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Laparoscopic bariatric surgery versus any non-surgical intervention for adolescents or adults with obesity: protocol for a systematic review with meta-analysis and trial sequential analysis of randomised clinical trials

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ABSTRACT

Introduction The number of people living with obesity is increasing rapidly worldwide, and the WHO estimates approximately 5 million deaths yearly from non-communicable diseases related to elevated body mass index (BMI). The most effective treatment for weight loss is bariatric surgery, but due to the associated risks and the need for lifelong care, this is not a viable treatment for every patient. With the advent of gut-hormone-based medications to treat obesity, the effectiveness of non-surgical treatment is approaching that of surgical interventions. We therefore aim to investigate the beneficial and harmful effects of laparoscopic bariatric surgery versus any non-surgical treatment.

Methods and analysis We will conduct a systematic review with meta-analysis applying our eight-step procedure to assess thresholds for clinical significance and trial sequential analysis to mitigate the risk of random errors. To identify relevant trials, we will search for both published and unpublished trials, without any language restriction, in major medical databases (CENTRAL, MEDLINE, EMBASE, LILACS, SCI-EXPANDED and CPCI-S) and trial registries. The date range covered by the search is from database inception until final search date—within 3 months prior to submission of final results manuscript. Two review authors will independently screen references, extract data and perform risk-of-bias assessment using the Cochrane Risk of Bias Tool 2 and the Grading of Recommendations, Assessment, Development and Evaluations. We will include randomised clinical trials comparing laparoscopic surgery currently in use with any non-surgical comparator in adults or adolescents with BMI >30 kg/m^2. Quasi-randomised studies or non-randomised studies will not be included. Our critical outcomes are all-cause mortality, serious adverse events and quality of life, and our important outcomes are major cardiovascular events, weight at follow-up, physical function and glycaemic control. In addition, we have two explorative outcomes: metabolic syndrome or Z-score and reported incident of alcohol abuse or other addictive disorder or self-inflicted harm.

Ethics and dissemination This review will collect and perform secondary analysis of data from publicly available sources and ethical approval is therefore not required. The findings will be published in peer-reviewed journals and presented at relevant scientific conferences. We will strive to publish with open access. Awareness will be made through social media platforms. This review aims to help clinicians in identifying best practices in the wide-spanning field of obesity treatment.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The methodology addresses the risks of random errors, systematic errors, external validity issues, heterogeneity and publication bias, drawing on Cochrane methodology, the eight-step assessment outlined by Jakobsen *et al*, trial sequential analysis and Grading of Recommendations, Assessment, Development and Evaluations assessment.
⇒ The review focuses on patient-important outcomes rather than surrogate measures.
⇒ A likely limitation is the heterogeneity of the interventions and comparators which will increase the risk of type I errors.
⇒ The available data may originate from a limited number of countries and ethnicities, thereby affecting the generalisability of the findings.

INTRODUCTION

Background

The prevalence of obesity is increasing rapidly around the world, affecting more than a quarter of adults in many high-income countries with significant impacts on individual health and healthcare systems. The WHO defines obesity as a body mass index (BMI) >30 kg/m^2 in adults with an excess of

body fat. In 2019, it was estimated that 5 million people died from non-communicable diseases related to raised BMI.[1] Patients living with obesity are at increased risk of developing numerous serious health conditions, including type 2 diabetes (T2D), cardiovascular disease, infertility and metabolic associated fatty liver disease.[2–7] Bariatric surgery is an effective treatment for obesity and in general reduces all-cause mortality compared with the comparator group[8 9] and leads to significant reductions in T2D and hypertension.[10] But not all patients with obesity are suitable candidates for surgery or are willing to accept the surgery associated risks, highlighting the need for alternative treatment plans.

Interventions for treatment of obesity

Lifestyle interventions

The widespread implications of living with obesity have over the past decades given rise to different strategies for weight-loss treatment. Historically, lifestyle changes have been the preferred approach, and any lifestyle resulting in fewer calories consumed than spent will lead to a weight loss.[11] Randomised clinical trials have demonstrated that intensive lifestyle changes compared with usual care can lead to a weight loss of about seven kg after 1 year, independent of the type of diet.[12 13] The LookAHEAD trial, a programme based on reduced energy intake, dieticians' counselling and increased physical activity compared with usual diabetes counselling, resulted in a weight loss of 8.6% from baseline but no difference in cardiovascular morbidity or mortality compared with the control group.[14]

An intensive and highly controllable dietary intervention is total diet replacement (TDR) that involves substitution of all or nearly all food intake with a formula-based meal replacement containing a maximum of 800 kcal/day (very-low calorie diet (VLCD)) or 800–1200 kcal/day (low calorie diet (LCD)) but all essential amino acids, fatty acids, vitamins and minerals. In clinical trials, VLCD TDR has proved very effective in delivering a rapid weight loss of about 15 kg after 1 year and partially sustained weight loss.[12 15]

Medications

A range of drugs for obesity treatment is available today. Bupropion/naltrexone reduces food intake and increases energy expenditure and yields a weight loss of about 8%.[16] Orlistat inhibits fat absorption but also limits the absorption of fat-soluble vitamins and requires vitamin supplementation.[17] Phentermine combined with topiramate suppresses appetite via the hypothalamus and raises metabolic rate to promote weight loss and results in a weight loss of around 5%.[18]

The newly emerging weight loss medications based on glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have advanced pharmacological treatments for obesity, achieving weight losses of 15% to 20% when combined with lifestyle changes.[19] Initially developed for diabetes management, GLP-1-RA medications like liraglutide and semaglutide, administered as injections, regulate appetite by acting on receptors in the hypothalamus and brainstem.[20 21] The effect of GLP-1-RA treatment on hard outcomes has been thoroughly assessed in patients with T2D and it shows significant reductions in cardiovascular events (14%), kidney events (17%) and all-cause mortality (12%).[22] In patients with obesity and established cardiovascular disease but without T2D, the SELECT trial found that semaglutide vs placebo reduced the 33-month composite of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke by 20%.[23]

GLP-1-RAs are already being combined with other gut hormones to enhance long-term weight loss, most recently in tirzepatide, which combines GLP-1-RA with gastric inhibitory polypeptide.[24] Several additional combination therapies are currently in development, highlighting a rapidly expanding pipeline of medical treatments for obesity.[25]

Bariatric surgeries

For decades, the most effective treatment for weight loss has been bariatric surgery, which leads to a weight loss of 20% to 30% with limited weight regain even after 15 years.[10 26] Today, bariatric surgery is therefore often referred to as the gold-standard treatment for severe obesity (BMI ≥40 kg/m^2).[27–29]

The field of bariatric surgery consists of a wide range of procedures. We have decided to group them according to Buchwald *et al*[30] into laparoscopic adjustable gastric banding (LAGB)-related procedures, laparoscopic sleeve gastrectomy (LSG)-related procedures, Roux-en-Y-gastric-bypass (RYGB)-related procedures, and biliopancreatic diversion/duodenal switch (BPD/DS)-related procedures. According to the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO), SG and RYGB are by far the most common procedures worldwide.[31] 60.4% of procedures performed in 2021–2022 were SG and 29.5% were RYGB.[31] We have decided to focus on surgeries performed laparoscopically, as this is the most widely used operating procedure[31] and endoscopic and laparotomic surgeries have different risk profiles from laparoscopic-performed procedures.

LAGB is a procedure where a saline water inflatable band is placed around the upper part of the stomach, increasing the time it takes for food items to enter the stomach and exerting a pressure on nerve endings resulting in a satiety signal.[32 33] A systematic review from 2019 including 17 reports on LAGB found a total weight loss of 24.5 kg after 3 years[34] and the By-Band-Sleeve randomised trial reports a weight loss of 14 kg at 3 years after the procedure.[35] However, LAGB has been associated with a frequent need for subsequent intervention procedures.[34] Moreover, remission from diabetes following LAGB (22.5%) is less common than after RYGB (57.0%).[36]

The LSG where a large part of the ventricle-sac is removed, and the incision is sewn or stapled together forming a sleeve-like pouch was first advocated for in

2003 (30). This procedure results in an average TWL of 23.4% after 10 years in the SLEEVEPASS trial and remission of T2D is seen in 26% of patients 10 years after the operation.[37] Common adverse reactions to the procedure are reflux symptoms and reduced uptake of vitamins and minerals necessitating lifelong supplementation.[38 39] Significantly higher reflux symptoms were found in patients with LSG compared with RYGB at 10-year follow-up.[37] A study of 224 718 sleeve gastrectomies performed in France between 2008 and 2018 finds that 12.2% of patients undergoing the operation will end up having revision surgery within the first 10 years, mostly due to insufficient weight loss or reflux symptoms.[40]

In RYGB, most of the stomach is stapled off to create a small pouch connected directly to the jejunum, bypassing the duodenum. The duodenum is then reattached further down the jejunum, allowing bile and enzymes to enter the digestive tract. There is good evidence that RYGB leads to higher weight loss than SG. For example, in the By-Band-Sleeve randomised clinical trial, TWL was 19.4% for SG and 26.8% for RYGB at 3 years,[35 37 41] but also evidence pointing to the contrary exists.[42 43] The Swedish Obese Subjects trial demonstrates an average TWL of 32% following RYGB (mostly performed as open surgery) and regain after 10 years is on average 7% of original weight,[26] a pattern like the findings of Salminen *et al*.[37] Diabetes remission in patients with T2D occurred in 33% of patients in the Salminen *et al* trial at 10-year follow-up[37] and in 50% of patients in the Oseberg trial at 5-year follow-up,[44] compared with 26% and 20% of the patients who had SG.[37 45] RYGB demonstrated a higher remission rate of hypertension than SG.[37] Common adverse effects to RYGB are dumping syndrome, where the patient experiences postprandial nausea, stomach cramps, diarrhoea, etc. usually after a meal high in sugar.[46 47] The uptake of vitamins and minerals is more affected by RYGB than by SG, necessitating lifelong supplementation, sometimes requiring injections with vitamin B_{12} and iron.[38] A modified type of bypass operation named one anastomosis gastric bypass (OAGB) has gained popularity during recent years, constituting 4.3% of the operations worldwide according to The IFSO and Metabolic Disorders.[31] The perioperative morbidity following SG and RYGB is low.[27]

BPD/DS involves a major reduction of the stomach and bypass of 75% of the small intestine.[48] The weight loss is the greatest among the operations utilised today. Unfortunately, it also has the highest mortality and complications rates, in part due to substantial problems with uptake of nutrients.[49]

Bariatric surgery in general reduces all-cause mortality compared with the comparator group both in patients with and without T2D[8 9] and leads to significant reductions in T2D and hypertension.[10] But in addition to the risk of complications, bariatric surgery is associated with the known adverse reactions of reduced uptake of vitamins and minerals necessitating life-long substitution.[38] Patients may also experience problems with acid reflux, dumping syndrome and, rarely, also postprandial hypoglycaemia.[10] Additionally, not all patients with obesity are suitable candidates for surgery or are willing to accept the surgery-associated risks, highlighting the need for alternative treatment plans.

Relevance of the planned review

Bariatric surgery has proven to be a highly effective treatment for obesity but is invasive and largely irreversible and comes with a marked risk of complications that warrant life-long follow-up. Moreover, not everyone living with obesity is fit to undergo surgery or may want to undergo a surgical procedure. Non-surgical treatments, while safer initially, may show less substantial or sustainable weight reductions. Also, clinicians aim to improve not just weight-related outcomes but also patients' quality of life, metabolic health and mortality. These topics were addressed in a 2014 update of a Cochrane review that compared bariatric surgery with any other weight-loss intervention.[10] The authors concluded that bariatric surgery was superior to other interventions with regards to kilograms lost, improvement in markers of diabetes and blood lipid profile.[10] Regarding health-related quality of life, two studies included in the Colquitt review compared surgical and non-surgical treatments using the Short Form 36 (SF-36) questionnaire[50] and found no statistically significant difference in overall mental component scores. However, since 2014, the number of randomised clinical trials assessing surgical interventions has grown and breakthrough gut hormone-based medications have been introduced worldwide, offering a very effective medication treatment without surgery. Furthermore, the most performed surgeries have changed, with RYGB and SG becoming the most performed operation types and the LAGB falling out of favour, and new surgeries like OAGB have emerged.[31] All this has led to a renewed focus on surgery vs medication in the treatment of obesity as reflected in the editorial for the STEP1 study in New England Journal of Medicine where head-to-head studies comparing surgery versus medication for the treatment of obesity are requested.[51]

In this new systematic review with meta-analysis, we aim to offer an updated and broad understanding of the trade-offs between bariatric surgery versus non-surgical interventions, that is essential in helping practitioners align treatment options with patient preferences. A particular strength will be the use of the trial sequential analysis (TSA) method designed to control the risk of type I and II errors,[52] which was not applied in the 2014 review.[10]

Objective

The objective is to investigate the benefits and harms of laparoscopic bariatric surgery vs any other non-surgical weight-loss intervention for adults or adolescents living with obesity.

METHODS AND ANALYSIS

This systematic review was registered in the PROSPERO database on 12 September 2025 (CRD420251135341) and the present protocol is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols 2015 statement.[53]

Criteria for study inclusion

Types of participants

We will include randomised clinical trials with human adults or adolescents (as defined by the trialists) with a BMI>30 kg/m^2. We will include trials irrespective of the participants' sex, gender, ethnicity, comorbidities or risk factors.

Types of interventions

Experimental interventions: We will include trials investigating laparoscopic bariatric surgery currently in use, categorised as LAGB, SG, RYGB, BPD/DS or any surgery relating to one of these categories, performed laparoscopically. Due to the difference in possible complications relating to the surgery, we will exclude trials with surgeries performed as open surgery. We have chosen to focus on the most widely used procedures, and surgeries performed endoscopically are beyond the scope of this review.

Types of comparators

Comparator interventions: Comparator interventions may be 'no intervention', or any non-surgical weight-loss intervention including lifestyle interventions and weight-loss medications.

Cointerventions: Trials with cointerventions will be included if all intervention groups had equal access to the cointervention(s).

Types of outcome measures

Critical outcomes

1. All-cause mortality (dichotomous data).
2. Serious adverse events: Proportion of participants with one or more serious adverse events (dichotomous data), defined as any untoward medical occurrence that resulted in death, was life-threatening, required hospitalisation or prolonging of existing hospitalisation and resulted in persistent or significant disability or jeopardised the patient.[54] If the trialists do not use the International Committee of Harmonisation-Good Clinical Practice (ICH-GCP) definition, we will include the data if the trialists use the term 'serious adverse event.' If the trialists do not use the ICH-GCP definition nor use the term serious adverse event, then we will also include the data if the event clearly fulfils the ICH-GCP definition for a serious adverse event.
3. Quality of life (continuous data) measured by either any validated weight-specific questionnaire such as the Impact of Weight on Quality of Life (IWQOL)-questionnaire and IWQOL-Lite[55] or any validated generic outcome measure such as the SF-36 questionnaire.[50] If the results are reported as mental and physical scores, we will use the mental and/or the global score for this outcome.

Important outcomes

1. Major cardiovascular events as defined by trialists (dichotomous data).
2. Physical function measured as defined by trialists or reported as a physical score in a quality-of-life questionnaire (continuous data).
3. Weight at follow-up (continuous data).
4. Glycaemic control, quantified by Haemoglobin A1C (HbA1c) and/or fasting glucose levels (continuous data).

Explorative outcome

Metabolic syndrome and/or Z-score (MetS-Z-score) at longest follow-up.

Reported incident of alcohol abuse or other addictive disorders or self-inflicted harm.

For all outcomes measuring continuous outcomes, we will consider calculating standardised mean differences (SMD).

Time points

We will assess all outcomes at longest follow-up.

Types of studies

We will include randomised clinical trials regardless of publication year, language, type or status. Also, preprints and trials not yet published will be included. We will not include quasi-randomised studies or non-randomised studies. We will only include the first period of cross-over trials should one be identified.

Patient and public involvement

Patients or members of the public were not directly involved in the development of this protocol. Nevertheless, the patient perspective has been a primary driver in the selection of outcomes. These outcomes were informed by the questions and priorities that the clinicians in the review team commonly experience patients raise, particularly regarding what they hope to achieve through weight loss. Therefore, this review emphasises outcomes of direct relevance to patients, such as quality of life, physical function and obesity-related or treatment-related illness, rather than focusing primarily on surrogate or laboratory measures.

Search methods

We will search Cochrane Central Register of Controlled Trials (CENTRAL), Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica database (EMBASE), Latin American and Caribbean Health Sciences Literature (LILACS), Science Citation Index Expanded (SCI-EXPANDED), and Conference Proceedings Citation Index—Science (CPCI-S) to identify relevant trials. We will search all databases from their inception to the present. Trials will be included

irrespective of language, publication status, publication year and publication type.

To identify unpublished trials, we will search clinical trial registries (eg, WHO's trial platform and ClinicalTrials.gov), websites of US Food and Drug Administration (FDA) and European Medicines Agency (EMA). To identify unpublished trials, we will search clinical trial registries (eg, WHO's trial platform and ClinicalTrials.gov), websites of US Food and Drug Administration (FDA) and European Medicines Agency (EMA). An initial search was first conducted on 9 July 2025 (online supplemental appendix 1); the search will be updated as close to submission of the final manuscript as possible, and at a minimum within 3 months prior to submission. Consequently, the exact date of the final search is not yet known.

Data collection and analysis

We will perform and report the review following the recommendations as described in the Cochrane Handbook for Systematic Reviews of Interventions.[56] Analyses will also be performed using TSA.[52]

Selection of trials

Two reviewers will independently screen the titles and abstracts. Full-text reports of relevant studies will be obtained, and two reviewers will independently assess these full texts, documenting the reasons for excluding any ineligible studies. Any disagreements between the reviewers will be resolved through discussion with consultation of a third reviewer if necessary.

Data extraction

The data extraction will be performed by two review authors, who will extract data independently from the included trials using a predefined form. Any disagreements will be resolved through discussion with a third author. If necessary, we will contact the trial authors via email to request any missing data that may not have been sufficiently reported or included in the publication. For studies with extended follow-up data (eg, long-term extension studies), data will be extracted both at longest originally planned follow-up and longest available extended follow-up.

Trial characteristics

We will extract data on: bias risk components (as defined below), trial design (parallel, factorial or crossover), number of intervention groups, length of follow-up, estimation of sample size, inclusion and exclusion criteria, publication year, setting.

Participant characteristics

We will extract data on: number of participants randomised, number of participants analysed for each outcome, age, sex ratio, weight at baseline, BMI range at baseline, all outcomes.

Intervention characteristics

We will extract data on: type of intervention, adjunct interventions and duration of intervention.

Comparator characteristics

We will extract data on: type of comparator, adjunct interventions and duration of intervention.

Outcomes

All outcomes will be extracted from each RCT, and it will be identified whether outcomes are incomplete or selectively reported according to the criteria described below in 'incomplete outcome data' bias domain and 'selective outcome reporting' bias domain.

Dichotomous outcomes

For dichotomous outcomes, risk ratios with 95% CIs and TSA-adjusted CIs will be calculated.

Continuous outcomes

We will calculate the mean differences (MDs) and consider calculating the SMD with 95% CIs and TSA-adjusted CIs will be calculated for continuous outcomes.

Assessment of risk-of-bias in the included trials

Our assessment of bias risk will follow the Cochrane Risk of Bias Tool, V.2 (RoB 2), as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*.[56] A publication will be considered at high risk of vested interests if the trial is industry-sponsored or if any author has an industry affiliation. Furthermore, we will assess the study methodology across the following bias domains:

Bias arising from the randomisation process

This domain includes the generation of the allocation sequence, its concealment and any baseline differences between trial arms.

- Low risk of bias: Allocation was adequately concealed, baseline imbalances across intervention groups appear to be due to chance, and an appropriate (random or otherwise unpredictable) method was used to generate the allocation sequence, or there is no information provided about the method used to generate the sequence.
- Some concerns: Allocation was adequately concealed, but there are issues with the sequence generation method, or baseline imbalances indicate potential problems with the randomisation process. Alternatively, no information is available regarding allocation concealment, yet baseline imbalances are consistent with chance, or there is insufficient information to answer any of the signalling questions.
- High risk of bias: Allocation sequence was not concealed, or there is no information on allocation concealment, and baseline imbalances suggest issues with the randomisation process.

Bias due to deviations from intended interventions

- Low risk of bias: Participants, caregivers and personnel were unaware of the assigned intervention

groups during the trial, OR they were aware, but any deviations from the intended interventions reflected standard practice, OR deviations were unlikely to impact the outcomes. Additionally, no participants were analysed based on the intervention they actually received instead of their randomised allocation.
- Some concerns: Participants, caregivers or personnel were aware of the intervention groups, and there is no information on whether deviations from usual practice, which could impact the outcome and were imbalanced between groups, occurred. Alternatively, some participants were analysed based on the intervention they received rather than their randomised allocation, but this is unlikely to have a substantial impact on the estimated effect of the intervention.
- High risk of bias: Participants, caregivers or personnel were aware of the intervention groups, and there were deviations from the intended interventions that were imbalanced between groups and likely to affect the outcomes. Additionally, some participants were analysed based on the intervention they received instead of their randomised allocation, with a substantial potential impact on the intervention effect estimates.

Bias due to missing outcome data

- Low risk of bias: There is no missing data, or missing data are non-differential (ie, similar proportions and reasons for missing data across comparison groups), or there is evidence that the effect estimate is robust to missing data, based on appropriate statistical methods and sensitivity analyses.
- Some concerns: There is an unclear amount of missing data, or information on the proportion and reasons for missing data is not provided. Additionally, there is no evidence to suggest that the effect estimate is robust to the missing data.
- High risk of bias: There is a high degree of missing data, and missing data are differential (ie, differing proportions or reasons for missing data between comparison groups), with no evidence that the effect estimate remains robust in the presence of such missing data.

Bias in measurement of the outcome

- Low risk of bias: The outcome assessors were unaware of the intervention received by study participants, or the outcome assessors were aware of the intervention received by study participants, but the assessment of the outcome was unlikely to be influenced by knowledge of the intervention received.
- Some concerns: There is no information available to determine whether the assessment of the outcome is likely to be influenced by knowledge of the intervention received.
- High risk of bias: The assessment of the outcome was likely to be influenced by knowledge of the intervention received by study participants.

Bias arising from selective reporting of results

- Low risk of bias: It is unlikely that the reported outcome data were selectively chosen based on the results from among multiple outcome measures (eg, different scales, definitions, or time points) within the outcome domain. Similarly, it is unlikely that the reported outcomes were selectively chosen from among multiple analyses of the data.
- Some concerns: There is insufficient information to rule out the possibility that the reported outcome data were selectively chosen based on the results from among multiple outcome measures or from multiple analyses of the data. Since analysis intentions are often not disclosed or reported in detail, this judgement is expected to apply to most trials.
- High risk of bias: It is likely that the reported outcome data were selectively chosen based on the results from among multiple outcome measures (eg, different scales, definitions or time points) within the outcome domain or from multiple analyses of the data, or both.

Overall risk of bias assessment

- Low risk of bias: The trial is considered to have a low risk of bias across all assessed domains for this specific outcome.
- High risk of bias: The trial is deemed to be at high risk of bias or to have some concerns in at least one domain for this specific outcome. We will conduct subgroup analyses comparing the intervention effects of trials with a low risk of bias to those with a high risk of bias (ie, trials with at least one domain rated as having some concerns or high risk).

We will evaluate the domains of bias due to 'deviations from intended interventions', 'missing outcome data', 'bias in the measurement of the outcome' and 'bias in the selection of the reported result' for each outcome. This will enable us to assess the risk of bias for each specific outcome, in addition to evaluating each trial. Our primary conclusions will be drawn from outcomes that are judged to have an overall low risk of bias.

Dealing with missing data

As specified above, all trial authors will be contacted to obtain any relevant missing data (ie, for data extraction and for assessment of risk of bias). Second, we will investigate the effects of missing data in sensitivity analyses, specified below.

Dichotomous outcomes

We will not impute missing values for any outcomes in our primary analysis. In our sensitivity analyses, we will impute data.

Continuous outcomes

We will primarily analyse scores assessed at single time points. If only changes from baseline scores are reported, we will analyse the results together with follow-up scores.[56] If SDs are not reported, we will calculate the SDs using trial data. We will not use intention-to-treat data if the

original paper did not contain such data. We will impute missing values for the continuous outcomes in the sensitivity analyses.

Assessment of heterogeneity

We will initially examine forest plots to visually assess potential signs of heterogeneity. Heterogeneity will be evaluated using the χ^2 test and quantified with the I^2 statistic. If substantial heterogeneity is detected, we will explore possible sources through subgroup analyses (see the 'Subgroup Analyses and Integration of Heterogeneity' section below). If the heterogeneity is significant, we may conclude that performing a meta-analysis is not appropriate.

Assessment of reporting biases

We will use a funnel plot to assess reporting bias if ten or more trials are included.[57] We will visually inspect funnel plots to assess the risk of bias. We are aware of the limitations of a funnel plot (ie, a funnel plot assesses as due to small sample size). When analysing continuous data, we will use Egger's test and Harbord test when analysing dichotomous data.

Data synthesis

Meta-analysis

We will undertake the meta-analysis according to the recommendations stated in the Cochrane Handbook for Systematic Reviews of Interventions,[56] and the eight-step assessment suggested by Jakobsen *et al*.[58] Both random-effects meta-analyses and fixed-effect meta-analyses will be used for assessing potential intervention effects. We will use the more conservative point estimate of the two,[58] which is the estimate closest to no effect. If the two estimates are similar, we will use the estimate with the widest CI.

Trial sequential analysis

Traditional meta-analyses are susceptible to random errors of type II and type I due to limited data and repeated testing as new data accumulates during review updates.[59] To mitigate the risks of both type I and type II errors, we will conduct TSA for all outcomes. This will allow us to calculate the required information size (ie, the number of participants needed in the meta-analysis to confirm or reject a specific intervention effect) and monitor the cumulative Z-curve's crossing of relevant trial sequential monitoring boundaries.[52] Further details on TSA are available in the TSA manual[59] and online at http://www.ctu.dk/tsa/.

We assess a total of three critical and four important outcomes, and we will therefore consider a p value of 1.25% or less as the threshold for statistical significance for both outcomes. We will use the eight-step procedure to assess if the thresholds for significance are crossed. Our primary conclusion will be based on results at low risk of bias.[58]

If minimal important differences for the outcomes exist, we will adhere to these. For HbA1c, US FDA has defined the minimal important difference as 0.3% (3.3 mmol/mol),[60] and for body weight, it is defined as 5%.[61] For quality of life, it depends on the questionnaire. For the SF-36 questionnaire, a clinically meaningful difference has been considered as a change from baseline of >3.8 points on the physical score and >4.6 on the mental score.[62] The IWQOL-Lite questionnaire has a change of 7.7–12 points as a clinically meaningful difference.[62]

For dichotomous outcomes, the required information size will be estimated using the proportion of patients with an event in the control group (the cumulative proportion of events relative to all patients in control groups), a relative risk reduction of 10%, an alpha of 1.25% for the critical outcomes and 1.25% for important outcomes, a beta of 10%, and the observed diversity as indicated by the trials in the meta-analysis. For other continuous outcomes, TSA will calculate variance based on the observed SD, a MD equal to half the observed SD as minimal important difference, an alpha of 1.25% for primary outcomes and 1.25% for secondary outcomes, a beta of 10%, and the observed diversity from the included trials.

Subgroup analysis (and integration of heterogeneity): We will perform subgroup analysis as listed below on all outcomes.

1. Trials at high risk of bias compared with trials at low risk of bias.
2. Preregistered trials compared with trials without preregistration.
3. Participants with and without diabetes.
4. According to surgery method.
5. Comparator intervention (eg, behavioural interventions (lifestyle, exercise, diet), type of medication (GLP-1-based vs other), no intervention or any combination of these).
6. Stratified according to the median study start date.
7. Follow-up period at or below 30 days and above or below median follow-up time for trials included in this study.
8. Sex.
9. Ethnicity.
10. If possible, we will perform subgroup analysis on adolescents compared with adults.

In order to provide relevant data for clinicians in the current field of obesity treatment, we will conduct head-to-head analysis of the most commonly performed surgery methods (SG and RYGB) against the novel gut-hormone-based medications (eg, GLP-1-RA-medications) if possible.

Sensitivity analyses

Dichotomous data

To assess the potential impact of the missing data for dichotomous outcomes, we will perform the two following sensitivity analyses on both the primary and secondary outcomes.

1. 'Best-worst-case' scenario: We will assume that all participants lost to follow-up in the experimental group did not die or had no serious adverse events. We will

assume the opposite for all participants lost to follow-up in the control group.
2. 'Worst-best-case' scenario: We will assume that all participants lost to follow-up in the experimental group died, had a serious adverse event. We will assume the opposite for all participants lost to follow-up in the control group.

We will present the results of both scenarios in our systematic review.

Continuous data

When analysing the robustness of a continuous 'beneficial' outcome, for example, quality of life, we will impute the group mean plus two SDs of the group mean. When dealing with a 'harmful outcome', we will impute the group mean minus two SDs of the group mean.[58] We will present the results of both scenarios in our review.

Other post hoc sensitivity analyses might be warranted if unexpected clinical or statistical heterogeneity is identified during the analysis of the review results.

Summary of findings table

We will create a summary of findings table for each comparison (seven) including each of the prespecified primary and secondary outcomes. We will use the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) considerations (bias risk, heterogeneity, imprecision, indirectness and publication bias) to assess the quality of a body of evidence.[58 63 64] We will assess imprecision using TSA, by comparing the accrued sample size to the diversity-adjusted required information size (DARIS) to see if the trial sequential monitoring boundaries have been reached. We will downgrade imprecision in TSA by three levels if the accrued number of participants is below 33% of the DARIS, two levels if between 33% and 66%, and one level if it is between 67% and 100% of DARIS. Furthermore, we will not downgrade if the cumulative Z-curve crosses the monitoring boundaries for benefit, harm or futility, or if DARIS is reached. We will justify all decisions to downgrade the quality of evidence using footnotes, and we will make comments to aid the reader's understanding of the review where necessary.

Deviations from the protocol

Any deviations from protocol will be reported in 'Differences between the protocol and the review'-section of the systematic review.

ETHICS AND DISSEMINATION

This study is based exclusively on secondary analyses of data from publicly available sources; therefore, ethical approval is not required. The results will be disseminated through publication in peer-reviewed scientific journals and presentation at national and international scientific conferences. Open-access publication will be pursued whenever possible. In addition, key findings will be communicated through relevant professional and public dissemination channels, including social media. The overall aim of dissemination is to support clinicians and other stakeholders in identifying best practices within the broad field of obesity treatment.

DISCUSSION

This review aims to assess the beneficial and harmful effects of laparoscopic bariatric surgery versus any non-surgical weight-loss intervention for people with obesity. The critical outcomes will be all-cause mortality, serious adverse events and quality of life. The important outcomes will be cardiovascular outcomes, weight at follow-up, physical function and glycaemic control.

The primary strength of our protocol is the methodology. The methodology is predefined, drawing on Cochrane methodology,[56] the eight-step assessment outlined by Jakobsen *et al*,[58] TSA[59] and GRADE assessment.[63 64] This comprehensive approach addresses the risks of random errors, systematic errors, external validity issues, heterogeneity and publication bias. Moreover, the review is addressing a treatment which becomes increasingly sought after by a larger and therefore more diverse population, which increases the need for quality evidence to guide clinical decision-making and patient counselling.

A main limitation will most likely be a limited number of RCTs comparing laparoscopic surgical vs non-surgical treatment of obesity, that is, only seven trials were included in the Cochrane review from 2014.[10] The RCTs will most likely also be quite similar in geographical origin and possibly also in ethnicity, which will limit external validity and generalisability of the results. Furthermore, there will probably be a high heterogeneity in interventions with both different surgical procedures and different non-surgical interventions, which will increase the risk of type I errors. We have adjusted the threshold for significance according to the number of outcomes, but not according to the number of interventions or subgroup analysis. We might also encounter different ways of reporting outcomes, for example, quality of life might be reported from different questionnaires. The follow-up time will probably be a few years at most for the majority of the trials, and we may therefore not be able to conclude on long-term health benefits and harms, which might be a concern for especially the outcomes such as 'all-cause mortality' and 'major cardiovascular events'.

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Competing interests KNB-M has on behalf of her institution received research funding from the Novo Nordisk Foundation and other foundations and has served as co-investigator (unpaid) for Amgen. None of these commitments have had any influence on the present work. CD has on behalf of his institution received research funding from the Novo Nordisk Foundation, and over the past 3 years received personal fees (lecturer, consultancy, committee member) from Novo Nordisk, AstraZeneca and Amylyx, and served in various unpaid roles (lecturer, chairperson, principal investigator) for Novo Nordisk, Amgen, AstraZeneca and Eli Lilly. SAJ has received total diet replacement products to support a publicly funded trial treatment donated by Nestlé. OD, M-LD, JL, JJP, JS and CG declare no competing interests.

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