BMJ Open Comparative long-term effectiveness and safety of primary bariatric surgeries in treating type 2 diabetes mellitus in adults: a protocol for systematic review and network meta-analysis of randomised controlled trials

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ABSTRACT

Introduction Bariatric surgeries are effective in treating obesity related comorbidities, including type 2 diabetes mellitus. More robust evidence is needed to facilitate choice of procedure. In this systemic review, we aim to investigate the comparative long-term effectiveness in inducing remission of type 2 diabetes, halting diabetic complications, reducing mortality and the safety of conventional and emerging bariatric surgeries.

Methods and analysis Databases including Cochrane Central Register, EMBASE, MEDLINE and clinical trial registries will be searched for randomised controlled trials with at least 3 years of follow-up, including direct and/or indirect evidence regarding primary bariatric surgeries in overweight or obese adults with type 2 diabetes mellitus, from inception of each database to 2019, with no language or publication type limits imposed. Dual selection of studies, data extraction and risk of bias assessments will be performed. Primary outcomes include full diabetes remission, composite outcome of full or partial diabetes remission and adverse event profiles. Secondary outcomes include anthropometric measurements, cardiovascular risk factor burden, medication burden, diabetic complications and all-cause mortality. Given sufficient homogeneity, network meta-analyses will be performed in a random-effects model based on the Bayesian framework, while assessing for consistency between direct and indirect estimates. Heterogeneities of studies will be explored through meta-regression analysis, and robustness of findings will be checked by sensitivity analysis, and an alternative method under a frequentist framework. All statistical analysis and graphical presentations will be conducted by R software V.3.3.3 (The R Project for Statistical Computing). The overall quality of the evidence will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation criteria for each outcome.

Ethics and dissemination Ethics approval is not required as individual patient data will not be included. This review will be subject for publication in a peer reviewed journal.

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Strengths and limitations of this study

- This will be the first systemic review and network meta-analysis to assess long-term relative effectiveness and safety of conventional and emerging bariatric surgeries in overweight or obese adults with type 2 diabetes mellitus.
- This study will comprehensively evaluate clinically important outcomes, including full or partial diabetes remission, anthropometric measurements, cardiovascular risk factor burden, medication burden, diabetic complications, all-cause mortality and major adverse events.
- This protocol proposes a cumulative score-based approach for integral assessment of safety of bariatric surgeries.
- This protocol defines detailed plan for data synthesis, additional analysis and validation of findings by an alternative method.
- Common to any aggregate data meta-analysis, the risk of heterogeneity across studies exists.

BACKGROUND

Bariatric surgeries have shown long-term benefits with respect to inducing disease remission, reducing mortality and decreasing microvascular and macrovascular complications in overweight or obese patients with type 2 diabetes mellitus, compared with non-surgical therapy.¹ Currently performed bariatric surgeries include Roux-en-Y gastric bypass, sleeve gastrectomy, adjustable gastric banding, biliopancreatic diversion with duodenal switch, greater curvature plication, one-anastomosis gastric bypass and single anastomosis duodenal-ileal bypass with sleeve gastrectomy.²⁻⁵ Previous studies indicated that bariatric surgeries differed in both

efficacy, durability, and mechanisms in inducing remission of type 2 diabetes and complication profiles.^{2 6–9} Current evidence is insufficient to support recommendation regarding choice of specific procedure clearly over others, and more robust evidence is needed to facilitate informed decision-making.² Since comparisons of only two or a few bariatric procedures can be achieved in randomised controlled trials, network meta-analysis, capable of integrating both direct and indirect evidence, is a reasonable approach in this scenario.

A recent elegant network meta-analysis of studies involving eight bariatric surgeries with median follow-up duration of 3 months to 5 years (median 1 year) indicated that biliopancreatic diversion and one-anastomosis gastric bypass achieved higher diabetes remission rates than the other procedures.⁶ However, biliopancreatic diversion is rarely performed currently due to unfavourable complication profiles, while one-anastomosis gastric bypass is a relatively new procedure, the safety and durability of which warrants further investigation.^{3 10} Furthermore, remission rates of comorbidities may change over time after bariatric procedures,^{11 12} thus comparing relative efficacies with different follow-up duration postbariatric surgeries may introduce bias.

Type 2 diabetes mellitus can lead to increased risk of cardiovascular events, renal failure, blindness, amputation and increased mortality. Most of the evidence regarding the effects of bariatric surgeries on diabetic complications and mortality is derived from observational studies and pairwise comparisons.² Defining the relative effectiveness of bariatric surgeries in halting diabetic complications and in decreasing mortality should be addressed with the most robust evidence possible, or at least, gaps in current knowledge should be identified to guide emphasis of future research.¹³

Complication profiles of bariatric surgeries differ among procedures and between patients with and without type 2 diabetes mellitus.^{14 15} However, efforts investigating comparative safety and tolerability of bariatric surgeries have been met with great difficulty, due to heterogeneity of adverse events encountered and in ways reported among studies. Efforts have been made for standard reporting of adverse events in studies of bariatric procedures.¹⁶ We would like to revisit this question, by defining major adverse event profiles of bariatric surgeries in adults with type 2 diabetes mellitus, a group of patients already predisposed to increased risks of surgical complications, depression and hypoglycaemia.^{17–19}

OBJECTIVES

The objectives of the study are to determine the relative effectiveness and safety of existing bariatric surgeries in treating overweight or obese adults with type 2 diabetes mellitus through systemic review and network meta-analysis, to perform meta-regression analysis, subgroup analysis and sensitivity analysis, if feasible, to explore what clinical and methodological characteristics explain the

heterogeneity in results, and to identify gaps in current studies to provide directions for future research.

METHODS

This protocol follows Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) protocols and the accompanying checklist, and the study will follow PRISMA.^{20 21} This protocol is registered with the International Prospective Register of Systematic Reviews. In circumstances when changes to the protocol are necessary, details and rationales of the changes in the reported systematic review will be reported.

Patient and public involvement

Patients or the public were not involved in the design of this systemic review protocol.

Eligibility criteria

Participants

We will include studies which include overweight or obese adults with type 2 diabetes mellitus. We will not include studies of participants restricted to specific diseases other than type 2 diabetes mellitus. In studies in which general overweight or obese participants are enrolled, or in which children or adolescents under the age of 18 are enrolled along with adults, we will extract the data for the adult population with type 2 diabetes exclusively.

Interventions

We will include interventions encompassing currently performed primary bariatric surgeries, including Roux-en-Y gastric bypass, sleeve gastrectomy, adjustable gastric banding, biliopancreatic diversion with duodenal switch, greater curvature plication, one-anastomosis gastric bypass and single anastomosis duodenal-ileal bypass with sleeve gastrectomy. We will not include studies examining revisional surgeries or procedures no longer performed, including biliopancreatic diversion without duodenal switch, jejunoileal bypass, horizontal or vertical gastropasty and banding that is not adjustable.

Comparators

We will include studies comparing currently performed bariatric surgeries with usual care with or without life-style interventions, or comparing at least two of the surgical procedures.

Study designs

We will include randomised controlled trials, with at least 3 years of follow-up. To minimise potential bias introduced by different follow-up periods among studies, when including studies with over 3 years of follow-up, data of measurements at 3 years (± 6 months) or earliest reported time point after 3 years and at 5 years (± 6 months) or earliest reported time point after 5 years, if applicable, will be included in analysis, respectively.

Setting

There will be no restrictions by type of setting.

Language

We will include studies reported in English and Chinese languages, and studies reported in other languages if adequate translation is feasible by Bing Translate. A list of possibly relevant studies not included in the review will be provided.

Publication status

Eligibilities of unpublished studies will be evaluated.

Outcomes measures and prioritisation

Primary outcomes

1. The number of patients in full remission of type 2 diabetes mellitus defined as HbA1c levels <6.0% at consecutive annual visits and no use of anti-hyperglycaemic medication at either visit,²² or as defined by the studies.
2. Composite outcome of number of patients in full or partial remission of type 2 diabetes mellitus. Partial remission of type 2 diabetes mellitus is defined as HbA1c levels <6.5% at consecutive annual visits, and no use of antihyperglycaemic medication at either visit,²² or as defined by the studies.
3. Cumulative scores of grade IIIa or higher complications according to Clavien-Dindo classification for surgical complications,²³ and grade 3 or other higher adverse events according to the Common Terminology Criteria for Adverse Events V.5.0,²⁴ based on translation of each grade IIIa, grade IIIb, grade IVa, grade IVb and grade V complication into 6, 7, 8, 9, 10 points, respectively, and grade 3, grade 4 and grade 5 adverse events other than surgical complications into 6, 8, 10 points, respectively, in the analogue scale (0=minimum severity, 10=maximum severity). Surgical complication is defined as any deviation from the normal postoperative course,²³ whereas adverse event is defined as any unfavourable and unintended sign, symptom or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure.²⁴ A scored appraisal of adverse event profiles serves in two ways. First, it allows evaluation of severity of adverse events based on the impact on patient regardless of their definition which may vary considerably among studies. Second, a cumulative score-based approach allowing integral assessment of safety among procedures. The reason for inclusion of only major adverse events is twofold. First, the intensity of surveillance may tamper over time during follow-up, so that only serious adverse events may be recognised and reported at later stages of follow-up, precluding the ideal comparison of all clinically significant adverse events among procedures. Second, we anticipate varied reporting of mild or moderate adverse events, for example, postsurgical

pain, which may be considered normal and not reported in some studies.

Secondary outcomes

1. Number of patients achieving diabetes management goals with respect to blood glucose, blood pressure and low-density lipoprotein cholesterol (LDL-C) defined as simultaneous achievement of HbA1c <7.0%, LDL-C <2.59 mmol/L and systolic BP <140 mmHg,²⁵ or as defined by the studies.
2. Weight loss is an important determinant of resolution of comorbidities including type 2 diabetes mellitus after bariatric surgery.²⁶ We will investigate anthropometric measurements including percentage total body weight loss, percentage excess weight loss, fat mass and fat free mass derived from bio-electrical impedance analysis or dual-energy X-ray absorptiometry, as well as body mass index (BMI) and weight, both at baseline and at follow-up.
3. Decrease in cardiovascular risk scores have been shown to translate into favourable cardiovascular outcomes postbariatric surgeries.²⁷ We will investigate the cardiovascular risk score of validated tools and parameters reflecting risk factor burden, including glycated haemoglobin, fasting blood glucose, total cholesterol, LDL-C, high-density lipoprotein cholesterol, triglyceride and systolic and diastolic blood pressures.
4. While persistence and relapse of type 2 diabetes mellitus is not uncommon postbariatric surgery, improvements can be reflected by the need for less intensive treatment.²⁸ We will collect outcome data concerning change of medication burden, including number of patients requiring less antidiabetic drugs at follow-up, and number of patients achieving discontinuation of insulin.
5. Number of patients exhibiting progression of diabetic retinopathy, nephropathy and neuropathy, and number of patients experiencing myocardial infarction, stroke, amputation of at least one-digit, ischaemic limb disease, heart failure and urine albumin/creatinine ratio as surrogate marker for end organ damage.
6. All-cause mortality.

Studies will not be excluded based on whether or not certain outcomes are reported.

Search methods for identification of studies

Comprehensive search of databases listed below will be conducted using medical subject headings or Embase subject headings (Emtree), as applicable, and text words, for studies in humans, from inception of each database to March 2019, without language or publication type restrictions. The search strategies are adapted from a previous research,¹⁰ revised with input from the project team, and refined by a methodologist with expertise in systematic review search. The search will be updated towards the end of the review to ensure efficacy of retrieving eligible studies. Cross-referencing of relevant systemic reviews retrieved and included studies will be conducted.

Preliminary search strategy for PubMed, which will be adapted for each other database as required, is shown in online supplementary material 1. We will search the following databases:

1. PubMed (Ovid interface).
2. EMBASE.
3. Cochrane Central Register of Controlled Trials (CENTRAL).
4. US National Institutes of Health Ongoing Trials Register (<https://www.clinicaltrials.gov/>).
5. WHO International Clinical Trials Registry Platform (<http://www.who.int/ictrp/en/>).
6. International Standard Randomised Controlled Trial Number Register (<http://www.isrctn.org/>).
7. Trials Central (<http://www.trialscentral.org/>).

Study records

Selection of eligible studies and data abstraction will be performed by two independent reviewers, with Covidence, an Internet based software facilitating collaboration. Screening questions based on the inclusion and exclusion criteria and data extraction form (see online supplementary file 2 for preliminary screening questions and data extraction form) will be developed, tailored in Covidence, tested and refined by the team through discussion and pilot calibration exercises before formal screening and data extraction, respectively. Discrepancies will be resolved first by discussions, and, if necessary, by a third arbitrator. We will contact investigators of studies, by a maximal of three email attempts, if additional information is warranted for evaluation of study eligibility, data extraction and risk of bias assessment of included studies.

Selection of studies

Literature search results will be imported to Covidence, which will identify and remove duplicates. Titles and abstracts of all references will be screened, and references will be graded as relevant, maybe relevant and not relevant. References that are relevant or maybe relevant will be subject to full-text screening for final decision on eligibility. Reasons for excluding studies will be recorded. Reviewers will not be blinded to journal titles or study authors or affiliations in study selection. Included studies will be checked for potential double counting by identifying multiple reports of the same study, overlapping or companion studies. We will record the selection process in detail. A PRISMA flow diagram and characteristics of excluded studies will be presented.

Data extraction and management

The following information will be extracted for subsequent risk of bias assessment, data synthesis and appraisal of possible effect-modifiers, that is, variables that affect the magnitude of the effects of bariatric surgeries on outcomes:

1. Study characteristics: Methodology characteristics including study design, methods for sequence generation, allocation concealment, blinding of patients,

interveners and/or evaluators of all or some outcomes, whether intentional analysis is adopted, setting, time span of enrollment, duration of follow-up, number and location of centres, funding, potential conflicts of interest, key conclusion of authors of studies and whether the study is concluded early, will be documented.

2. Participants: Number of participants, diagnostic criteria of type 2 diabetes mellitus, inclusion and exclusion criteria and baseline characteristics of participants including age, BMI, ethnicity, gender and duration of type 2 diabetes will be extracted.
3. Interventions: Number of participants allocated to, and number and reasons for attrition in each comparator arm will be extracted along with description of interventions, co-interventions, if any, and comparisons.
4. Outcomes: Planned and reported primary and secondary outcomes and time of observation will be extracted and compared for discrepancies. Criteria for diagnosis or evaluation will be extracted. For laboratory investigation, assay method, unit, and reference range will be extracted. Laboratory data adopting a different analysis method will be transformed if known linear correlation has been reported. For cardiovascular risk score, name of tool used, score range and if higher or lower value is favourable will be extracted. Necessary transformation will be made when indicated to ensure alignment of the scales. For adverse events, information regarding timing, severity, presentation, diagnosis and management of all reported adverse events will be extracted, and sent to two independent reviewers, who are blind to information regarding which study the data is extracted from and what intervention preceded the onset of the adverse event, for score translation. A third arbitrator, also blind to information regarding the study and intervention, will resolve inconsistencies that persist despite discussion. The sequence in which adverse events are organised will be randomised by an online List Randomizer (<https://www.random.org>) before score translation, to further minimise the risk of bias. Corresponding score for each intervention in each study will be added for data synthesis.

Means and measures of dispersion will be approximated from figures in the reports by the measuring tools of Adobe Acrobat Reader when necessary if original data cannot be obtained from the authors. Whenever possible, we will use results from an intention to treat analysis. If number of missing data does not concord with attrition, the reason will be specified.

Risk of bias (quality) assessment

Risk of bias at the individual study level will be assessed by two independent reviewers, using the Cochrane risk of bias tool. Studies will be classified to be at high, low or unclear risk of bias based on adequacy of sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, method of addressing incomplete data, selective reporting and other biases. Blinding of outcome assessment will be

subdivided into subjective and objective assessments. Subjective assessments include evaluation of disease remission, adverse events, achieving treatment goals, progression of diabetic complications and medication. Objective assessments include anthropometric measurements, cardiovascular risk score, laboratory investigations and all-cause mortality. Disagreements will be resolved first by discussion and then by consulting a third arbitrator. Graphic representations of potential bias within and across studies will be generated using RevMan V.5.1.

Data analysis

Measures of treatment effect

Dichotomous outcomes will be pooled using risk ratio (RR) with 95% credible intervals (CrI) or CIs, as applicable. Continuous outcomes will be pooled using weighted mean differences (with 95% CrI or CI) if uniform measurement scales are used, or standardised mean differences (with 95% CrI or CI) if different measurement scales are adopted. Adverse event profiles will be assessed with mean (with 95% CrI or CI) of weighted adverse events per patient of each surgical procedure, determined by cumulative adverse event score divided by the number of patients in the corresponding treatment arm in each study.

Dealing with missing data

In case of missing data, such as the SD or other important variability measures, we will first try to calculate through algebraic manipulation of the available information such as CIs, p or t values.²⁹ When such attempts fail, an imputation method will be used,³⁰ which will be tested in sensitivity analysis.

Assessment of heterogeneity

Heterogeneity among included studies will be appraised by evaluating the variability in participants (including age, ethnicity, BMI and comorbidities) and in trials (including blinding, attrition, surgical techniques and co-interventions). Statistical heterogeneity will be assessed by the Cochran Q (X^2) and Higgins I^2 statistics. If high levels of heterogeneity among the trials exist (Q statistic ≤ 0.10 and/or I^2 value $> 50\%$), the study design and characteristics in the included studies will be analysed. Source of heterogeneity will be rigorously investigated by subgroup analysis, sensitivity analysis and meta-regression.

Data synthesis

If studies are sufficiently homogeneous in terms of design and comparator, we will conduct network meta-analyses in a random-effects model using generalised linear model under a Bayesian framework, while assessing for consistency between direct and indirect estimates of comparative effectiveness of each study arm.^{31 32} Geometry of the network will be depicted by a network map, and the treatments that are directly compared against each other and the amount of evidence available for each treatment and its comparator will be described qualitatively. The assumption of transitivity will be appreciated

and systematic tabulated information extracted regarding potential effect modifiers, including patient and study characteristics, will be provided. Non-informative priors for model parameters will be used. We will run Markov Chain Monte Carlo sampling for four chains. Results will be based on 100 000 iterations after a 100 000 iterations of burn in. Convergence will be judged based on visual inspection of time-series plots and the Brooks-Gelman-Rubin test. Goodness of fit of the model will be tested using the Deviance Information Criterion. Local inconsistency will be evaluated by comparing the magnitude and direction of effect estimates from direct and indirect comparisons. Global inconsistency will be evaluated with the pairwise p-values for inconsistency via back-calculation. Findings will be summarised in treatment-level forest plots, rank probability matrix and rank plot, with the latter two illustrating empirical probabilities that each treatment is ranked from best through worst, along with corresponding estimates and absolute difference of pairwise comparisons between interventions. To determine adverse event profiles, linear regression analysis will be performed with the type of surgical procedure as covariate, the adverse event outcome as the dependent variable, and a dummy variable for each of the studies to adjust for differences in risk profiles and study setup between trials, as described by Kessler *et al.*³³

An alternative method based on graph theory methodology under a frequentist framework will be adopted to validate the findings with league tables and rankings of treatments.^{34 35}

All statistical analysis and graphical procedures will be conducted by R software V.3.3.3 (The R Project for Statistical Computing).

If heterogeneity is substantial ($I^2 > 90\%$), meta-analysis will not be performed; a narrative, qualitative summary will be presented in text and tables to summarise the characteristics of the included studies and findings, both within and between the included studies, in accordance with the guidance from the Centre for Reviews and Dissemination.

Investigation of heterogeneity and subgroup analysis

Heterogeneity among included studies will be appraised, if possible, by evaluating the variability in potential effect-modifiers, including characteristics of participants (including age, gender-distribution, baseline BMI, duration of type 2 diabetes mellitus and comorbidities), in trials (including whether exclusively including patients with type 2 diabetes mellitus, whether including patients with baseline BMI < 30 , < 35 , < 40 , > 50 or > 60 kg/m², whether including patients over 60 years old, whether adopting intensive life-style intervention as control or during the follow-up period of bariatric surgeries in the same effective arm, whether surgical procedures are laparoscopic, open, or both, whether an intention-to-treat analysis was reported, publication year, publication status, and risk of bias items including attrition, blinding and missing data) through meta-regression analysis for primary outcomes.

Subgroup analysis will be performed based on factors identified through meta-regression. The likely impact of risk of bias, if studies of moderate or high risk of bias are included in the analysis, on the results will be discussed. Robustness of primary findings will be tested with sensitivity analysis by excluding trials with high risk of bias, by performing leave-one-out analysis, and by excluding studies requiring data imputation.

Meta bias

Reports will be checked against protocol to detect potential selective reporting and inconsistencies with respect to description of the design, number of patients analysed, chosen significance level, and outcomes among all reports of the same study. Reporting bias will be further explored by the Egger test. Visual inspection of funnel plots, along with trim-and-fill analysis for estimating and adjusting for the number and outcomes of missing studies, will be performed if ≥ 10 studies are available.

Grading of quality of evidence

The overall quality of the body of evidence of the meta-analysis findings, if feasible, will be judged using the Grading of Recommendations, Assessment, Development and Evaluation approach. We will assess the quality of the evidence across the domains of risk of bias, consistency, directness, precision, publication bias and additional domains where appropriate. The overall strength of evidence will be adjudicated as high, moderate, low or very low for each outcome measure.

DISCUSSION

Obesity is an important risk factor for type 2 diabetes mellitus, and bariatric surgery is effective in inducing weight-loss and resolution of obesity-related comorbidities.³⁶ Bariatric surgeries are growing worldwide, but are still underused.³⁷ Barriers preventing patients' access to bariatric surgeries include availability of surgical resources, concerns about postoperative complications, misperception regarding bariatric surgery effectiveness and professional society statement heterogeneity.³⁸ It is important to appreciate the long-term benefit-risk ratio of bariatric surgeries in adults with type 2 diabetes mellitus, to facilitate decision-making by patients, clinicians and policy makers. This review will summarise the current scientific findings, and will identify gaps for further research.

Ethics and dissemination

Ethics approval is not required, because individual patient data will not be included in this review. This review will be published in a peer reviewed journal.

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Contributors ML is the guarantor. Research question and eligibility criteria were defined by ML, CZ, LD, YF, YZ, HL, DQ, ST, JC and QH. LD, CZ and YF contributed to the development of search strategy and data extraction form. CZ provided methodological support for this review. The manuscript was first drafted by LD and YF, and was revised and approved by all authors.

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Competing interests None declared.

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