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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 randomized 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 randomized 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 events 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-effect 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 (Version 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.

Registration Details PROSPERO registration number CRD42018110775.

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 clinical 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 an innovative scoring system for integral assessment of safety of bariatric surgeries.

►This protocol defines detailed plan for data synthesis, additional analysis concerning consistency, goodness-of-fit of models, potential effect modifiers, and validation of findings by an alternative method.

► Common to any aggregate data meta-analysis, the risk for ecological fallacy and heterogeneity across studies exits.

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, comparing with non-surgical therapy.[1] The 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 randomized 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 unfavorable complication profiles, while one-anastomosis gastric bypass is a relatively new procedure, the safety and durability of which warrant 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 post bariatric 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 upon 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 morality 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 in 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 events 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 hypoglycemia.[17-19]

OBJECTIVES

The objectives of the study is 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 Protocols and the accompanied checklist, and the study will follow Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analyses.[20, 21] This protocol is

registered with the International Prospective Register of Systematic Reviews (registration number CRD42018110775). 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 gastroplasty, and banding that is not adjustable.

Comparators

We will include studies comparing currently performed bariatric surgeries with non-surgical

treatment, or comparing at least 2 of the surgical procedures.

Study designs

We will include randomized controlled trials, with at least 3 years of follow-up. To minimize potential bias introduced by different follow-up period 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 will be included in analysis.

Setting

There will be no restrictions by type of setting.

Language

We will include studies reported in the 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 prioritization

Primary outcomes

1. The number of patients in full remission of type 2 diabetes mellitus defined as HbA1c levels of 6.0% at consecutive annual visits, and no use of anti-hyperglycemic 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 of 6.5% at consecutive annual visits, and no use of anti-hyperglycemic 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 higher other adverse events according to the Common Terminology Criteria for Adverse Events version 5.0,[24] based on translation of each 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 unfavorable 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 events profiles serves in two ways. Firstly, it allows evaluation of severity of adverse event based on its impact upon patient regardless of its definition which may vary considerably among studies. Secondly, a cumulative score based approach allow integral assessment of safety among procedures. The reason for inclusion of only major adverse event is twofold. Firstly, the intensity of surveillance may tamper overtime during follow-up, so as to only serious adverse event may be recognized and reported at later stages of follow-up, precluding the ideal comparison of all clinical significant adverse events among procedures. Secondly, we anticipate varied reporting of mild or moderate adverse event, for example, post-surgical pain, which may be considered normal and not reported in some studies.

Secondary outcomes

1. Number of patients achieving diabetic management goals with respect to blood glucose, blood

pressure and LDL-cholesterol defined as simultaneous achievement of HbA1c of less than 7.0%, LDL-C of less than 2.59mmol/L, and systolic BP of less than 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 excess weight loss, body mass index, and weight at follow-up.

3. Decrease in cardiovascular risk scores have been shown to translate into favorable cardiovascular outcome post bariatric surgeries.[27] We will investigate the cardiovascular risk score of validated tools, and parameters reflecting risk factor burden, including glycated hemoglobin, fasting blood glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, systolic and diastolic blood pressures.

4. While persistence and relapse of type 2 diabetes mellitus is not uncommon post bariatric surgeries, 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 anti-diabetic 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, ischemic limb disease, and 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 (MeSH) or Embase subject headings (Emtree), as applicable, and text words, for studies in human, from inception of each database to December 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 searching. The search will be updated toward 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 supplementary material 1. We will search the following databases:

1. PubMed (Ovid interface)

2. EMBASE

3. Ovid 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 Randomized 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 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 with discussion, 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. Relevant or maybe relevant references will be subject to full-text screening for final decision upon 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 Preferred Reporting Items for Systematic Reviews and Meta-Analyses 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:

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 centers, 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, body mass index, ethnicity, gender, duration of type 2 diabetes, will be extracted.

3. Interventions: number of participants allocated to, and number and reasons for attrition of 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 different analysis method will be transformed if known linear correlation have been reported. For cardiovascular risk score, name of tool used, score range, if higher or lower value is favorable, 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 will be sent to two independent reviewers, who are blind to information regarding from which study the data is extracted, and what intervention preceded the onset of the adverse event, for score translation. A third arbitrator, also blind to information regarding study and intervention, will resolve inconsistencies despite discussion. The sequence in which adverse events are organized will be randomized by an online List Randomizer (https://www.random.org) before score translation, to further minimize 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 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 doesn't 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 5.1 (Review Manager 5.1).

Data analysis

Measures of treatment effect.

Dichotomous outcomes will be pooled using risk ratio (RR) with 95% credible intervals (CrI) or confidence intervals (CI), as applicable. Continuous outcomes will be pooled using weighted mean differences (with 95% CrI or CI) if uniform measurement scales are used, or standardized

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 standard deviation or other important variability measures, we will first try to calculate through algebraic manipulation of the available information such as confidence intervals, 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, body mass index, and comorbidities), in trials (including blinding, attrition, surgical techniques, and co-interventions). Statistical heterogeneity will be assessed by the Cochran Q (Chi-squared) and Higgins I-squared 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 analyzed. 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-effect model using generalized 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 100000 iterations, after a 100000-iterations 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 summarized 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, a linear regression analysis will be performed with type of surgical procedure as covariates, 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 (Version 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 summarize 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 body mass index, 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 less than 30, less than 35, less than 40, over 50, or over 60kg/m^2, 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, upon 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 analyzed, 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 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 summarize 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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AUTHOR CONTRIBUTORS ML is the guarantor. Research question and eligibility criteria were defined by ML, CJZ, LD, YXF, YLZ, HL, DWQ, SFT, JQC, and QH. LD, CJZ, and YXF contributed to the development of search strategy and data extraction form. CJZ provided methodological support for this review. The manuscript was first drafted byLD and YXF, and was revised and approved by all authors.

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considered for publication elsewhere and does not duplicate material already published. All authors consent to publication of this Work and authorize the granting of this licence.

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Supplementary material 1

Preliminary Search Strategy in Medline (Ovid interface) for 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 randomized controlled trials

#1 exp obesity/

#2 exp type 2 diabetes mellitus/

#3 exp weight loss/

#4 obes*.ti,ab.

#5 over?weight.ti,ab.

#6 diabetes.ti,ab.

#7 T2D*.ti,ab.

#8 NIDDM.ti,ab.

#9 or/1-8

#10 obesity/su

#11 exp Obesity, Morbid/su

#12 exp bariatric surgery/

#13 (surg* adj5 bariatric).ti,ab.

#14 anti?obesity adj5 surg*.ti,ab.

#15 malabsorptive adj5 procedure*.ti,ab.

#16 (obes* adj5 surg*).ti,ab.

#17 (metaboli* adj5 surg*).ti,ab.

#18 exp gastric bypass/

#19 (gastroplast* or gastrogastrostom* or gastro?gastrostom* or gastroenterostom* or (gastric bypass) or (gastric surger*) or (restrictive surger*)).ti,ab.

#20 ((one Anastomosis) or (one-Anastomosis) or mini or (single Anastomosis)) adj5 (bypass or switch).ti,ab.

#21 ((greater curvature) or (gastric*)) adj5 plicat*.ti,ab.

#22 gastrectom*.ti,ab.

#23 LSG.ti,ab.

#24 VSG.ti,ab.

#25 gastrointestinal adj5 surg*.ti,ab.

#26 gastrointestinal diversion*.ti,ab.

#27 exp biliopancreatic diversion/

#28 biliopancreatic diversion.ti,ab.

#29 biliopancreatic bypass.ti,ab.

#30 gastric adj5 stapl*.ti,ab.

#31 duodenal adj5 switch*.ti,ab.

#32 gastric band*.ti,ab.

#33 silicon band*.ti,ab.

#34 exp gastroenterostomy/

#35 gastroplasty/

#36 LAGB.ti,ab.

#37 stomach adj5 stapl*.ti,ab.

#38 laparoscop* adj5 band*.ti,ab.

#39 lap?band*.ti,ab.

#40 malabsorptive adj5 surg*.ti,ab.

#41 mason* adj5 procedure.ti,ab.

#42 Roux-en-Y.ti,ab.

#43 anastomosis, Roux-en-Y/

#44 or/12-43

#45 9 and 44

#46 10 or 11 or 45

#47 limit 46 to yr=2004 - 2018

#48 limit 47 to (clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or evaluation studies or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial or scientific integrity review or technical report or

twin study or validation studies or systemic review)

#49 randomized controlled trial.pt

#50 controlled clinical trial.pt

#51 randomized.ab

#52 placebo.ab

#53 clinical trials as topic.sh.

#54 randomly.ab

#55 trial.ti

#56 groups.ti,ab

#57 or/49-56

#58 exp animals/ not humans.sh.

#59 57 NOT 58

#60 47 and 59

#61 48 or 60

ab=abstract; adj = adjacent; exp =exploded; pt=publication type; sh = MeSH (Medical subject heading); su=surgery; ti=title; the asterisk mark (*) substitutes one or no characters; the question mark (?) substitutes one character.

Supplementary material 2

Preliminary Screening questions and Data Extraction Form for 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 randomized controlled trials

Reference code_____

Basic information			
Code of Original study		Code of Report	
Code of Valuator		Date of Evaluation	
Contact info of Author			
Quotation format(author, study title, journal, Year of publication, volume)			
Inclusion and exclusion criteria			
Inclusion criteria	**Participants** ① Include overweight or obese adults with type 2 diabetes mellitus yes □ no□ **Interventions and control** ② Procedures and/or controls involved *Roux-en-Y gastric bypass* □ *sleeve gastrectomy* □ *adjustable gastric banding* □ b*iliopancreatic diversion with duodenal switch* □ *greater curvature plication* □ *one-anastomosis gastric bypass* □ *single anastomosis duodenal-ileal bypass with sleeve gastrectomy* □ *Other surgical procedure(s)* ***except*** *procedures no longer performed, (including biliopancreatic diversion without duodenal switch, jejunoileal bypass, horizontal or vertical gastroplasty, and banding that is not adjustable)* _____ □ *non-surgical treatments* □ **Comparisons** ③ Includes comparisons of at least two of the items above yes □ no□ **Study designs** ④ Randomized controlled trial yes □ no□ ⑤ Duration of follow-up≧3 years yes □ no□		
Exclusion criteria	**Participants** ① Restrict participatns to specific diseases other than type 2 diabetes mellitus yes □ no□ ② Do not include adults yes □ no□ ③ Do not include participants with type 2 diabetes mellitus **Interventions and comparison**		

	④ Revisional procedures yes □ no□ Comparisons between/among surgical procedure(s) no longer performed (biliopancreatic diversion without duodenal switch, jejunoileal bypass, horizontal or vertical gastroplasty, not adjustable banding, other _____) or between such procedures and non-surgical treatment yes □ no□ Comparisons between different techniques of the same procedure yes □ no□ **Study designs** ⑤ Non-RCT, comparative studies yes □ no□ ⑥ Duration of follow-up < 3 year yes □ no□ ⑦ Animal studies. yes □ no□
Conclusion of inclusion or exclusion	□inclusion □exclusion □undetermined Support for judgement: _____ _____

Characteristics of Methodology	
Study design(multiple choice)	□ RCT □quasi-RCT □non-RCT □ cluster randomized trial □cross-over trial Support for judgement: _____
Duration of study	Study beginning time: _____year_____month Study ending time: _____year_____month Mean(±SD) or median[inter-quartile range] follow-up period: _____
Sequence generation	randomized □ non-randomized□ qusi-randomized□ undetermined □ Support for judgement: _____
allocation concealment	yes □ no□ undetermined □ Support for judgement: _____
Blinding participants*	□patients □intervenor □evaluator of all outcomes □evaluator of some, but not all outcomes □Statistical analyst comments(if blinding differs among outcomes):_____ Support for judgement: _____
Other factors that may introduce bias?	yes □ no□ Support for judgement: _____
Intentional analysis	yes □ no□ Support for judgement: _____
Other information of study	1. study site: single center □ multi-center□ Location of center(s) _____ 2. early conclusion of study: yes □ no□ 3. funding of study: _____ 4. potential conflict of interest: _____
Baseline information	comparable □; non-comparable □; undetermined □ Support for judgement:(Mean±SD for continuous varibles) intervention 1 intervention2 intervention3 intervention4 sex(M/F) __/__ __/__ __/__ __/__ Age(year) __±__ __±__ __±__ __±__ Weight(kg) __±__ __±__ __±__ __±__ BMI(kg/m^2) __±__ __±__ __±__ __±__
Characteristics of participants	
Total participants	_____
Settings	□hospital □community □nursing home □outpatient □chronic care institution Others: _____
Type of population	Healthy population: yes □ no□ BMI: BMI_____to_____kg/m^2 Or without complication BMI_____to_____kg/m^2 with complication BMI_____to_____kg/m^2 Type 2 diabetes: _____ Duration of type 2 diabetes: □unlimited □more than_____months
Age	_____to_____years old mean _____ SD _____ median_____ interquartile range _____
Sex	□Unlimited □Male only □Female only
Country	_____
Ethnicity	_____

Attrition	Lost to follow-up: Number of participants lost to follow-up: Group 1 _____, reason _____ Group 2 _____, reason _____ Group 3 _____, reason_____ Group 4 _____, reason_____		
	Drop-out: Number of drop-out participants: Group 1 _____, reason _____ Group 2 _____, reason _____ Group 3 _____, reason_____ Group 4 _____, reason_____		
Intervention			
Group	Number of Participants	Intervention	Description of intervention(intensity, frequency and duration etc.)
Group 1			
Group 2			
Group 3			
Group 4			
Integrity of interventions			
Outcome Data			
Planned outcomes	Planned: _____ Difference between report and plan: _____		
Planned time of Observation	Plan: _____ Difference between report and plan: _____		
Outcome data	Definition Diagnosis or evaluation: criteria for diagnosis or evaluation; Laboratory examination; assay method, unit, reference range; Scale: name, score range, state if higher or lower value is favorable If the evaluation time doesn't concord with the follow-up time, the time point of evaluation should be specified If number of missing data doesn't concord with attrition, the reason should be specified		
Full diabetes remission	Evaluation criteria: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____		
Partial diabetes remission	Evaluation criteria: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____		
Major adverse event	Evaluation criteria: _____ Criteria of major adverse effect: _____ Evaluation time (if not consistent) early complication: post-op _____day; late complication: post-op_____day-_____year Reason for extra missing data_____		
Diabetes management goal	Evaluation criteria: _____ Evaluation time (if not consistent)_____		

including HbA1c, BP and LDL-C	Reason for extra missing data _____
Percentage excess weight loss (% EWL)	Definition: _____ Unit: □% □Other_____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Body mass index (BMI) at follow-up	Definition: _____ Unit: □kg/m^2 □Other_____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Weight (Wt) at follow-up	Definition: _____ Unit: □kg □Other_____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Cardiovascular risk score	Scale name: _____ Score range: _____ which value is favorable □high score □low score Evaluation time (if not consistent)_____ Reason for extra missing data _____
Glycated hemoglobin (HbA1C)	Method: _____ Reagent info _____ Unit: _____ Reference range: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Fasting blood glucose (FBG)	Method: _____ Reagent info _____ Unit: _____ Reference range: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
total cholesterol (TC)	Method: _____ Reagent info _____ Unit: _____ Reference range: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
low-density lipoprotein cholesterol (LDL)	Method: _____ Reagent info _____ Unit: _____ Reference range: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
high-density lipoprotein cholesterol (HDL)	Method: _____ Reagent info _____ Unit: _____ Reference range: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
triglyceride (TG)	Method: _____ Reagent info _____ Unit: _____ Reference range: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Systolic blood pressure	Method: _____ Model _____ Unit: _____ Reference: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Diastolic blood pressure	Method: _____ Model _____ Unit: _____ Reference: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Requirement of less anti-diabetic drugs at follow-up	Evaluation criteria: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
discontinuation of insulin	Evaluation criteria: _____ Evaluation time (if not consistent)_____

	Reason for extra missing data _____
Progression of diabetic retinopathy	Evaluation criteria: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Progression of diabetic nephropathy	Evaluation criteria: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Progression of diabetic neuropathy	Evaluation criteria: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Number of pts experiencing myocardial infarction	Evaluation criteria: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Number of pts experiencing stroke	Evaluation criteria: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Number of pts experiencing amputation of at least one digit	Evaluation criteria: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Number of pts experiencing ischemic limb disease	Evaluation criteria: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Number of pts experiencing heart failure	Evaluation criteria: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
urine albumin/creatinine ratio (ACR)	Method: _____ Reagent info _____ Unit: _____ Reference range: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
All-cause mortality	Evaluation criteria: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Other information	
Key conclusion of authors	
Correspondence required	Study author contacted: yes □ no□ Study author replied: yes □ no□ Information asked: _____ Information provided: _____

Outcome data-Continuous data-1													
	Group 1 (Intervention_____)				Group 2 (Intervention_____)								
	Total number of participants	Reported cases for each outcome	mean	SD	Total amount	Case number	mean	SD	p-value	Estimate of effect	95%CI Lower limit	95%CI Upper limit	Comments (e.g., if the results shown in median and quartile range)
percentage excess weight loss													
BMI at follow-up													
Weight at follow-up													
Cardiovascular risk score													
Glycated hemoglobin (HbA1C)													
Fasting blood glucose (FBG)													
total cholesterol (TC)													
low-density lipoprotein													

cholesterol (LDL)													
high-density lipoprotein cholesterol (HDL)													
triglyceride (TG)													
Systolic blood pressure (SBP)													
Diastolic blood pressure (DBP)													
urine albumin/creatinine ratio													
Outcome data-Continuous data-2 (when applicable, i.e. more than 2 comparative arms involved)													
	Group 3 (Intervention_____)				Group 4 (Intervention_____)								
	Total number of participants	Reported cases for each outcome	mean	SD	Total amount	Case number	mean	SD	p-value	Estimate of effect	95%CI Lower limit	95%CI Upper limit	Comments (e.g., if the results shown in median and quartile range)
percentage excess weight loss													
BMI at follow-up													
Weight at follow-													

up													
Cardiovascular risk score													
Glycated hemoglobin (HbA1C)													
Fasting blood glucose (FBG)													
total cholesterol (TC)													
low-density lipoprotein cholesterol (LDL)													
high-density lipoprotein cholesterol (HDL)													
triglyceride (TG)													
Systolic blood pressure (SBP)													
Diastolic blood pressure (DBP)													
urine albumin/creatinine ratio													

Outcome data-dichotomous data-1											
	Group 1 (Intervention_____)			Group 2 (Intervention_____)							
	Total number of participants	Reported participants for each outcome	Case number	Total number of participants	Reported participants for each outcome	Total number of participants	p-value	Estimate of effect	95%CI Lower limit	95%CI Upper limit	Comments
Full remission of type 2 diabetes mellitsu											
Full or partial remission of type 2 diabetes mellitsu											
Achieve treatment goals with regard to blood glucose, blood pressure and lipids											
Requirement of less anti-diabetic drugs at follow-up											
Discontinuation of insulin											
Progression of diabetic retinopathy											
Progression of diabetic											

nephropathy											
Progression of diabetic neuropathy											
Number of patients experiencing myocardial infarction											
Number of patients experiencing stroke											
Number of patients experiencing amputation of at least one digit											
Number of patients experiencing ischemic limb disease											
Number of patients experiencing heart failure											
All-cause mortality											
Outcome data-dichotomous data-2 (when applicable, i.e. more than 2 comparative arms involved)											
	Group 3 (Intervention_____)			Group 4 (Intervention_____)							
	Total number of participants	Reported participants for each	Case number	Total number of participants	Reported participants for each	Total number of participants	p-value	Estimate of effect	95%CI Lower limit	95%CI Upper limit	Comments

		outcome			outcome						
Full remission of type 2 diabetes mellitsu											
Full or partial remission of type 2 diabetes mellitsu											
Achieve treatment goals with regard to blood glucose, blood pressure and lipids											
Requirement of less anti-diabetic drugs at follow-up											
Discontinuation of insulin											
Progression of diabetic retinopathy											
Progression of diabetic nephropathy											
Progression of diabetic neuropathy											
Number of patients experiencing											

myocardial infarction											
Number of patients experiencing stroke											
Number of patients experiencing amputation of at least one digit											
Number of patients experiencing ischemic limb disease											
Number of patients experiencing heart failure											
All-cause mortality											

Outcome data-adverse event 1. Coding of Adverse event: ###(study code) – ##(group number) – ###(adverse event number) 2. After sequence randomization, the adverse event will be re-numbered sequentially before sent for score translation)		
Group 1 (Intervention_____) (Lines may be added when necessary)		
Coding of Adverse event	Quotation from report regarding timing, severity, presentation, diagnosis, and management of adverse event	Anologue score of adverse event
Group 2 (Intervention_____) (Lines may be added when necessary)		
Coding of Adverse event	Quotation from report regarding timing, severity, presentation, diagnosis, and management of adverse event	Anologue score of adverse event

Group 3 (if applicable) (Intervention_____) (Lines may be added when necessary)		
Coding of Adverse event	Quotation from report regarding timing, severity, presentation, diagnosis, and management of adverse event	Anologue score of adverse event
Group 4 (if applicable) (Intervention_____) (Lines may be added when necessary)		
Coding of Adverse event	Quotation from report regarding timing, severity, presentation, diagnosis, and management of adverse event	Anologue score of adverse event

PRISMA-P Checklist for *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 randomized controlled trials*

This checklist has been adapted for use from Table 3 in Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic reviews. 2015;4:1.

Section/topic	#	Checklist item	Information reported		Page (P) and Line (L) Number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	√		*P1,L4-12*
Update	1b	If the protocol is for an update of a previous systematic review, identify as such			N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	√		*P2, L58*
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	√		*P1, L14-41; P18, L43-54*
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	√		*P18, L14-25*
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments			N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	√		*P18, L30-36*
Sponsor	5b	Provide name for the review funder and/or sponsor			N/A
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	√		*P*18, *L*35-41
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	√		*P3, L43 - P5, L25*
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	√		*P5, L32-46*
METHODS					

Section/topic	#	Checklist item	Information reported		Page (P) and Line (L) Number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	√		*P6, L17 – P9, L59*
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	√		*P10, L4-49*
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	√		Supplementary material 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	√		*P10, L53 - P11, L10*
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	√		*P10, L53 - P11, L12; P11, L22-44*
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	√		*P10, L53 - P11, L18*
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	√		*P11, L45 - P13, L15*
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	√		*P7, L40 – P9, L60; P3, L43 - P5, L25*
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	√		*P13, L17-46; P16, L14-54*
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	√		*P14, L50-60; P16, L4-13*
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	√		*P13, L50-P15, L60*
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	√		*P16, L14-54*
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	√		*P16, L4-13*
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	√		*P16, L56 – P17, L15*

Section/topic	#	Checklist item	Information reported		Page (P) and Line (L) Number(s)
			Yes	No	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	√		*P17, L17-34*

Abbreviations: N/A: not applicable.

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 randomized controlled trials

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Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Evidence based practice
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, Adult surgery < SURGERY, Adverse events < THERAPEUTICS

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 randomized 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 randomized 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 events 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-effect 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 (Version 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.

Registration Details PROSPERO registration number CRD42018110775.

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 for heterogeneity across studies exits.

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] The 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 randomized 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 unfavorable complication profiles, while one-anastomosis gastric bypass is a relatively new procedure, the safety and durability of which warrant 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 post bariatric 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 upon 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 morality 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 in 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 events 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 hypoglycemia.[17-19]

OBJECTIVES

The objectives of the study is 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 Protocols and the accompanied checklist, and the study will follow Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analyses.[20, 21] This protocol is registered with the International Prospective Register of Systematic Reviews (registration number CRD42018110775). 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 gastroplasty, 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 2 of the surgical procedures.

Study designs

We will include randomized controlled trials, with at least 3 years of follow-up. To minimize potential bias introduced by different follow-up period 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 the 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 prioritization

Primary outcomes

1. The number of patients in full remission of type 2 diabetes mellitus defined as HbA1c levels of less than 6.0% at consecutive annual visits, and no use of anti-hyperglycemic 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 of less than 6.5% at consecutive annual visits, and no use of anti-hyperglycemic 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 higher other adverse events according to the Common Terminology Criteria for Adverse Events version 5.0,[24] based on translation of each 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 unfavorable 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 events profiles serves in two ways. Firstly, it allows evaluation of severity of adverse event based on its impact upon patient regardless of its definition which may vary considerably among studies. Secondly, a cumulative score based approach allow integral assessment of safety among procedures. The reason for inclusion of only major adverse event is twofold. Firstly, the intensity of surveillance may tamper overtime during follow-up, so as to only serious adverse event may be recognized and reported at later stages of follow-up, precluding the ideal comparison of all clinically significant adverse events among procedures. Secondly, we anticipate varied reporting of mild or moderate adverse event, for example, post-surgical pain, which may be considered normal and not reported in some studies.

Secondary outcomes

1. Number of patients achieving diabetic management goals with respect to blood glucose, blood pressure and LDL-cholesterol defined as simultaneous achievement of HbA1c of less than 7.0%,

LDL-C of less than 2.59mmol/L, and systolic BP of less than 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 and weight both at baseline and at follow-up.

3. Decrease in cardiovascular risk scores have been shown to translate into favorable cardiovascular outcome post bariatric surgeries.[27] We will investigate the cardiovascular risk score of validated tools, and parameters reflecting risk factor burden, including glycated hemoglobin, fasting blood glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, systolic and diastolic blood pressures.

4. While persistence and relapse of type 2 diabetes mellitus is not uncommon post bariatric surgeries, 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 anti-diabetic 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, ischemic limb disease, and 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 (MeSH) or Embase subject headings (Emtree), as applicable, and text words, for studies in human, from inception of each database to December 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 searching. The search will be updated toward 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 supplementary material 1. We will search the following databases:

1. PubMed (Ovid interface)

2. EMBASE

3. Ovid 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 Randomized 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 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 with discussion, 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. Relevant or maybe relevant references will be subject to full-text screening for final decision upon 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 Preferred Reporting Items for Systematic Reviews and Meta-Analyses 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, i.e. 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 centers, 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, body mass index, ethnicity, gender, duration of type 2 diabetes, will be extracted.

3. Interventions: number of participants allocated to, and number and reasons for attrition of 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 different analysis method will be transformed if known linear correlation have been reported. For cardiovascular risk score, name of tool used, score range, if higher or lower value is favorable, 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 will be sent to two independent reviewers, who are blind to information regarding from which study the data is extracted, and what intervention preceded the onset of the adverse event, for score translation. A third arbitrator, also blind to information regarding study and intervention, will resolve inconsistencies despite discussion. The sequence in which adverse events are organized will be

randomized by an online List Randomizer (https://www.random.org) before score translation, to further minimize 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 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 doesn't 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 5.1 (Review Manager 5.1).

Data analysis

Measures of treatment effect.

Dichotomous outcomes will be pooled using risk ratio (RR) with 95% credible intervals (CrI) or

confidence intervals (CI), as applicable. Continuous outcomes will be pooled using weighted mean differences (with 95% CrI or CI) if uniform measurement scales are used, or standardized 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 standard deviation or other important variability measures, we will first try to calculate through algebraic manipulation of the available information such as confidence intervals, 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, body mass index, and comorbidities), in trials (including blinding, attrition, surgical techniques, and co-interventions). Statistical heterogeneity will be assessed by the Cochran Q (Chi-squared) and Higgins I-squared 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 analyzed. 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-effect model using generalized 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 100000 iterations, after a 100000-iterations 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 summarized 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, a linear regression analysis will be performed with type of surgical procedure as covariates, 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 (Version 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 summarize 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 body mass index, 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 less than 30, less than 35, less than 40, over 50, or over 60kg/m^2, 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, upon 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 analyzed, 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 summarize 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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AUTHOR CONTRIBUTORS ML is the guarantor. Research question and eligibility criteria were defined by ML, CJZ, LD, YXF, YLZ, HL, DWQ, SFT, JQC, and QH. LD, CJZ, and YXF contributed to the development of search strategy and data extraction form. CJZ provided methodological support for this review. The manuscript was first drafted by LD and YXF, and was revised and approved by all authors.

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Supplementary material 1

Preliminary Search Strategy in Medline (Ovid interface) for 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 randomized controlled trials

#1 exp obesity/

#2 exp type 2 diabetes mellitus/

#3 exp weight loss/

#4 obes*.ti,ab.

#5 over?weight.ti,ab.

#6 diabetes.ti,ab.

#7 T2D*.ti,ab.

#8 NIDDM.ti,ab.

#9 or/1-8

#10 obesity/su

#11 exp Obesity, Morbid/su

#12 exp bariatric surgery/

#13 (surg* adj5 bariatric).ti,ab.

#14 anti?obesity adj5 surg*.ti,ab.

#15 malabsorptive adj5 procedure*.ti,ab.

#16 (obes* adj5 surg*).ti,ab.

#17 (metaboli* adj5 surg*).ti,ab.

#18 exp gastric bypass/

#19 (gastroplast* or gastrogastrostom* or gastro?gastrostom* or gastroenterostom* or (gastric bypass) or (gastric surger*) or (restrictive surger*)).ti,ab.

#20 ((one Anastomosis) or (one-Anastomosis) or mini or (single Anastomosis)) adj5 (bypass or switch).ti,ab.

#21 ((greater curvature) or (gastric*)) adj5 plicat*.ti,ab.

#22 gastrectom*.ti,ab.

#23 LSG.ti,ab.

#24 VSG.ti,ab.

#25 gastrointestinal adj5 surg*.ti,ab.

#26 gastrointestinal diversion*.ti,ab.

#27 exp biliopancreatic diversion/

#28 biliopancreatic diversion.ti,ab.

#29 biliopancreatic bypass.ti,ab.

#30 gastric adj5 stapl*.ti,ab.

#31 duodenal adj5 switch*.ti,ab.

#32 gastric band*.ti,ab.

#33 silicon band*.ti,ab.

#34 exp gastroenterostomy/

#35 gastroplasty/

#36 LAGB.ti,ab.

#37 stomach adj5 stapl*.ti,ab.

#38 laparoscop* adj5 band*.ti,ab.

#39 lap?band*.ti,ab.

#40 malabsorptive adj5 surg*.ti,ab.

#41 mason* adj5 procedure.ti,ab.

#42 Roux-en-Y.ti,ab.

#43 anastomosis, Roux-en-Y/

#44 or/12-43

#45 9 and 44

#46 10 or 11 or 45

#47 limit 46 to yr=2004 - 2018

#48 limit 47 to (clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or evaluation studies or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial or scientific integrity review or technical report or

twin study or validation studies or systemic review)

#49 randomized controlled trial.pt

#50 controlled clinical trial.pt

#51 randomized.ab

#52 placebo.ab

#53 clinical trials as topic.sh.

#54 randomly.ab

#55 trial.ti

#56 groups.ti,ab

#57 or/49-56

#58 exp animals/ not humans.sh.

#59 57 NOT 58

#60 47 and 59

#61 48 or 60

ab=abstract; adj = adjacent; exp =exploded; pt=publication type; sh = MeSH (Medical subject heading); su=surgery; ti=title; the asterisk mark (*) substitutes one or no characters; the question mark (?) substitutes one character.

Supplementary material 2

Preliminary Screening questions and Data Extraction Form for 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 randomized controlled trials

Reference code_____

Basic information			
Code of Original study		Code of Report	
Code of Valuator		Date of Evaluation	
Contact info of Author			
Quotation format(author, study title, journal, Year of publication, volume)			
Inclusion and exclusion criteria			
Inclusion criteria	**Participants** ① Include overweight or obese adults with type 2 diabetes mellitus yes □ no□ **Interventions and control** ② Procedures and/or controls involved *Roux-en-Y gastric bypass* □ *sleeve gastrectomy* □ *adjustable gastric banding* □ *biliopancreatic diversion with duodenal switch* □ *greater curvature plication* □ *one-anastomosis gastric bypass* □ *single anastomosis duodenal-ileal bypass with sleeve gastrectomy* □ *Other surgical procedure(s)* ***except*** *procedures no longer performed, (including biliopancreatic diversion without duodenal switch, jejunoileal bypass, horizontal or vertical gastroplasty, and banding that is not adjustable)* _____ □ *non-surgical treatments* □ **Comparisons** ③ Includes comparisons of at least two of the items above yes □ no□ **Study designs** ④ Randomized controlled trial yes □ no□ ⑤ Duration of follow-up≧3 years yes □ no□		
Exclusion criteria	**Participants** ① Restrict participatns to specific diseases other than type 2 diabetes mellitus yes □ no□ ② Do not include adults yes □ no□ ③ Do not include participants with type 2 diabetes mellitus **Interventions and comparison**		

	④ Revisional procedures yes □ no□ Comparisons between/among surgical procedure(s) no longer performed (biliopancreatic diversion without duodenal switch, jejunoileal bypass, horizontal or vertical gastroplasty, not adjustable banding, other _____) or between such procedures and non-surgical treatment yes □ no□ Comparisons between different techniques of the same procedure yes □ no□ **Study designs** ⑤ Non-RCT, comparative studies yes □ no□ ⑥ Duration of follow-up < 3 year yes □ no□ ⑦ Animal studies. yes □ no□
Conclusion of inclusion or exclusion	□inclusion □exclusion □undetermined Support for judgement: _____ _____

Characteristics of Methodology	
Study design(multiple choice)	□ RCT □quasi-RCT □non-RCT □ cluster randomized trial □cross-over trial Support for judgement: _____
Duration of study	Study beginning time: _____year_____month Study ending time: _____year_____month Mean(±SD) or median[inter-quartile range] follow-up period: _____
Sequence generation	randomized □ non-randomized□ qusi-randomized□ undetermined □ Support for judgement: _____
allocation concealment	yes □ no□ undetermined □ Support for judgement: _____
Blinding participants*	□patients □intervenor □evaluator of all outcomes □evaluator of some, but not all outcomes □Statistical analyst comments(if blinding differs among outcomes):_____ Support for judgement: _____
Other factors that may introduce bias?	yes □ no□ Support for judgement: _____
Intentional analysis	yes □ no□ Support for judgement: _____
Other information of study	1. study site: single center □ multi-center□ Location of center(s) _____ 2. early conclusion of study: yes □ no□ 3. funding of study: _____ 4. potential conflict of interest: _____
Baseline information	comparable □; non-comparable □; undetermined □ Support for judgement:(Mean±SD for continuous varibles) intervention 1 intervention2 intervention3 intervention4 sex(M/F) ___/___ ___/___ ___/___ ___/___ Age(year) ___±___ ___±___ ___±___ ___±___ Weight(kg) ___±___ ___±___ ___±___ ___±___ BMI(kg/m^2) ___±___ ___±___ ___±___ ___±___
Characteristics of participants	
Total participants	_____
Settings	□hospital □community □nursing home □outpatient □chronic care institution Others: _____
Type of population	Healthy population: yes □ no□ BMI: BMI_____to_____kg/m^2 Or without complication BMI_____to_____kg/m^2 with complication BMI_____to_____kg/m^2 Type 2 diabetes: _____ Duration of type 2 diabetes: □unlimited □more than_____months
Age	_____to_____years old mean _____ SD _____ median_____ interquartile range _____
Sex	□Unlimited □Male only □Female only
Country	_____
Ethnicity	_____

Attrition (year 3)	Lost to follow-up at year 3: Number of participants lost to follow-up: Group 1 _____, reason _____ Group 2 _____, reason _____ Group 3 _____, reason_____ Group 4 _____, reason_____		
	Drop-out at year 3: Number of drop-out participants: Group 1 _____, reason _____ Group 2 _____, reason _____ Group 3 _____, reason_____ Group 4 _____, reason_____		
Attrition (year 5)	Lost to follow-up at year 5: Number of participants lost to follow-up: Group 1 _____, reason _____ Group 2 _____, reason _____ Group 3 _____, reason_____ Group 4 _____, reason_____		
	Drop-out at year 5: Number of drop-out participants: Group 1 _____, reason _____ Group 2 _____, reason _____ Group 3 _____, reason_____ Group 4 _____, reason_____		
Intervention			
Group	Number of Participants	Intervention	Description of intervention(intensity, frequency and duration etc.)
Group 1			
Group 2			
Group 3			
Group 4			
Integrity of interventions			
Outcome Data			
Planned outcomes	Planned: _____ Difference between report and plan: _____		
Planned time of Observation	Plan: _____ Difference between report and plan: _____		
Outcome data	Definition Diagnosis or evaluation: criteria for diagnosis or evaluation; Laboratory examination; assay method, unit, reference range; Scale: name, score range, state if higher or lower value is favorable If the evaluation time doesn't concord with the follow-up time, the time point of evaluation should be specified If number of missing data doesn't concord with attrition, the reason should be specified		
Full diabetes remission	Evaluation criteria: _____ Evaluation time (if not consistent)_____		

	Reason for extra missing data _____
Partial diabetes remission	Evaluation criteria: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Major adverse event	Evaluation criteria: _____ Criteria of major adverse effect: _____ Evaluation time (if not consistent) early complication: post-op _____day; late complication: post-op_____day-_____year Reason for extra missing data_____
Diabetes management goal including HbA1c, BP and LDL-C	Evaluation criteria: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Percentage excess weight loss (% EWL)	Definition: _____ Unit: □% □Other_____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Body mass index (BMI) at follow-up	Definition: _____ Unit: □kg/m^2 □Other_____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Weight (Wt) at follow-up	Definition: _____ Unit: □kg □Other_____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Cardiovascular risk score	Scale name: _____ Score range: _____ which value is favorable □high score □low score Evaluation time (if not consistent)_____ Reason for extra missing data _____
Glycated hemoglobin (HbA1C)	Method: _____ Reagent info _____ Unit: _____ Reference range: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Fasting blood glucose (FBG)	Method: _____ Reagent info _____ Unit: _____ Reference range: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
total cholesterol (TC)	Method: _____ Reagent info _____ Unit: _____ Reference range: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
low-density lipoprotein cholesterol (LDL)	Method: _____ Reagent info _____ Unit: _____ Reference range: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
high-density lipoprotein cholesterol (HDL)	Method: _____ Reagent info _____ Unit: _____ Reference range: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
triglyceride (TG)	Method: _____ Reagent info _____ Unit: _____ Reference range: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____

Systolic blood pressure	Method: _____ Model _____ Unit: _____ Reference: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Diastolic blood pressure	Method: _____ Model _____ Unit: _____ Reference: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Requirement of less anti-diabetic drugs at follow-up	Evaluation criteria: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
discontinuation of insulin	Evaluation criteria: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Progression of diabetic retinopathy	Evaluation criteria: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Progression of diabetic nephropathy	Evaluation criteria: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Progression of diabetic neuropathy	Evaluation criteria: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Number of pts experiencing myocardial infarction	Evaluation criteria: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Number of pts experiencing stroke	Evaluation criteria: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Number of pts experiencing amputation of at least one digit	Evaluation criteria: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Number of pts experiencing ischemic limb disease	Evaluation criteria: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Number of pts experiencing heart failure	Evaluation criteria: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
urine albumin/creatinine ratio (ACR)	Method: _____ Reagent info _____ Unit: _____ Reference range: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
All-cause mortality	Evaluation criteria: _____ Evaluation time (if not consistent)_____ Reason for extra missing data _____
Other information	
Key conclusion of authors	
Correspondence required	Study author contacted: yes □ no□ Study author replied: yes □ no□ Information asked: _____ Information provided: _____

Outcome data (year 3)-Continuous data-1													
	Group 1 (Intervention_____)				Group 2 (Intervention_____)								
	Total number of participants	Reported cases for each outcome	mean	SD	Total amount	Case number	mean	SD	p-value	Estimate of effect	95%CI Lower limit	95%CI Upper limit	Comments (e.g., if the results shown in median and quartile range)
percentage excess weight loss													
BMI at follow-up													
Weight at follow-up													
Cardiovascular risk score													
Glycated hemoglobin (HbA1C)													
Fasting blood glucose (FBG)													
total cholesterol (TC)													
low-density lipoprotein													

cholesterol (LDL)													
high-density lipoprotein cholesterol (HDL)													
triglyceride (TG)													
Systolic blood pressure (SBP)													
Diastolic blood pressure (DBP)													
urine albumin/creatinine ratio													
Outcome data-Continuous data (year 3)-2 (when applicable, i.e. more than 2 comparative arms involved)													
	Group 3 (Intervention_____)				Group 4 (Intervention_____)								
	Total number of participants	Reported cases for each outcome	mean	SD	Total amount	Case number	mean	SD	p-value	Estimate of effect	95%CI Lower limit	95%CI Upper limit	Comments (e.g., if the results shown in median and quartile range)
percentage excess weight loss													
BMI at follow-up													
Weight at follow-													

up													
Cardiovascular risk score													
Glycated hemoglobin (HbA1C)													
Fasting blood glucose (FBG)													
total cholesterol (TC)													
low-density lipoprotein cholesterol (LDL)													
high-density lipoprotein cholesterol (HDL)													
triglyceride (TG)													
Systolic blood pressure (SBP)													
Diastolic blood pressure (DBP)													
urine albumin/creatinine ratio													

Outcome data (year 3)-dichotomous data-1											
	Group 1 (Intervention_____)			Group 2 (Intervention_____)							
	Total number of participants	Reported participants for each outcome	Case number	Total number of participants	Reported participants for each outcome	Total number of participants	p-value	Estimate of effect	95%CI Lower limit	95%CI Upper limit	Comments
Full remission of type 2 diabetes mellitsu											
Full or partial remission of type 2 diabetes mellitsu											
Achieve treatment goals with regard to blood glucose, blood pressure and lipids											
Requirement of less anti-diabetic drugs at follow-up											
Discontinuation of insulin											
Progression of diabetic retinopathy											
Progression of diabetic											

nephropathy											
Progression of diabetic neuropathy											
Number of patients experiencing myocardial infarction											
Number of patients experiencing stroke											
Number of patients experiencing amputation of at least one digit											
Number of patients experiencing ischemic limb disease											
Number of patients experiencing heart failure											
All-cause mortality											
Outcome data-dichotomous data (year 3)-2 (when applicable, i.e. more than 2 comparative arms involved)											
	Group 3 (Intervention_____)			Group 4 (Intervention_____)							
	Total number of participants	Reported participants for each	Case number	Total number of participants	Reported participants for each	Total number of participants	p-value	Estimate of effect	95%CI Lower limit	95%CI Upper limit	Comments

		outcome			outcome						
Full remission of type 2 diabetes mellitsu											
Full or partial remission of type 2 diabetes mellitsu											
Achieve treatment goals with regard to blood glucose, blood pressure and lipids											
Requirement of less anti-diabetic drugs at follow-up											
Discontinuation of insulin											
Progression of diabetic retinopathy											
Progression of diabetic nephropathy											
Progression of diabetic neuropathy											
Number of patients experiencing											

myocardial infarction											
Number of patients experiencing stroke											
Number of patients experiencing amputation of at least one digit											
Number of patients experiencing ischemic limb disease											
Number of patients experiencing heart failure											
All-cause mortality											

Outcome data-adverse event (year 3) 1. Coding of Adverse event: ###(study code) – ##(group number) – ###(adverse event number) 2. After sequence randomization, the adverse event will be re-numbered sequentially before sent for score translation)		
Group 1 (Intervention_____) (Lines may be added when necessary)		
Coding of Adverse event	Quotation from report regarding timing, severity, presentation, diagnosis, and management of adverse event	Anologue score of adverse event
Group 2 (Intervention_____) (Lines may be added when necessary)		
Coding of Adverse event	Quotation from report regarding timing, severity, presentation, diagnosis, and management of adverse event	Anologue score of adverse event

Group 3 (if applicable) (Intervention_____) (Lines may be added when necessary)		
Coding of Adverse event	Quotation from report regarding timing, severity, presentation, diagnosis, and management of adverse event	Anologue score of adverse event
Group 4 (if applicable) (Intervention_____) (Lines may be added when necessary)		
Coding of Adverse event	Quotation from report regarding timing, severity, presentation, diagnosis, and management of adverse event	Anologue score of adverse event

Outcome data (year 5, if applicable)-Continuous data-1

	Group 1 (Intervention_____)				Group 2 (Intervention_____)								
	Total number of participants	Reported cases for each outcome	mean	SD	Total amount	Case number	mean	SD	p-value	Estimate of effect	95%CI Lower limit	95%CI Upper limit	Comments (e.g., if the results shown in median and quartile range)
percentage excess weight loss													
BMI at follow-up													
Weight at follow-up													
Cardiovascular risk score													
Glycated hemoglobin (HbA1C)													
Fasting blood glucose (FBG)													
total cholesterol (TC)													
low-density lipoprotein cholesterol (LDL)													

high-density lipoprotein cholesterol (HDL)													
triglyceride (TG)													
Systolic blood pressure (SBP)													
Diastolic blood pressure (DBP)													
urine albumin/creatinine ratio													
Outcome data-Continuous data (year 5, if applicable)-2 (when more than 2 comparative arms involved)													
	Group 3 (Intervention_____)				Group 4 (Intervention_____)								
	Total number of participants	Reported cases for each outcome	mean	SD	Total amount	Case number	mean	SD	p-value	Estimate of effect	95%CI Lower limit	95%CI Upper limit	Comments (e.g., if the results shown in median and quartile range)
percentage excess weight loss													
BMI at follow-up													
Weight at follow-up													

Cardiovascular risk score													
Glycated hemoglobin (HbA1C)													
Fasting blood glucose (FBG)													
total cholesterol (TC)													
low-density lipoprotein cholesterol (LDL)													
high-density lipoprotein cholesterol (HDL)													
triglyceride (TG)													
Systolic blood pressure (SBP)													
Diastolic blood pressure (DBP)													
urine albumin/creatinine ratio													

Outcome data (year 5, if applicable)-dichotomous data-1											
	Group 1 (Intervention_____)			Group 2 (Intervention_____)							
	Total number of participants	Reported participants for each outcome	Case number	Total number of participants	Reported participants for each outcome	Total number of participants	p-value	Estimate of effect	95%CI Lower limit	95%CI Upper limit	Comments
Full remission of type 2 diabetes mellitsu											
Full or partial remission of type 2 diabetes mellitsu											
Achieve treatment goals with regard to blood glucose, blood pressure and lipids											
Requirement of less anti-diabetic drugs at follow-up											
Discontinuation of insulin											
Progression of diabetic retinopathy											
Progression of diabetic											

nephropathy											
Progression of diabetic neuropathy											
Number of patients experiencing myocardial infarction											
Number of patients experiencing stroke											
Number of patients experiencing amputation of at least one digit											
Number of patients experiencing ischemic limb disease											
Number of patients experiencing heart failure											
All-cause mortality											
Outcome data-dichotomous data (year 5, if applicable)-2 (when more than 2 comparative arms involved)											
	Group 3 (Intervention_____)			Group 4 (Intervention_____)							
	Total number of participants	Reported participants for each	Case number	Total number of participants	Reported participants for each	Total number of participants	p-value	Estimate of effect	95%CI Lower limit	95%CI Upper limit	Comments

		outcome			outcome						
Full remission of type 2 diabetes mellitsu											
Full or partial remission of type 2 diabetes mellitsu											
Achieve treatment goals with regard to blood glucose, blood pressure and lipids											
Requirement of less anti-diabetic drugs at follow-up											
Discontinuation of insulin											
Progression of diabetic retinopathy											
Progression of diabetic nephropathy											
Progression of diabetic neuropathy											
Number of patients experiencing											

myocardial infarction											
Number of patients experiencing stroke											
Number of patients experiencing amputation of at least one digit											
Number of patients experiencing ischemic limb disease											
Number of patients experiencing heart failure											
All-cause mortality											

Outcome data-adverse event (year 5, if applicable) 1. Coding of Adverse event: ###(study code) – ##(group number) – ###(adverse event number) 2. After sequence randomization, the adverse event will be re-numbered sequentially before sent for score translation) 3. Only adverse events not included in the "Outcome data-adverse event (year 3)" table will be listed.		
Group 1 (Intervention_____) (Lines may be added when necessary)		
Coding of Adverse event	Quotation from report regarding timing, severity, presentation, diagnosis, and management of adverse event	Anologue score of adverse event
Group 2 (Intervention_____) (Lines may be added when necessary)		
Coding of Adverse event	Quotation from report regarding timing, severity, presentation, diagnosis, and management of adverse event	Anologue score of adverse event

Group 3 (if applicable) (Intervention_____) (Lines may be added when necessary)		
Coding of Adverse event	Quotation from report regarding timing, severity, presentation, diagnosis, and management of adverse event	Anologue score of adverse event
Group 4 (if applicable) (Intervention_____) (Lines may be added when necessary)		
Coding of Adverse event	Quotation from report regarding timing, severity, presentation, diagnosis, and management of adverse event	Anologue score of adverse event

PRISMA-P Checklist for *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 randomized controlled trials*

This checklist has been adapted for use from Table 3 in Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic reviews. 2015;4:1.

Section/topic	#	Checklist item	Information reported		Page (P) and Line (L) Number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	√		*P1,L4-12*
Update	1b	If the protocol is for an update of a previous systematic review, identify as such			N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	√		*P2, L58*
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	√		*P1, L14-41; P18, L43-54*
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	√		*P18, L14-25*
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments			N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	√		*P18, L30-36*
Sponsor	5b	Provide name for the review funder and/or sponsor			N/A
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	√		*P18, L35-41*
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	√		*P3, L43 - P5, L25*
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	√		*P5, L32-46*
METHODS					

Section/topic	#	Checklist item	Information reported		Page (P) and Line (L) Number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	√		*P6, L17 – P9, L59*
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	√		*P10, L4-49*
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	√		Supplementary material 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	√		*P10, L53 - P11, L10*
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	√		*P10, L53 - P11, L12; P11, L22-44*
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	√		*P10, L53 - P11, L18*
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	√		*P11, L45 - P13, L15*
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	√		*P7, L40 – P9, L60; P3, L43 - P5, L25*
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	√		*P13, L17-46; P16, L14-54*
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	√		*P14, L50-60; P16, L4-13*
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	√		*P13, L50-P15, L60*
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	√		*P16, L14-54*
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	√		*P16, L4-13*
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	√		*P16, L56 – P17, L15*

Section/topic	#	Checklist item	Information reported		Page (P) and Line (L) Number(s)
			Yes	No	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	√		*P17, L17-34*

Abbreviations: N/A: not applicable.