Meta-analysis of the effects of preoperative weight loss through behavioural lifestyle changes on outcomes following surgery

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ABSTRACT

Background

To investigate whether preoperative weight loss results in improved clinical outcomes in surgical patients.

Methods

Design: Systematic review and aggregate data meta-analysis of randomised controlled trials and cohort studies**.**

Data sources: Cochrane Central Register of Controlled Trials, Clinical Trials.gov, PubMed, MEDLINE, EMBASE, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) Plus databases were searched from inception to February 2018.

Eligibility criteria for selecting studies: Studies assessing the effect of weight loss interventions (low energy diets with or without an exercise component) on clinical outcomes in patients undergoing any surgical procedure. Reported data on 30-day or all-cause in hospital mortality and postoperative thromboembolic complications, operation time, infection, and resource use was extracted and synthesised with meta-analyses.

Results

Four randomised controlled trials and 12 cohort studies enrolling a total of 6060 patients in European and North American centres were identified. All studies had significant methodological limitations. All but one study were in bariatric surgery. Preoperative weight loss interventions were not associated with reduction of mortality (Odds ratio 1.20, 95% confidence interval 0.24 to 8.4; I^2 = 0%, P=0.66). Reduced lengths of hospital stay were shown in the weight loss groups but no differences were shown in the other secondary outcomes.

Conclusion

Preoperative weight loss for patients with obesity undergoing surgery is not supported by the limited existing evidence.

BACKGROUND

Globally, obesity has more than doubled since 1980. In 2016, more than 1.9 billion adults were overweight and over 600 million were obese.[1] As a consequence, overweight and patients with obesity are increasingly referred for surgical treatments.[2] This presents challenges to healthcare workers as operations may be technically more difficult in patients with obesity, perioperative care may be more complex, and the presence of obesity associated comorbidities such as diabetes, hypertension or obstructive sleep apnoea increases the risks of postoperative complications and infections.[3,4]

It is common for treatment to be deferred in obese and overweight patients until they have lost weight, typically following dietary modification with or without exercise.[3] In some countries, overweight and obese patients have restrictions to routine surgery unless they have undergone a successful weight loss programme.[2,5,6] In contrast, observational analyses suggest that overweight and patients with obesity may have improved outcomes following surgery when compared to normal weight or underweight patients.[7-9] To address this apparent contradiction, we performed a systematic review to evaluate the evidence supporting pre-operative body weight reduction through life style changes in obese subjects undergoing any type of surgery. Previous systematic reviews were identified as part of this search, but these either only assessed the correlation between pre-operative and post-operative weight loss, without review of other clinical outcomes[10], were limited to bariatric surgery patients only[11], or restrictive to a very low calorie diet[12]. We hypothesised that, if beneficial, pre-surgery weight loss programmes would result in improved clinical outcomes

METHODS

This systematic review and aggregate data meta-analysis was performed using the methods described in the Cochrane Handbook for Systematic Reviews of Interventions[13] and reported according to PRISMA guidelines.[14] The review protocol was registered in the PROSPERO International prospective register of systematic reviews (CRD: 42017059109) on March 12th, 2017 and updated in February 2018. The MOOSE reporting guidelines were used.[15]

Study Eligibility

Randomised controlled trials, controlled before- and –after studies, cohort studies, cross-sectional studies and case-control studies.

Data Sources

Potentially eligible manuscripts were identified by searching the PUBMED, MEDLINE, EMBASE and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) Plus, and grey literature using a combination of subject headings and text words to identify relevant publications from inception to February 2018. The grey literature included but was not restricted to: conference papers, ongoing clinical trials, academic papers, theses, facts sheets, bulletins, research and committee reports, government reports. The AACODS (Authority, Accuracy, Coverage, Objectivity, Date and Significance) assessment was used to evaluate grey literature materials.[16] The following search terms, were defined in the **Appendix.** The keyword search engine used was the NICE Healthcare Databases Advanced Search Engine (https://hdas.nice.org.uk/). All the responsible searchers were medically qualified (MR/DM/SP). Additionally, the reference lists of eligible trials and reviews were examined for eligibility that may have met our inclusion criteria. Searches were not restricted by language or publication status. Translation of non-English studies was performed using certified translators if applicable.

Study selection

Three reviewers (MR, DM, SP) screened the results of the literature search independent of each other and identified studies that met the inclusion criteria. The selected studies were stored and processed by using the EndNote X7 software. Full texts of these studies were retrieved and further assessed for inclusion, with agreement between the three reviewers. Excluded studies and the reason for exclusion were recorded. Disagreements were resolved by discussion and consensus. In instances where this was not possible GJM determined whether or not the study was included.

Data extraction

Using a standardised form, three reviewers (MR, DM, AM) extracted study data from the included studies on: year and language of publication; country; study type, setting, and population; sample size; participant demographics and baseline characteristics; type of surgery; type of weight loss intervention and outcomes assessed.

- *Participants:*

All patients subjected to behavioural lifestyle changing weight loss interventions and undergoing any type of surgery. No age restrictions were applied (**eTable 1).**

- *Interventions:*

Dietary interventions (with/without exercise) for weight loss prior to surgery. Studies evaluating pharmacological weight loss therapies such as GLP-1 agonists were excluded.

- *Controls:*

Patients not receiving dietary (with/without exercise) interventions, or alternative goal directed therapy groups.

- *Primary Outcome Measures:*

The primary outcome was 30-day mortality or all-cause in hospital mortality.

- *Secondary Outcome Measures:*

Postoperative secondary outcomes at any time-point included: intervention related weight loss; perioperative bleeding (defined as clinical, laboratory, and/or imaging evidence of bleeding); operative time; length of hospital stay (days from the date of intervention to discharge); pulmonary embolism; myocardial infarction, acute kidney injury; infections; need for re-operation and overall complications rate.

Risk of bias assessment

Risk of bias was evaluated by two authors (MR, DM) using the Cochrane risk of bias tool for randomised controlled trials[17] and the Newcastle-Ottawa Scales for cohort and case-control studies.[18] The assessment of bias assessed the selected studies for any of the following: random sequence generation; allocation concealment, blinding of participants, healthcare providers or outcome assessors, incomplete outcome data, attrition, and other sources of bias including source of funder.

Where 10 (based on the number of studies selected for quantitative analysis) or more studies were identified for each outcome two authors assessed publication bias by the visual assessment of funnel plots and Eggers intercept test.[19]

Data Synthesis

Meta-analyses were performed using the software package Review Manager version 5.3.[13] Random-effects models were used to calculate pooled effect estimates for dichotomous data.[20] For continuous outcomes, pooled mean differences were calculated using the inverse variance method.

- *Measures of treatment effect:*

For dichotomous variables, the odds ratio (OR) with 95% confidence interval (CI) was calculated. For continuous variables, the mean difference (MD) with 95% CI for outcomes was calculated.

- *Dealing with missing data:*

When possible, the analysis was limited to those studies that reported results according to intention-to-treat versus per protocol. For dichotomous data presented only as percentages, the frequencies were estimated by using reported sample sizes for this outcome. For continuous outcomes, if the mean and the standard deviation were not available from the trial report, this information was sought from the trial authors. or were calculated from median (interquartile ranges) using the software available in Review Manager Version 5.3.[21]

- *Assessment of Heterogeneity:*

The heterogeneity within each meta-analysis was explored by using the Cochran's Q test and expressed as the percentage of heterogeneity due to variation rather than to chance as I^2.[22] A p value of <0.1 was considered statistically significant. Heterogeneity was defined as follows: I^2 0-40%: no or mild inconsistency, I^2 40-80%: moderate inconsistency, I^2 > 80%: severe inconsistency.

- *Subgroup Analyses:*

The results were expressed as mean difference (MD) for continuous or odds ratio (OR) with non-overlapping 95% CI for dichotomous variables. *Post hoc* moderator analyses explored interactions for variance between studies based on: type of studies (RCT vs. non-RCT), laparoscopic vs. open surgery, or diet vs. diet and exercise interventions studies. A two-

tailed p value of <0.05 was considered statistically significant.[23] No meta-regression was performed due to the limited number of studies included.

Patient and Public Involvement

The patients or public were not involved in the design or conduct of this study.

RESULTS

Description of studies

A total of 11841 references were retrieved through electronic searches of the PubMed (n=3675), MEDLINE (n=3774), EMBASE (n=3526), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) Plus (n=866). After the exclusion of duplicates and irrelevant articles according to title and abstracts (n=11627), 222 full-text articles remained for further evaluation (**Figure 1**). The majority of the excluded studies were conducted in non-surgical patients (115), studied only post-operative weight loss as a result of bariatric surgery (38), used a pharmacological agent for weight loss (31) or were non-interventional studies (no intervention identified in the study) (12). In these studies, a prospective study [24] was identified that analysed preoperative weight loss as a predictor for weight reduction after 3-4 years follow–up and was excluded. We excluded a randomized trial [25] where a dietary weight loss intervention was applied in both groups. A third study [26] evaluated the relationship between the number of preoperative weight loss attempts or the maximal preoperative weight loss using conventional methods on the individual's postoperative successful weight loss. We excluded a further two reports [27,28] that presented follow-up data from two previously reported studies. Of the remaining studies, 21 studies met the inclusion criteria. Following detailed assessment of the full manuscripts, 5 studies (2 were reviews[11,12], 2 had no control groups[29,30] and 1 had no relevant reported outcomes[31]) were further excluded. The remaining 16 publications included: 4 randomized controlled trials, [32-35] 12 cohort studies, of which 3 were prospective [36-38] and 9 retrospective. [37,39-48] No additional references were identified by reference searching leaving 16 articles that met the inclusion criteria and provided quantitative data for inclusion in the analysis (**Figure 1**).

Participants

The quantitative analysis included 6060 participants (3552 treated and 2508 controls) in these 16 studies published between 1995 and 2017. All but one[45] of the studies considered patients undergoing bariatric surgery. The enrolled patients underwent the following types of surgery: 5 studies (2 RCT[32,34] and 3 cohort studies[39,41,43]) - laparoscopic Roux-en-Y

gastric bypass, 3 studies [36,37,44] - open (O-LRYGB) or LRYGB laparoscopic Roux-en-Y gastric bypass, 4 studies[38,40,42,47] - ORYGB, and 2 studies[28,46] - mixed types of gastric banding procedures; vertical banded gastroplasty (VBG) or laparoscopic adjustable gastric bands (LAGB), one study - bilio-pancreatic diversion[35] and one cohort study - total knee or hip replacement[45]. The mean age of participants in these trials ranged from 39 to 50 years, and the mean follow-up time was 6 – 51 months (**Table 1**).In eight studies dietary modification was combined with an exercise programme.[28,35,37-39,41,44,47]

Assessment of bias

None of the RCTs was classified as at low risk of bias. The individual bias domains are presented in the 'Risk of bias' graph and a 'Risk of bias' summary figure. The majority of the studies were subject to attrition and reporting bias. (**eFigures 2a and 2b**) There was a high risk of allocation and selection bias in 1 trial [34]. Five studies [35,38,43,44,46] were at high risk of performance bias, detection bias and incomplete outcome data. Quality assessment for observational studies identified no studies being of high quality defined as scoring maximal points in all 3 domains of the Newcastle-Ottawa score (**eTable 2**).

Effects of Weight Loss Intervention

The summary effect estimates and the details for all primary and secondary outcomes are described in **Table 2, Figure 2** and **Figure 3.**

Primary Outcome

The primary outcome of either all-cause in hospital mortality [32,34,36,39,40,42,43] or mortality related to the surgery occurring within 30 days [33,37] was reported in 9 studies, (3 RCT and 6 cohort studies). Random effects meta-analysis did not show a statistically significant difference in mortality between the intervention and control groups; Odds ratio (OR) 1.20 (95% CI 0.24 to 8.4, p=0.71), with no inconsistency, I^2 = 0%, Q test p=0.66 (**Table 2**).

Secondary outcomes

Preoperative weight loss: was reported in 12 out of 16 studies that included 1572 participants from 3 RCTs[32,33,49] and 9 cohort studies [35,37,39-44,46]. The pooled effect estimate suggested that the interventions resulted in significant weight reduction relative to controls, MD -8.64kg (95% CI -8.1 to -9.2, p<0.00001), however there was severe inconsistency for this outcome I^2 = 96%, Q test p<0.00001.

Operative time: was available in six studies with 1025 participants (2 RCTs[32,34] and 4 cohort studies[39,41-43]). While operative time was lower in the intervention groups, this finding

was not statistically significant, MD -11.6minutes (95% CI -26.4 to 3.26, p=0.13), however there was severe inconsistency for this outcome, I^2 = 95%, Q test p<0.00001.

Hospital Length of Stay: Six studies with 1433 participants reported this outcome (1 RCT[34] and 5 cohort studies[36,38,39,41,42]). The pooled effect estimate suggested that hospital length of stay was less in the intervention groups (Mean 3.2 vs 4.4 days), MD -1.26 days (95% CI -2.1 to 0.41, p=0.003), however there was severe inconsistency for this outcome, I^2 = 97%, Q test p<0.00001.

Perioperative bleeding: Five studies with 1011 participants reported this outcome (2 RCTs[32,34] and 3 cohort studies[39,43,44]). The use of a preoperative weight loss intervention did not result in reductions in perioperative bleeding, OR 1.00 (95% CI 0.44 to 2.31, p=0.59), with mild inconsistency, I^2=3%, Q test p=0.39.

Myocardial infarction: Five studies with 930 participants reported this outcome (2 RCT[32,34] and 3 cohort studies[39,42,43]). The preoperative weight loss intervention did not result in significant reductions in myocardial infarction rates, OR 0.43 (95% CI 0.02 to 11.09, p=0.61). The level of inconsistency could not be calculated due to one single case reported.

Pulmonary embolism: Six studies with 1257 participants reported this outcome (2 RCT[32,34] and 4 cohort studies[37,39,42,43]). The preoperative weight loss intervention did not result in significant reductions in perioperative pulmonary embolism, OR 1.54 (95% CI 0.31 to 7.58, p=0.6), with no inconsistency, I^2=0%, Q test p=0.63.

Infections: Nine studies with 4669 participants reported this outcome (2 RCTs[32,34] and 7 cohort studies[37,39-41,43-45]). The preoperative weight loss intervention did not result in reductions in postoperative infections, OR 0.79 (95% CI 0.53 to 1.18, p=0.25), with no inconsistency, I^2=0%, Q test p=0.89.

Correction of comorbidities: Two studies with 527 participants reported this outcome (2 cohort studies[37,43]). Preoperative weight loss intervention did not significantly lead to a correction of comorbidities, OR 1.04 (95% CI 0.61 to 1.79, p=0.89), with no inconsistency, I^2=0%, Q test p=0.85.

Reoperation: Three studies with 617 participants reported this outcome (1 RCT[34] and 2 cohort studies[39,43]). Preoperative weight loss intervention did not significantly reduce the overall reoperation rates, OR 1.21 (95% CI 0.33 to 4.42, p=0.78), with no inconsistency, I^2=0%, Q test p=0.51.

Overall complications: Ten studies with 1570 participants reported this outcome (2 RCTs[32,34] and 8 cohort studies[37,39-44]). Preoperative weight loss intervention reduced overall

rates of perioperative complications however this was not statistically significant, OR 0.8 (95% CI 0.55 to 1.17, p=0.26), with mild inconsistency, I^2=27%, Q test p=0.19 (**Table 2**).

Publication bias

As only two studies reported the primary outcome (**eFigure 1**), Egger's test was not performed.

Subgroup Analyses

Subgroup analyses demonstrated significant interactions between study type (RCT vs observational studies) and operation type (open versus laparoscopic) with the effect estimates for mean preoperative weight loss (**Table 3**).

The mean difference in weight loss reported in observational analyses, MD 15.50kg, 95%CI 12.52 to 18.48kg was greater than that reported for RCTs, MD 4.5kg, 95%CI 3.69 to 5.31. The mean difference in weight loss was also greater in studies of open bariatric surgery, MD 15.5kg, 95%CI 12.5 to 18.5, versus laparoscopic surgery, MD 4.5kgs, 95%CI 3.7-5.3, Q test p=0.0001. There was also an interaction between operation type and hospital length of stay. The difference in length of stay in studies of open bariatric surgery was MD -0.70 days, 95%CI -0.83 to -0.57, and for laparoscopic procedures -0.07days, 95%CI -0.25 to 0.11, Q test $p < 0.00001$.

Sensitivity Analyses

No sensitivity analysis stratified by methodological quality was performed as no study was considered at low risk of bias.

CONCLUSION

Main findings

This systematic review evaluated the clinical effects of preoperative weight loss in overweight and obese surgical patients identified in 16 studies, all of which had significant methodological limitations. Meta-analysis demonstrated that preoperative weight loss interventions showed no evidence on reduction of all-cause in hospital or 30-day mortality. Analyses of secondary outcomes did not demonstrate differences observed between weight loss and controls for infection, myocardial infarction, thromboembolism, reduction in comorbidities, reoperation rates or overall. Subgroup analyses indicated that the inconsistency between studies for the outcome operation time was attributable to study design and operation type (open versus laparoscopic), and that the inconsistency for the

outcome hospital stay was attributable to differences in operation type. Sub-group analysis suggested that pre-surgery weight loss may reduce operative times in laparoscopic and open bariatric surgery, and hospital stay in patients undergoing open surgery. Severe inconsistency was present for these outcomes.

Strengths and limitations

To our knowledge, this is the first systematic review to assess the clinical effects of pre-surgery weight loss on postoperative clinical outcomes in patients undergoing any type of surgery. The review used comprehensive search strategies in a wide range of registries and data sources, had access to the full texts of all identified trials, used contemporary risk of bias assessments, and assessed a wide range of outcomes after surgery. A previous systematic review addressed the effect of pre-operative weight loss on sustained weight loss after bariatric surgery[10], but did not assess any other clinical outcomes and showed severe inconsistency. Other previous reviews were either limited to bariatric surgery patients only[11], or restrictive to a very low calorie diet[12].

This review includes studies published between 1995 and 2017, which can be a potential limitation and source of heterogeneity in this study, due to the changes in clinical practice and type of intervention (weight loss lifestyle changes). Additionally, the source of inconsistency in the non-randomised studies may reflect the presence of selection or confounding bias in these studies (e.g. comorbidities, clinical setting or different weight loss targets as intervention).

Another limitation of the review is that we did not have access to patient level data; consistent analyses of all studies can only be done when data on individual patients are combined. All 16 studies had limitations in terms of design and methodological quality. In the 3 RCTs identified in the review the risk of procedural, detection, attrition and reporting bias was high; with only one trial being single-blinded to the surgeon. The protocol compliance was not reported, and trial protocols were not published or registered. The observational studies identified in our review also had significant methodological limitations; specifically, all 13 studies compared the intervention group to unmatched controls and 7/13 were at risk of attrition bias. The reporting of outcomes was also heterogeneous between studies, thereby limiting the number of studies that could be included in the analysis of each outcome.

We also demonstrated severe inconsistency for the operation time and hospital length of stay. The sub-group analyses demonstrated that observational studies reported larger

benefits in terms of shorter operating times relative to RCTs. This inconsistency can be attributed to the type of surgery performed. The study with patients undergoing hip/knee replacement was excluded from the subgroup analysis to avoid skewed data, based on the study having sepsis as its only outcome relevant to this review. More recent studies that have evaluated laparoscopic bariatric surgery also demonstrated reductions in operating time and hospital stay versus open bariatric surgery. Thereby, one may speculate that the technical challenges faced by the operator are attenuated by reductions in liver size that accompany low energy diets to a greater degree in laparoscopic versus open surgery.[49] The numbers of studies and patients in each sub group analysis was small and these subgroup analyses were conducted *post hoc*. These findings should be therefore be considered hypothesis generating. Lastly, only short-term clinical effects of pre-surgery weight loss were evaluated in the studies identified in our searches. We cannot therefore exclude that pre-surgery weight loss will often have longer-term clinical benefits.

Clinical importance

Obese and overweight patients are often considered at increased risk of postoperative complications. As a consequence, it is common practice to defer surgery until significant weight loss has been achieved. Indeed, in the UK it is now mandated by some clinical commissioning groups that patients with obesity must demonstrate evidence of weight loss (10%)[2,5] before being considered eligible for surgical treatments. This review highlights the difference in pre-operative weight loss targets in the included studies, which could contribute to the inconsistency and influence the studied outcomes. We performed a comprehensive search of published studies that have evaluated the clinical benefits of preoperative weight loss and found no evidence to support current practice. All but one study identified by our searches included patients that were undergoing bariatric surgery. Patients undergoing bariatric surgery are severely obese and have metabolic syndrome, including type 2 diabetes in many cases. Short term lifestyle weight loss interventions have limited efficacy in these conditions due to the hormonal and metabolic changes that favour weight gain.[50-52] Indeed, the very limited number of studies that have evaluated the effects of weight loss in non-bariatric surgery patients, and the significant limitations of the evidence in this review, highlights a significant knowledge gap. This also indicates that current practice is not supported by evidence across multiple patients' groups. One final consideration is that obesity is often associated with improved clinical outcomes in surgery patients relative to normal weight or underweight individuals.[3,7-9] This obesity paradox is commonly attributed to bias and confounding in observational analyses, however the basis for the obesity

paradox remains poorly understood and this further underlines the need for the evaluation of weight loss interventions in surgical patients in clinical trials.

CONCLUSIONS

A systematic review of studies that evaluated the effects of weight loss interventions in surgical patients found that existing studies that have addressed this question have significant methodological limitations and were mainly limited to patients undergoing bariatric surgery. We were unable to confirm or refute our hypothesis on the basis of the available evidence. These results highlight an important knowledge gap that should be addressed by further research.

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Author Contributions

All of the study authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. GJM, KK and MJD conceived and designed the study. GJM, MR, and GFS, wrote the protocol, undertook the systematic review, and drafted the report. MR, FS, FL performed the analysis. MR, GFS, AM, DM and the medical students SP and AG performed the searches and data extraction. All the authors reviewed the report for important intellectual content and approved the final version. GJM is the senior author and guarantor for the study.

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Data Sharing

No additional data available.

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