2021-10-20

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10.1007/s11695-021-05743-w
Obesity Surgery
Springer Science and Business Media LLC

The effect of pre-operative exercise intervention on patient outcomes following bariatric surgery: a systematic review and meta-analysis

Shortened title: Exercise pre bariatric surgery.

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ABSTRACT

This systematic review aimed to assess the effect of pre-operative exercise intervention on short- and long-term health and clinical outcomes for adult patients undergoing bariatric surgery (BS). We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled

Trials (CENTRAL), SPORTDiscus, and reference lists of relevant papers, through March 2021. Five randomized controlled trials were included (n = 199 patients). Modest increases in cardiorespiratory fitness (VO_{2max}) were found at both pre-operative (0.73 $mL \cdot kg^{-1} \cdot min^{-1}$, $P \leq 0.001$) and maximum follow-up time points (0.98 $mL \cdot kg^{-1} \cdot min^{-1}$, $P \leq 0.04$). There was no significant effect of exercise intervention on %total weight loss (%TWL). Pre-operative exercise can induce significant short- and long-term improvements in fitness in individuals with obesity. There is insufficient evidence to determine whether pre-operative training impacts other post-operative clinical outcomes.

(3) Key Points

- In obese patients, pre-BS exercise can induce short- and long-term fitness improvements
- There is insufficient evidence on pre-BS training and post-operative clinical outcomes
- More exercise interventions vs clinical outcomes are required in bariatric patients

INTRODUCTION

Obesity is a significant public health problem globally. The World Health Organization estimated that in 2016 more than 1.9 billion adults were overweight. Of these, over 650 million were obese (1). Class 2 obesity, defined as having a BMI $\geq$ 35, has a significantly negative impact on quality of life (2), physical health (3) and life expectancy (4). Despite the costs and invasiveness, bariatric surgery (BS) is recognised as the most successful long-term treatment for weight loss (5). The documented benefits of surgery include an improved metabolic profile and, in the majority of those with type 2 diabetes, remission of the disease. However, the long term efficacy of BS is less promising, with diabetes recurring in between 21-43% of these patients within nine years (6). In addition, most BS patients experience an initial loss of lean muscle mass (7) which negatively impacts metabolism. Overall, the long term 'failure rate' in achieving optimal BMI is approximately 20% for those with Class 2 obesity and 35% for Class 3 (8).

There is growing evidence that modifiable health behaviours may play a significant role in patients' health outcomes and weight loss following BS (9-11). Among individuals who have attempted weight loss, the vast majority of patients who keep the weight off report high levels of physical activity (PA) (12, 13). Candidates for BS typically exhibit low levels of PA, both before and after surgery (14, 15), and have reduced functional capacity (16). Compromised cardiometabolic health, reduced fitness, and excess pre-operative body weight are individually acknowledged as predictors of post-operative mortality in a range of populations (14, 16-20). Despite this knowledge, there are currently no evidence-based exercise guidelines for BS candidates, but instead broad PA recommendations (21). Specific pre-operative exercise intervention has been proposed as one strategy to improve fitness, body composition, and other markers of health in patients undergoing BS (21).

The pre-operative waiting period may represent an ideal opportunity to facilitate healthy lifestyle change, as patients are engaged in the process of preparing for surgery and are not yet facing post-operative recovery challenges. Substantial evidence supports pre-operative exercise interventions in other types of major surgery, such as cardiothoracic surgery, orthopaedic and abdominal cancer (22-24), where it has been demonstrated that a fitter surgical population will have lower incidence of post-operative morbidity and mortality. There remain limited studies, especially reviews, which have examined this association in BS patients.

The benefits of exercise for those with obesity include improved cardiovascular disease risk factors including cardiorespiratory fitness (VO_{2max}) (25) and reduced risk of mortality (26). In the pre-operative setting, the improvement in VO_{2max} is particularly important because of its inverse association with higher risk of surgical complications and mortality (27).

Although a positive relationship between exercise and body composition has been established, few studies support the efficacy of exercise alone to achieve weight loss. However, even when exercise does not result in weight loss, it has been shown to confer significant health benefits to people who are overweight or obese (25, 26). In addition, studies do support the efficacy of exercise to prevent weight gain (28). A review published in 2018 synthesized findings from 15 studies involving post-operative exercise training programs. The authors concluded that exercise interventions performed after BS were effective in optimising weight and specifically fat mass loss, which resulted in improved physical fitness (29). It is important to acknowledge that previous PA interventions in obese

populations have described exercise barriers that are unique to this cohort, in addition to those experienced by the general population (30, 31).

There have so far been no systematic reviews to investigate the effects of pre-operative exercise intervention on these variables among BS candidates. Therefore, we aimed to summarize the evidence from randomized controlled trials (RCTs) comparing the effects of pre-operative exercise-based interventions on fitness and clinical outcomes for BS patients. The hypothesis being tested in this review is that patients with obesity who undertake preoperative exercise training will have improved fitness and %TWL, fewer complications, and reduced hospital length of stay.

MATERIALS AND METHODS

Literature search strategy

The PICO (Population, Intervention, Comparison, and Outcome) framework was used to design the search. A comprehensive list of search terms was established after consultation with a specialist librarian, and included: ‘bariatric surgery’, ‘prehabilitation’, ‘exercise therapy’, ‘exercise’, ‘physical activity’, ‘fitness’, ‘physical fitness’, 'crossover procedure', 'double-blind procedure', 'randomised controlled trial', 'single-blind procedure', factorial’, ‘crossover’, ‘RCT’.
MeSH terms/keywords and free text were used together with the terms (AND/OR/NOT). Language or time restrictions were not used.

A literature search was conducted to identify all published and unpublished randomised controlled trials. The literature search identified potential studies in all languages. The

following electronic databases were searched: MEDLINE, Embase, Cochrane Central Register of Controlled Clinical Trials, SPORTDiscus, Web of Science and Scopus. The main database search was performed on 1st May 2020. This search was updated on 2nd March 2021.

Two independent reviewers (BD and DF) appraised all the potential studies identified by the search. Relevant full texts were retrieved, and the reviewers identified studies for inclusion, then recorded reasons for exclusion of ineligible studies. Disagreements were resolved by consensus. Duplicate references were identified and excluded, and multiple reports derived from the same study were collated.

Reference lists of all primary studies and review articles were checked for additional references. Further, authors of identified trials were contacted and asked to identify other published and unpublished studies.

Inclusion and Exclusion Criteria

Eligible studies included RCTs of pre-operative exercise intervention in a study population of adult BS patients. Studies included were reported as full text, those published as abstract only, and unpublished data. We specifically excluded studies with interventions that were limited only to a specific muscle group, for example inspiratory muscle training, because we viewed these as fundamentally different from whole-body PA trials. We also excluded any studies without a control group. Our protocol was prospectively registered with PROSPERO International Prospective Register of Systematic Reviews (PROSPERO 2020 CRD42020173918) available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020173918

We included adults (aged 18 years and above) with obesity (BMI ≥ 30 kg•m^{-2}) included in exercise intervention RCTs whilst awaiting BS.

Included trials compared exercise intervention with usual care in the pre-operative setting for BS. Exercise is defined as any planned and structured activity carried out to sustain or improve health and fitness. The pre-operative period is specified as between initial primary care referral, to the date of surgery.

Studies that used mixed-modal pre-operative intervention, for example, exercise plus other lifestyle modification deviating from standard care, were excluded. This was to ensure any measured effect could be attributed to exercise intervention alone. Interventions included in this category involved nutrition, or cognitive behaviour therapy.

A set of agreed standardised core outcomes has been developed for bariatric and metabolic surgery using formal consensus methods involving patients and health professionals (32). These nine items, as well as two additional outcomes (serious adverse events and fitness), were included in this review.

The primary outcomes assessed were 1) all-cause mortality in the short-term (30-days) and/or longer-term (maximal follow-up), 2) post-operative short-term morbidity (measured via post-operative morbidity survey [POMS]), 3) overall quality of life (measured via QoL scale / questionnaire), and 4) serious adverse events (short-term and longer-term, respectively, measured using Clavien-Dindo)

The secondary outcomes assessed were treatment associated costs, length of hospital stay, number of days of lost work (maximal follow-up), changes in fitness (pre-operative and maximal follow-up), re-operation / re-intervention and its classification of severity, change in weight (%TWL) diabetes status, technical complications of the specific operation, and micronutrient status.

Data extraction

Two review authors (BD and DF) independently extracted study characteristics and outcome data from included studies using a pre-piloted extraction form. Data collected included the following study characteristics: year and country of publication, number of patients in each treatment arm, number of post-randomisation exclusions, details of each intervention, and baseline patient characteristics. If outcomes were reported multiple times (for example, change in weight was reported at 6 weeks and 3 months) the later time point (i.e., 3 months) was chosen for data extraction.

Where an identified study was published as abstract only, we contacted investigators to verify key study characteristics and obtain missing numerical outcome data. If we were unable to obtain the information from study investigators, we imputed the standard deviation from standard error, interquartile range, or P values according to the Cochrane Handbook for Systematic Reviews of Interventions (33).

Assessment of risk of bias in included studies

The quality of reporting each trial was evaluated by two independent reviewers (BD and DF) using the revised Cochrane risk of bias 2 (RoB2) tool (34). The results of the RoB2 quality assessment (whether a study was of ‘low risk’, ‘there are some concerns’, or ‘high risk’ of

bias) were used to judge the quality of evidence using GRADE criteria (35). Disagreements between the reviewers were resolved by consensus.

Statistical analysis

Data of included studies were pooled using relevant effect measures. Dichotomous data (all-cause mortality, proportion of people with, and number of, serious adverse events, re-operation/re-intervention) were analysed as risk ratios with 95% confidence interval. Continuous data were analysed as mean difference with 95% confidence interval, when the outcome was reported or converted to the same units in all the trials. Conversion equations were used for fitness data where it was not presented as VO_2 (36).

Meta-analysis was undertaken only when considered meaningful, for instance, if the treatments, participants, and the underlying clinical questions were similar. Meta-analysis was performed using RevMan 5.4 software (37).

Subgroup analysis

The following subgroup analyses were planned:

1. Different BMI categories (Obesity Class 1, 2 and 3)
2. Trials at low risk of bias compared to trials at high risk of bias
3. Definition used by authors for serious adverse events and any adverse events (International Conference on Harmonisation Expert Working Group vs other methods)
4. Any differences in methods of bariatric surgery
5. Based on the period of follow-up (short term vs medium or long term)
6. Based on the length of time prior to surgery (more or less than a year)

7. Based on different delivery method of exercise (supervised vs unsupervised)

All primary outcomes were to be used in the subgroup analyses.

Assessment of heterogeneity

Effect sizes were presented as weighted mean differences with 95% confidence intervals. Heterogeneity was assessed on the basis of study design, intervention treatments, stratification, subject type, and statistical methods.

RESULTS

Identification of studies is described in the PRISMA flow diagram (Figure 1). 2,423 articles were found by the systematic search. Following removal of duplicates, 2099 documents were considered, with full-text screening required for 34.

Articles were excluded if the intervention, sample, study design, or outcome did not fulfil the criteria listed in the PICO. The full texts of the remaining 34 studies were reviewed. Five studies satisfied our selection criteria and were included in the systematic review (38-42), with a combined total of 199 participants. Within the studies the mean age ranged from 38 to 47 years and mean baseline BMI ranged from 45 to 47 $kg \bullet m^{-2}$. Post-intervention follow-up ranged from pre-operatively (2 weeks) (41) to 12 months post-operatively (38).

Included studies

Among the included trials, no outcome data were identified on mortality, morbidity, quality of life, serious adverse events (long-term), treatment associated costs, days of lost work, re-operation, diabetes status, technical complications of the specific operation or micronutrient status. Four studies assessed fitness outcomes in a total of 163 obese adults. Three studies

examined body weight outcomes in 142 obese adults. One study assessed serious adverse events and length of hospital stay in 22 participants. Three of the studies were conducted in Canada (38, 41, 42) and 2 were conducted in the USA (39, 40). A summary of the included studies is shown in Table 1.

Table 1: Characteristics of included studies

Study	Intervention	Participants	Outcomes
Baillot et al 2018	12-week pre-operative PA intervention.	N=25 (20 females) adult participants (mean age 43 years) with obesity (mean BMI 46 $kg•m^{-2}$)	Cardiorespiratory fitness via six-minute walk test (6MWT), measured at baseline, pre-operatively (12 weeks) and 12-months post-operatively.
Bond et al 2017	6-week pre-operative PA intervention.	N= 36 (31 females) adult participants (mean age 47 years) with obesity (mean BMI 45.8 $kg•m^{-2}$)	Weight, measured at baseline, pre-operatively (6 weeks) and post-operatively (6-months).
Creel et al 2016	6-week pre-operative PA intervention.	N= 36 (31 females) adult participants (mean age 47 years) with obesity (mean BMI 45.8 $kg•m^{-2}$)	Weight, measured at baseline, pre-operatively (6 weeks) and post-operatively (6-months).
Kwok et al 2016	12-week pre-operative PA intervention.	N=32 (25 females) adult participants	Cardiorespiratory fitness (6MWT)

		(mean age 47 years) with obesity (mean BMI 45.7 kg•m^{-2})	measured at baseline and pre-operatively (12 weeks).
Li et al 2013	8-week pre-operative PA trial.	N=22 (15 females) adult participants (mean age 38 years) with obesity (mean BMI 47 kg•m^{-2}) awaiting gastric bypass surgery in Canada.	%TWL and cardiorespiratory fitness (VO_{2max}) were measured at baseline, before surgery (8 weeks), and 10-weeks after surgery.

Intervention characteristics are outlined in Table 2. There was a behavioural component to the interventions in all studies, including exercise counselling, reviewing self-monitoring records and progress towards goals, problem-solving barriers, teaching behaviour change strategies, developing action plans to achieve goals, and interdisciplinary lifestyle management. Durations of interventions ranged from 2 to 12 weeks, and exercise modalities varied from self-determined walking to individually prescribed high-intensity interval training (HIIT).

Table 2: Intervention Characteristics

	Baillot et al	**Bond et al**	**Creel et al**	**Kwok et al**	**Li et al**
Duration:	12 weeks	6 weeks	2 weeks	12 weeks	8 weeks
Supervision:	Partial	Unsupervised	Unsupervised	Full	Partial

Modality:	Aerobic, strength	Walking	Walking	Aerobic, strength	Aerobic, strength, HIIT
Intensity: Low (L), Moderate (M), Vigorous (V)	M - V: 55 – 85% heart rate reserve (HRR)	M: Habitual exercise plus additional 5,000 steps/day OR 30 min/day	M: 10,000 steps/day	M - V	M - V: 45 – 100% HRR
Frequency/week:	3 days	7 days	7 days	3 days	5 days
Time/week:	240 min	210 min	n/a	180-225 min	120-210 min

Risk of bias in included studies

The results of the risk of bias assessment are reported in Figure 2. Three studies were reported to have high overall risk of bias, and 2 had some concerns. Subjects and assessors were not blinded in any study, however, the difficulty of blinding in exercise interventions is acknowledged. More than 15% of patients randomised were excluded in 3 of 5 studies (38-40) due to surgery not going ahead as planned. All 5 studies performed intention-to-treat analyses so these patients were included in analysis.

Effects of interventions

It was not possible to evaluate all-cause mortality, post-operative short-term morbidity, quality of life, number of days of lost work, re-operation / re-intervention and its classification of severity, diabetes status, technical complications of the specific operation, micronutrient status or cost-effectiveness using meta-analyses, as no studies assessed these outcomes.

The risk ratio for serious adverse events following BS (short-term) showed no difference between intervention and control groups, however this was only based on one study (42) (Figure 3). Only one study reported length of hospital stay (Li 2013) (Figure 4). They reported no difference between intervention (mean 2.6 days) and control groups (mean 2.5 days). Confidence intervals were not estimable. Estimates of the between-study variances are presented in Figures 5, 6 and 7.

Meta-analyses were conducted on the changes in fitness and %TWL. Results indicated that there were increases in VO_{2max} ($mL \bullet kg^{-1} \bullet min^{-1}$) at both pre-operative (mean difference (MD) 0.73, $P \leq 0.001$) and maximum follow-up time points (MD 0.98, $P \leq 0.04$), relative to baseline, as illustrated in Figures 5 and 6. Figure 7 illustrates no significant effect of exercise intervention on %TWL (MD 0.94, 95% CI -1.61 - 3.48).

Heterogeneity

There was no significant heterogeneity for both short and longer-term fitness change analysis. The corresponding I^2 values were 62% and 0%, respectively. There was significant heterogeneity in weight loss analysis (I^2 = 70%).

DISCUSSION

This systematic review found 5 RCTs that investigated the effects of pre-operative exercise intervention in bariatric patients. The pre-operative exercise intervention had a small but significant and lasting effect on cardiorespiratory fitness (0.98 $mL \bullet kg^{-1} \bullet min^{-1}$ increase in VO_{2max}). However, the clinical significance of the increase in fitness could not be determined since few relevant clinical measures were reported in the included studies.

Only 1 of the 5 studies (42) measured serious adverse events. Of the 22 patients in this study, one control group participant experienced 1 serious adverse event: anastomotic leakage following surgery. One study (42) measured length of hospital stay, which showed no difference between groups following an 8 week pre-operative exercise intervention. However, within other clinical populations (43, 44) positive benefits of pre-operative exercise interventions on clinical outcomes, such as length of hospital stay and serious adverse events, have been demonstrated.

The modest cardiorespiratory improvements identified both pre-and post-operatively in the current review (0.73 - 0.98 $mL \bullet kg^{-1} \bullet min^{-1}$) equate to approximately 1/3 MET. Three studies (38, 41, 42) measured pre-operative changes in fitness with interventions ranging from 8-12 weeks, and 120-240 minutes per week of moderate – vigorous intensity. Three studies measured post-operative changes in fitness, where maximum follow-up was assessed between 10 weeks and 12-months post-operatively (38, 40, 42) with interventions ranging from 2-12 weeks. Across all studies only one (41) measured adherence (60% within the intervention group) and compliance (75% attendance at planned sessions).

Cardiorespiratory fitness, or the efficiency of utilising oxygen, has been shown to be a powerful predictor of all-cause mortality and life expectancy in both the general population (45) and in clinical populations (46-48). Franklin et al (47) identified that for every 1 MET increase (3.5 $mL \bullet kg^{-1} \bullet min^{-1}$) there is an associated improvement in all-cause mortality from 22-30%. However, there is a lack of studies that objectively measure aerobic capacity and clinical outcomes following surgery. It is therefore impossible to accurately quantify the clinical benefits following physiological adaptation.

It should be noted that we found substantial evidence of heterogeneity for short-term cardiorespiratory fitness changes based on the I^2 value of 62%. Therefore, these results should be interpreted cautiously.

Body weight changes were reported in 3 (39, 40, 42) of the 5 studies at maximum follow-up. A meta-analysis showed no significant effect of pre-operative exercise intervention on %TWL. The remaining two studies only reported BMI. Collectively the mean was not different between the intervention and control groups, averaging 28.9 and 28.0 $kg•m^{-2}$, respectively. However, measurement of %TWL does not differentiate between fat mass and fat-free mass, therefore no conclusions could be drawn about the contribution of each to overall weight change. Since lean tissue loss following BS is common, exercise should be prioritised to attenuate these negative impacts on metabolism (7). There was substantial evidence of heterogeneity for %TWL based on the I^2 value of 70%. Therefore, these results should be interpreted cautiously.

CONCLUSION

This review and meta-analysis have shown modest improvements in short and long-term cardiorespiratory fitness as a result of pre-operative exercise interventions. However, given the small number of studies and sample sizes, together with inconsistent exercise prescription and outcomes measures, it was not possible to draw conclusions about clinical outcomes. To help overcome this shortcoming, and in line with Coulman and colleagues (32), we recommend adherence to the Core Outcome Set (COS) for future research in this patient cohort. Further, high quality RCTs, adhering to the COS are required in order to definitively

investigate whether pre-operative exercise interventions are beneficial for patients undergoing bariatric surgery.

This review supports the rationale that pre-operative exercise should be initiated prior to surgery for those awaiting bariatric surgery, for the purpose of improving patients' fitness – a key aspect of health.

We conclude that there is a need for further studies investigating the association between pre-operative exercise training and clinical outcomes in bariatric patients. The 5 studies included in this review showed a wide variation of interventions, and few common outcomes.

Figures:

Fig.1 PRISMA flow diagram.

Fig. 2 Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Fig. 3 Risk ratio for serious adverse events (number of events) following bariatric surgery using a random-effects model.

Fig. 4 Length of hospital stay following bariatric surgery in a random-effects model.

Fig. 5 Meta-analysis of pre-operative change in VO_{2max} ($mL \bullet kg^{-1} \bullet min^{-1}$) in a random-effects model

Fig. 6 Meta-analysis of change in VO_{2max} ($mL \bullet kg^{-1} \bullet min^{-1}$) at maximum follow-up post bariatric surgery in a random-effects model.

Fig. 7 Meta-analysis of %total weight loss following bariatric surgery in a random-effects model.

Conflict of Interest: Belinda Durey, Dominic Fritche, Daniel Martin and Lawrence Best declare that they have no conflict of interest.

Statement of informed consent: As this is a review, informed consent does not apply.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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