 180 participants undergoing elective cardiac surgery were allocated randomly to receive either standard pre-operative care or prehabilitation, consisting of pre-operative exercise and inspiratory muscle training. The primary outcome was change in six-minute walk test distance from baseline to pre-operative assessment. Secondary outcomes included change in inspiratory muscle strength (maximal inspiratory pressure); sarcopenia (handgrip strength); quality of life and compliance. Safety outcomes were pre-specified surgical and pulmonary complications and adverse events. All outcomes were assessed at baseline; at pre-operative assessment; and 6 and 12 weeks following surgery. Mean (SD) age was 64.7 (10.2) years; 33/180 (18%) were women. In total, 65/91 (71.4%) participants who were allocated to prehabilitation attended at least four of eight supervised in-hospital exercise classes; participants aged > 50 years were more likely than younger participants to attend (odds ratio (95%CI) of 4.6 (1.0–25.1)). Six-minute walk test was not significantly different between groups (mean difference (95%CI) -7.8 m (-30.6–15.0), p = 0.503) in the intention-to-treat analysis. Subgroup analyses based on tests for interaction indicated improvements in six-minute walk test distance were larger amongst sarcopenic patients in the prehabilitation group (p = 0.004). Change in maximal inspiratory pressure from baseline to all time-points was significantly greater in the prehabilitation group, with the greatest mean difference (95%CI) observed 12 weeks after surgery (10.6 cmH_2O (4.6–16.6) cmH_2O, p < 0.001). There were no differences in handgrip strength or quality of life up to 12 weeks after surgery. There was no significant difference in postoperative mortality (one death in each group), surgical or pulmonary complications. Of 71 pre-operative adverse events, six (8.5%) were related to prehabilitation. The combination of exercise and inspiratory muscle training in a prehabilitation intervention before cardiac surgery was not superior to standard care in improving functional exercise capacity measured by six-minute walk test distance pre-operatively. Future trials should target patients living with sarcopenia and include inspiratory muscle strength training.

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The prehabilitation in elective patients undergoing cardiac surgery (PREPs) trial investigators are listed in online Supporting Information Appendix S1.
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Introduction

The average age of patients undergoing cardiac surgery is increasing, and they frequently have multiple comorbidities and concomitant frailty. Older, more frail patients, especially those with sarcopenia and comorbidities, are more likely to suffer significant functional decline, before, during and after hospitalisation for cardiac surgery [1, 2]. Frailty describes a state of heightened vulnerability to a stressor event [3], and is associated with increased rates of peri- and postoperative complications; increased length of hospital stay and resource use; and delayed recovery [4–6]. There is an urgent need to develop strategies across the entire cardiac surgery clinical pathway to improve outcomes for this growing vulnerable population. Cardiac rehabilitation following cardiac surgery has been routinely provided for many years based on evidence of improved clinical outcomes and is recommended in international guidelines [7]. A similarly effective intervention in the clinical pathway, aimed at optimising patients before surgery (prehabilitation), will lead to changes in international guidelines and clinical practice.

Prehabilitation occurs pre-operatively and has been compared with training before a marathon, based on evidence that structured and sustained exercise over time leads to cardiovascular, respiratory and muscular conditioning [1]. In other surgical disciplines, prehabilitation is associated with improvements in mortality rates; functional exercise capacity; frailty; postoperative complications; and quality of life [1]. However, it has not been implemented routinely for patients undergoing cardiac surgery because of concerns about feasibility, safety, lack of evidence of efficacy and concerns about acceptability of possible delays to surgery. These concerns have been reinforced by international guidelines that recommend limited physical exertion in patients with, for example, severe aortic stenosis. Only 4 of 29 (13%) units we surveyed in the UK provide prehabilitation for patients awaiting elective cardiac surgery. In contrast, such a service is provided for 66% of patients undergoing other types of surgery (e.g. cancer surgery) in the same institutions [8].

The recognition amongst clinicians of the urgent need for a trial to determine if prehabilitation is feasible, effective and safe, was corroborated by a priority-setting exercise conducted by the James Lind Alliance in the UK in 2019. This identified the question of whether prehabilitation benefited patients before cardiac surgery as one of the 10 priority research areas [9]. Therefore, the prehabilitation in elective patients undergoing cardiac surgery trial was designed to establish whether a prehabilitation intervention improves the overall functional exercise capacity of patients before elective cardiac surgery.

Methods

We conducted a prospective, pragmatic, parallel-group, randomised controlled trial at a single NHS tertiary institution following ethical approval. The trial design is described in the published protocol [10]. Day-to-day management was conducted by Newcastle Clinical Trials Unit alongside a wider trial management group; the trial was overseen by an independent trial oversight committee (see online Supporting Information Appendix S2). The trial is reported according to CONSORT guidelines [11].

All participants provided written informed consent before any trial activity. Patients aged ≥ 18 y and scheduled for elective cardiac surgery were eligible. The exclusion criteria were as follows: unstable angina requiring urgent surgery; malignant arrhythmias; contraindications to exercise prehabilitation; and contraindications to inspiratory muscle training. Eligible participants were allocated randomly in a 1:1 ratio to either standard pre-operative care (control) or to prehabilitation (intervention) by the research team using a 24-hour, central, secure, web-based randomisation system with concealed allocation. Randomisation was performed using a minimisation scheme that accounted for baseline six-minute walk test distance (6MWT, <250 m; 250–450 m; >450 m); Rockwood clinical frailty scale (<1–3 (not frail); 4–6 (mildly frail); >6 (frail)); age (<50; 50–70; >70 y); and sex, to balance key factors that are potentially associated with the primary outcome. It was not possible to conceal the allocation of treatment from the participant, or the team delivering the intervention and measuring the primary outcome. Whilst not formally blinded, each operating surgeon was not informed of the allocation.

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Participants allocated to the control group received standard pre-operative care consisting of routine appointments with the clinical team and specialist nurses for consultation, advice and consent in relation to their upcoming surgery. Participants allocated to the intervention group received standard care in addition to cardiac prehabilitation which consisted of initial fitness assessment; face-to-face supervised exercise programme of two 60-min sessions per week planned over 4 weeks; and prescription of an unsupervised home exercise programme consisting of up to 45 min daily exercise and high intensity-inspiratory muscle training. High intensity-inspiratory muscle training involved twice-daily training using an inspirometer device, which continued throughout the intervention and up to the day of surgery.

All participants were asked to complete an exercise diary for any activity undertaken from the point of consent up to the day of surgery. Participants were also asked to record any healthcare visit details over the same period. Participants were followed up at clinic appointments before surgery, during surgical admission and at 6 and 12 weeks following index surgery.

The primary outcome was the change in functional exercise capacity, measured by the change in 6MWT from baseline to pre-operative assessment. Secondary outcomes were change from baseline in inspiratory muscle strength measured by maximal inspiratory pressure; sarcopenia measured by handgrip strength assessed using a hand-held dynamometer; quality of life measured by EQ-5D-5L; and anxiety and depression measured with the Hospital Anxiety and Depression Scale (HADS). Safety outcomes were length of ICU and hospital stay; incidence of postoperative surgical and pulmonary complications (see online Supporting Information Table S1) up to 12 weeks after surgery; and adverse events during the intervention period (pre-operative). Compliance with the intervention was prespecified as attendance at four or more (of a possible eight) in-person classes. The per-protocol population were specified as providing diary evidence of home exercise at least once per week during the intervention period; attending pre-operative assessment within 2 weeks after the final class; and meeting the compliance threshold of four of eight classes.

Two sub-studies, one exploring the use of activity monitors to objectively measure change in physical activity and a qualitative study of staff and participant experiences of prehabilitation, were also undertaken and will be reported separately.

All data were analysed at the end of the study, with no interim analysis. The sample size was based on detecting a significant improvement in 6MWT after the prehabilitation programme compared with the 6MWT at baseline. We assumed a minimal clinically important difference in 6MWT of 25 m with a standard deviation of 56.5 m for pre-operative participants [12, 13]. Based on detecting a moderate effect size of 0.44, 164 participants (82 in each group) were needed to provide 80% power to detect a difference of 25 m in the 6MWT. To account for 10% missing data, 180 participants were recruited for the trial. A full description of the sample size calculation is in the published protocol [10].

The primary outcome was analysed with an intention-to-treat analysis, according to randomisation and regardless of whether the participant received or adhered to the allocated treatment. Per-protocol and as-treated analyses were conducted as sensitivity and exploratory analyses. There was no correction of the potential type-1 error rate for multiple testing across secondary outcomes.

The primary analysis testing the impact of the cardiac prehabilitation programme on pre-operative functional exercise capacity (measured by 6MWT) was based on a linear mixed-effects model accounting for baseline randomisation factors, except for baseline 6MWT which was explicitly incorporated in the model to calculate change from baseline. The model accounted for intra-patient correlation using a random intercept model, where baseline 6MWT was explicitly incorporated as part of the outcome vector with the constraint of a common baseline mean across treatment groups. Pre-specified subgroup analyses were based on tests for interaction between each variable and treatment.

Secondary outcomes were also examined with intention-to-treat analyses. Continuous secondary outcomes with repeated measurements (maximal inspiratory pressure; handgrip strength; quality of life) were analysed using the same approach as used for the primary outcome. Anxiety and depression scores with HADS were constructed as categorical variables, with scores 0–7 classed as normal, 8–10 as borderline and ≥11 as confirmed anxiety or depression [14]; these were analysed using logistic regression. Continuous and categorical outcomes measured at single time-points were analysed using linear and logistic regression models, respectively; length of hospital stay was analysed using Poisson regression. Where patients had more than one planned surgery type, they were assigned to just one for the purposes of subgroup analysis and comparisons. Frequency tables summarise safety and adverse events data by study groups and time-points. All analyses were performed using R 4.2 (R Foundation, Vienna, Austria).

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Results

From November 2019 to December 2022, 1037 patients were screened, of which 180 were enrolled and allocated randomly to either prehabilitation (n = 91) or control (n = 89) (Fig. 1). In total, 167 (92%) completed follow-up to 12 weeks. The most common reason for potentially eligible participants to decline recruitment was travel constraints. This was the case in over 50% of eligible patients. Patient and clinical characteristics of the two groups were well matched at baseline (Table 1).

In all, 65 of 91 participants (71.4%) fulfilled the prespecified criteria for compliance of a minimum of four classes for adherence to the intervention. Participants who were aged ≥ 50 y were more likely to adhere to the intervention than those aged < 50 y, though numbers were small (OR (95%CI) 4.64 (1.01–25.13)). Compliance did not differ by any other variable assessed including sex, frailty (based on Rockwood score) or type of planned surgery. Of the 91 participants receiving the intervention, 70 (76.9%) and 72 (79.1%) completed and returned diaries in which inspiratory muscle training and at-home exercise, respectively, during the intervention period were recorded.

Overall, the mean (SD) baseline 6MWT was 401.9 (110.4) m, which was similar in the two groups (Table 2). The 6MWT at all follow-up time-points for both groups is shown in Fig. 2. The primary outcome of mean difference (95%CI) in 6MWT from baseline to pre-operative assessment was not significantly different in the prehabilitation group compared with the control group (-7.8 (-30.6–15.0) m, p = 0.503) in the intention-to-treat analysis. This finding was consistent between the per-protocol and as-treated analyses (Fig. 3).

Pre-specified subgroup analysis indicated effect modification by handgrip strength (sarcopenia) at baseline, in which improvements in 6MWT were larger amongst those classed as sarcopenic based on their handgrip strength in the prehabilitation group (p = 0.004, see online Supporting Information Figure S1). This difference in effect was not observed at the 6- or 12-week follow-up visits. No statistically significant differences in treatment effect from baseline to pre-operative time-points were detected in any of the other subgroups analysed (see online Supporting Information Figure S2).

The change in maximal inspiratory pressure from baseline was significantly greater in the prehabilitation group at all time-points, with the greatest difference between groups observed 12 weeks after surgery (mean difference (95%CI) 10.6 (4.6–16.6) cmH_2O, p < 0.001) (Table 2 and online Supporting Information Figure S3). There were no significant differences in other outcomes (Tables 2 and 3).

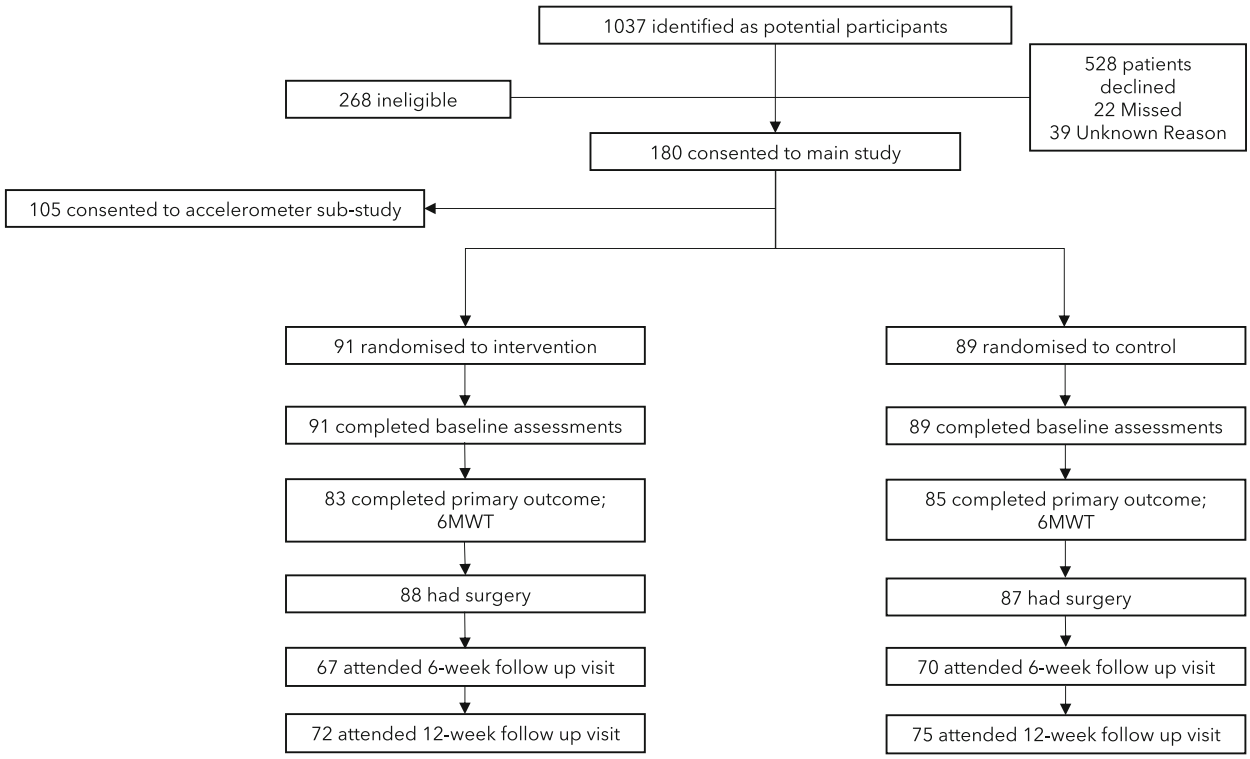

Figure 1 Study flow chart.

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Table 1 Baseline characteristics of patients included in this study. Values are number (proportion).

	Prehabilitation n = 91	Control n = 89	Overall n = 180
Sex			
Male	75 (82.4%)	72 (80.9%)	147 (81.7%)
Age; y			
<50	8 (8.8%)	7 (7.9%)	15 (8.3%)
50–70	53 (58.2%)	53 (59.6%)	106 (58.9%)
70	30 (33%)	29 (32.6%)	59 (32.8%)
Rockwood frailty score			
<1–3 (active)	82 (90.1%)	80 (89.9%)	162 (90%)
4–6 (inactive)	9 (9.9%)	9 (10.1%)	18 (10%)
6 (very frail)	0	0	0
Baseline 6MWT			
<250 m	8 (8.8%)	8 (9%)	16 (8.9%)
250–450 m	49 (53.8%)	47 (52.8%)	96 (53.3%)
450 m	34 (37.4%)	34 (38.2%)	68 (37.8%)
Planned type of surgery			
Coronary artery bypass graft	48 (52.7%)	54 (60.7%)	102 (56.7%)
Aortic valve surgery	43 (47.3%)	32 (36%)	75 (41.7%)
Mitral valve surgery	14 (15.4%)	15 (16.9%)	29 (16.1%)
Tricuspid valve surgery	0	2 (2.2%)	2 (1.1%)
Aortic procedure	14 (15.4%)	4 (4.5%)	18 (10.0%)
Other surgery	5 (5.5%)	4 (4.5%)	9 (5.0%)

6MWT, six-minute walk test.

There were two deaths in each group; in both groups, one participant died before surgery and one after surgery. There were seven serious adverse events of which only one was classified as related to the intervention. Five serious adverse events were in participants booked for valve surgery and two participants were booked for coronary artery bypass grafting (see online Supporting Information Table S3). There were 71 adverse events reported before surgery, of which 6 (8.5%) were considered to be related to the prehabilitation intervention. There were no significant differences between the groups in postoperative outcomes (Table 4).

Discussion

This is the first pragmatic trial combining exercise and inspiratory muscle training in elective patients before cardiac surgery, and the first specifically designed to test the impact of the intervention on exercise capacity before surgery. A significant improvement in pre-operative functional exercise capacity was not observed in the prehabilitation group over standard care but was observed in patients exhibiting sarcopenia. Secondary outcomes suggest an impact of the intervention on inspiratory muscle function, with improvements in maximal inspiratory pressure observed at pre-operative assessment and 6 and 12 weeks after surgery in the participants who received prehabilitation. Whilst this trial demonstrates good compliance with both the hospital and home-based elements of the intervention, the most common reason for potentially eligible participants to decline recruitment was travel constraints. These concerns suggest that any future prehabilitation intervention will have to be delivered dynamically using locations and times more suitable to the clinically encountered population.

The choice of the primary outcome of change in pre-operative 6MWT from baseline was made after consultation with patients; reduced 6MWT is associated with moderate or severe complications after both non-cardiac [15] and cardiac surgery [16]; conversely, improved 6MWT has been validated as an indicator of recovery in patients undergoing cardiac surgery [12, 14, 17]. Although a significant improvement in pre-operative exercise capacity was not observed in the prehabilitation cohort over standard care, it was observed in patients exhibiting sarcopenia measured by handgrip strength, which represented over a quarter of the trial population.

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Table 2 Secondary outcomes and treatment effects in each group to 12 weeks following surgery. Values are mean (SD) or mean difference (95%CI).

	Prehabilitation		Control			
Time-points	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Mean difference (95%CI)**	**p value**
6MWT						
Baseline	91	412.1 (105.6)	89	391.5 (114.7)	–	
Pre-operative assessment	83	409.7 (111.9)	85	402.1 (113.7)	-7.8 (-30.6–15.0)	0.503
6 weeks	64	421.5 (116.0)	64	412.3 (98.1)	-5.8 (-31.5–19.9	0.660
12 weeks	67	440.6 (111.4)	72	441.1 (97.9)	-17.9 (-42.7–6.9)	0.158
Maximal inspiratory pressure						
Baseline	91	66.0 (27.2)	89	70.3 (22.5)	–	
Pre-operative assessment	87	80.2 (26.8)	87	73.1 (24.6)	8.9 (3.4–14.4)	0.002
6 weeks	65	68.7 (23.4)	67	61.6 (19.9)	9.9 (3.7–16.1)	0.002
12 weeks	69	74.3 (23.2)	73	65.9 (23.5)	10.6 (4.6–16.6)	0.001
Sarcopenia (handgrip strength)						
Baseline	91	36.9 (10.9)	89	33.4 (11.3)	–	
Pre-operative assessment	88	38.0 (11.6)	87	35.2 (10.3)	0.8 (-1.4–3.0)	0.475
6 weeks	65	37.1 (10.8)	67	32.5 (11.1)	2.4 (-0.1–4.9)	0.577
12 weeks	69	37.6 (12.1)	73	34.9 (10.1)	1.1 (-1.3–3.5)	0.355
EQ-5D-5L index score						
Baseline	91	0.8 (0.2)	89	0.7 (0.2)	–	
Pre-operative assessment	88	0.7 (0.2)	87	0.7 (0.2)	-0.0 (-0.1–0.0)	0.348
6 weeks	85	0.7 (0.2)	83	0.7 (0.2)	0.0 (-0.0–0.1)	0.417
12 weeks	83	0.8 (0.2)	84	0.7 (0.2)	0.0 (-0.1–0.1)	0.707
EQ-5D-5L VAS						
Baseline	91	67.6 (16.4)	89	64.7 (19.5)	–	
Pre-operative assessment	88	66.5 (20.4)	88	69.9 (18.9)	-4.5 (-9.7–0.8)	0.100
6 weeks	85	72.4 (18.1)	83	71.0 (20.0)	0.5 (-4.9–5.9)	0.863
12 weeks	83	75.8 (17.3)	84	75.5 (19.9)	-0.5 (-5.9–4.9)	0.860

VAS, visual analogue scale.

Importantly, the intervention had a significant impact on maximal inspiratory pressure, with improvements observed in the prehabilitation group at pre-operative assessment and sustained up to 12 weeks after surgery. This suggests that studies of clinical efficacy could focus on patients living with sarcopenia, because this trial was not sufficiently powered to demonstrate causality in this subgroup of patients and should include inspiratory muscle training as an intervention and pulmonary complications as an outcome.

Safety outcomes revealed that adverse event rates during prehabilitation were higher than in the standard care group. However, only a minority were related to the intervention suggesting the possibility of observer bias, as patients in the prehabilitation group attended hospital and were questioned about adverse events more frequently than in the standard care group. Larger studies would be needed to provide definitive evidence of safety for prehabilitation but these results are reassuring, particularly in the context of parity in surgical and pulmonary complications between groups.

The trial has several limitations. It was not blinded, and participants and assessors were aware of allocation. However, to minimise the risk of bias, objective outcome measures like 6MWT and maximal inspiratory pressure were used. The trial only recruited patients undergoing elective surgery, so the results may not be applicable to patients with unstable or clinically urgent disease, although patients with clinically urgent disease are less likely to have time to fully complete a rehabilitation programme and are more likely to have complications should they do so. The trial was performed in a single centre but recruited patients who had typical demographic and operative features allowing wide application of its findings. Prehabilitation could be a more complex intervention and include numerous other components like nutritional and psychological interventions

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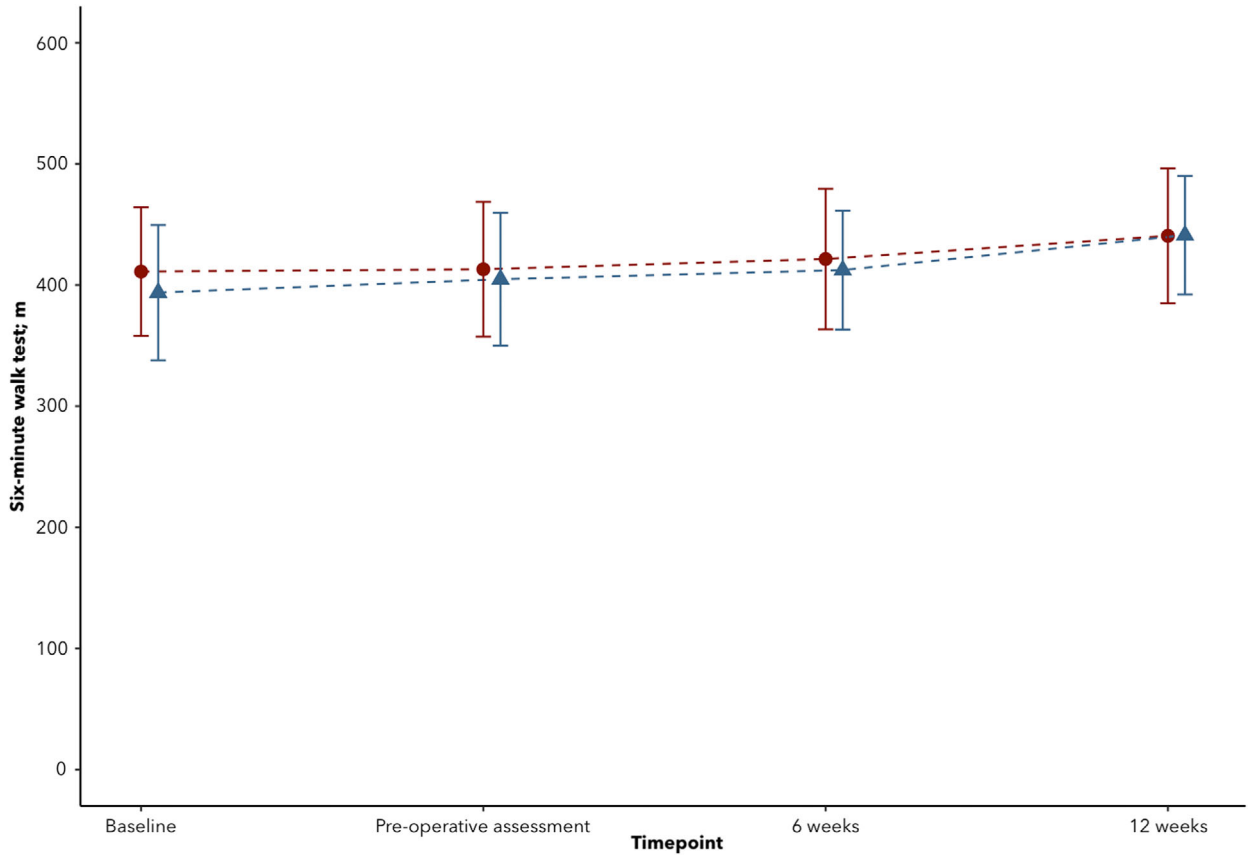

Figure 2 Change in 6MWT across study time-points and from baseline to pre-operative in prehabilitation (red) and control (blue) groups.

Type of analysis	Timepoint	Prehabilitation arm n	Prehabilitation arm Mean (SD)	Control arm n	Control arm Mean (SD)	Treatment effect (95%CI)
Primary analysis	Baseline	91	412.1 (105.6)	89	391.5 (114.7)	
	Pre-surgery	83	409.7 (111.9)	85	402.1 (113.7)	-7.8 (-30.6-15.0), p=0.503
Per-protocol analysis	Baseline	51	422.3 (81.5)	89	391.5 (114.7)	
	Pre-surgery	51	440.0 (82.1)	85	402.1 (113.7)	16.5 (-7.0-40.1), p=0.170
As-treated analysis	Baseline	84	420.4 (103.3)	96	385.8 (114.2)	
	Pre-surgery	79	417.9 (105.4)	89	395.2 (118.1)	3.3 (-20.2-26.7), p=0.786

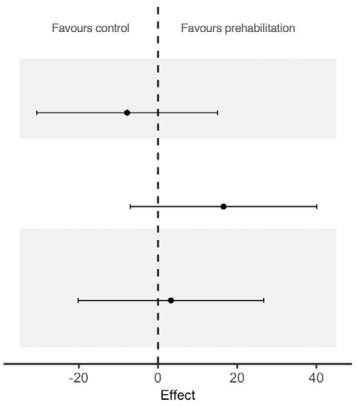

Figure 3 Change in 6MWT from baseline to pre-operative in prehabilitation and control groups.

as well as optimisation of chronic conditions like anaemia, diabetes and coagulopathy. In this trial, the prehabilitation intervention was limited to exercise and inspiratory muscle training, based on data from our systematic review finding that these were the only two interventions for which there may be evidence of benefit [17]. Finally, there is a risk of selection bias given that half of those who were eligible declined, and those who agreed might have been those more likely to comply and have acceptable outcomes.

In conclusion, this is the largest randomised controlled trial combining exercise and inspiratory muscle training in patients undergoing elective cardiac surgery. The was no

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Table 3 Hospital anxiety and depression scale (HADS) and treatment effects in each group to 12 weeks following surgery. Values are number (proportion) or odds ratio (95%CI).

	Prehabilitation		Control			
	Normal	Borderline/ confirmed case	Normal	Borderline/ confirmed case	Odds ratio (95%CI)	p value
HADS anxiety						
Baseline	56 (61.5%)	35 (38.5%)	62 (69.7%)	27 (30.3%)	–	
Pre-operative assessment	60 (68.2%)	28 (31.8%)	61 (69.3%)	27 (30.7%)	1.0 (0.5–1.9)	0.898
6 weeks	72 (84.7%)	13 (15.3%)	70 (84.3%)	13 (15.7%)	0.9 (0.4–2.1)	0.791
12 weeks	68 (81.9%)	15 (18.1%)	69 (82.1%)	15 (17.9%)	1.0 (0.4–2.2)	0.921
HADS depression						
Baseline	75 (82.4%)	16 (17.6%)	72 (80.9%)	17 (19.1%)	–	
Pre-surgical assessment	74 (84.1%)	14 (15.9%)	63 (71.6%)	25 (28.4%)	0.5 (0.2–1.1)	0.094
6 weeks	74 (87.1%)	11 (12.9%)	66 (79.5%)	17 (20.5%)	0.6 (0.2–1.3)	0.174
12 weeks	74 (89.2%)	9 (10.8%)	70 (83.3%)	14 (16.7%)	0.7 (0.3–1.7)	0.378

Table 4 Safety outcomes; comparison of peri-operative and postoperative outcomes. Values are mean (SD), number (proportion) or mean difference (95%CI).

	Prehabilitation n = 88*	Control n = 87*	Mean difference (95%CI)	p value
Hospital length of stay; days	6.3 (4.6)	6.5 (4.7)	-0.1 (-0.2–0.1)	0.404
ICU length of stay; h	36.3 (37.7)	43.0 (93.0)	-7.7 (-28.2–12.7)	0.458
Any surgical complications†			1.1 (0.6–2.1)	
Yes	62 (70.5%)	59 (67.8%)		0.764
No	26 (29.5%)	28 (32.2%)		
Any pulmonary complications†			0.7 (0.4–1.3)	0.295
Yes	29 (33.0%)	35 (40.2%)		
No	59 (67.0%)	52 (59.8%)		
Prolonged hospital stay (>10 days)	7 (8.0%)	8 (9.2%)	0.8 (0.2–2.5)	0.688
Early discharge from hospital (≤4 days)	34 (38.6%)	29 (33.3%)	1.3 (0.7–2.5)	0.409

*Five participants (n = 3 in prehabilitation, n = 2 in control) did not have surgery.
†Complications were measured from surgery to 12 weeks following surgery and are defined in online Supporting Information Table S1.

difference in pre-operative functional exercise capacity between those that had prehabilitation and those that did not. Future clinical trials of prehabilitation should be conducted that include inspiratory muscle training and target patients living with sarcopenia.

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Supporting Information

Additional supporting information may be found online via the journal website.

Appendix S1. PREPs trial investigators.

Appendix S2. Non-collaborative authors and trial oversight committee.

Table S1. Non-collaborative authors and trial oversight committee.

Table S2. Definition of surgical and pulmonary complications.

Table S3. Summary of deaths, serious adverse events and related adverse events.

Figure S1. Subgroup analysis of the primary outcome (6MWT).

Figure S2. Interaction plot of change in 6MWD by sarcopenia based on handgrip strength.

Figure S3. Treatment effect estimates as change from baseline on maximal inspiratory pressure at all study time points.

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