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ORIGINAL CONTRIBUTIONS

Network Meta-Analysis of Metabolic Surgery Procedures for the Treatment of Obesity and Diabetes

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Abstract

Background Metabolic surgery is part of a well-established treatment intensification strategy for obesity and its related comorbidities including type 2 diabetes (T2DM). Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG) and one-anastomosis gastric bypass (OAGB) are the most commonly performed metabolic surgeries worldwide, but comparative efficacy is uncertain. This study employed network meta-analysis to compare weight loss, T2DM remission and perioperative complications in adults between RYGB, SG and OAGB.

Methods MEDLINE, EMBASE, trial registries were searched for randomised trials comparing RYGB, SG and OAGB. Study outcomes were excess weight loss (at 1, 2 and 3–5 years), trial-defined T2DM remission at any time point and perioperative complications.

Results Twenty randomised controlled trials were included involving 1803 patients investigating the three metabolic surgical interventions. RYGB was the index for comparison. The excess weight loss (EWL) demonstrated minor differences at 1 and 2 years, but no differences between interventions at 3–5 years. T2DM remission was more likely to occur with either RYGB or OAGB when compared to SG. Perioperative complications were higher with RYGB when compared to either SG or OAGB. Two-way analysis of EWL and T2DM remission against the risk of perioperative complications demonstrated OAGB was the most positive on this assessment at all time points.

Conclusion OAGB offers comparable metabolic control through weight loss and T2DM remission to RYGB and SG whilst minimising perioperative complications.

Registration number: CRD42020199779 (https:// www.crd.york.ac.uk/PROSPERO)

Keywords Metabolic surgery · Obesity · Type 2 diabetes · Network meta-analysis

Introduction

Metabolic surgery improves mortality and morbidity outcomes in patients with obesity [1] and has been shown to be cost-effective [2, 3]. A Cochrane systematic review found metabolic surgery was more effective than non-surgical obesity treatment [4]. Data from the Swedish Obese Subjects Study found a 25% weight loss at 10 years in those

Key Points

- Excess weight loss similar for RYGB, SG and OAGB
- T2DM remission more likely with RYGB or OAGB
- Perioperative complications more common with RYGB
- RYGB, SG or OAGB should be considered as primary metabolic surgical procedures

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undergoing gastric bypass surgery with a 24% decrease in mortality compared with the control group [1]. Metabolic surgery improves functional impairment and cardiovascular disease and reduces cancer risk and mortality related to type 2 diabetes (T2DM) [5–8]. Furthermore, metabolic surgery has been shown in a number of trials to induce remission of T2DM and has been endorsed by 200 diabetes organisations worldwide as a standard of care [9]. People living with obesity have been shown to have higher intensive care admissions and mortality during the recent coronavirus pandemic [10, 11] which has brought focus to the delivery of metabolic surgical services [12, 13]. However, studies demonstrate only a small proportion of the eligible population receive surgical intervention for obesity-related metabolic disease [14, 15].

Metabolic surgery is part of a well-established treatment intensification strategy for obesity-related comorbidities [16, 17], but the role of individual operative approaches is less certain. The Fourth Global International Federation for the Surgery of Obesity (IFSO) Registry in 2018 reported that of the 190,177 primary metabolic operations, sleeve gastrectomy (SG) was the most common (87,467; 46.0%) followed by Roux-en-Y gastric bypass (RYGB) (72,645; 38.2%) and one-anastomosis gastric bypass (OAGB) (14,516; 7.6%) [18]. Previously published standard pairwise meta-analyses have produced inconsistent findings [19–22]. With the evolution of procedures and the increasing use and understanding of one-anastomosis gastric bypass [23], an updated comparative efficacy assessment is required to aid healthcare decision making.

This study employed network meta-analysis (NMA) to compare weight loss, type 2 diabetes remission and perioperative complications in adults between Roux-en-Y gastric bypass, sleeve gastrectomy and one-anastomosis gastric bypass.

Methods

A systematic review was undertaken to identify all published randomised controlled trials (RCTs) evaluating Roux-en-Y gastric bypass, sleeve gastrectomy and one-anastomosis gastric bypass. The review was conducted in line with the PRISMA statement [24] and PRISMA-Network meta-analysis extension [25]. The review was registered in the PROSPERO database (CRD42020199779).

Search Strategy

Medline, Embase, the Cochrane Register of Clinical Trials and the International Standard Randomised Controlled Trial Number (ISRCTN) Registry (controlled-trials.com) were searched from January 2000 until August 2020 using a search strategy based on excess weight loss, remission of type 2 diabetes and perioperative complications for (1) Roux-en-Y gastric bypass (RYGB), (2) sleeve gastrectomy (SG) or (3) one-anastomosis gastric bypass (OAGB) (Appendix). Randomised controlled trials evaluating at least two of the techniques in adult patients for the treatment of obesity or related comorbidities were included. Trials recruiting only children and those not reporting any of the primary outcomes of interest were excluded. No language restrictions were employed. Abstracts and conference proceedings were not included as they provide insufficient detail. Two authors trained in systematic review techniques (ACC & AA) completed the search strategy and screening, with disagreements resolved through consensus of the wider study team.

Outcome Measures

All RCTS including the primary outcomes of interest, including percentage excess weight loss, remission of diabetes (trialist-defined) and perioperative complications (trialist-defined), were included.

Data Extraction

Arm level data were extracted from the included studies, from communication with authors or from previous meta-analyses where the original study authors had been contacted for data verification. After a calibration exercise, three authors (ACC, AA & AF) independently performed data extraction. Disagreement at all stages was resolved by discussion with the senior author (KM).

Quality Assessment

Potential biases were identified using the Cochrane risk of bias tool [26]: sequence generation, allocation concealment, blinding, if the outcomes reported were prespecified, completeness of outcome data and other potential sources of bias. Three authors (ACC, AA & AF) independently performed the quality assessment. Disagreement was resolved by discussion with the wider study team.

Statistical Methods

Random-effects network meta-analysis using the frequentist approach was applied to synthesis evidence for the primary outcomes. Evidence was summarised in a network map for each outcome. A common within network estimate for heterogeneity was estimated with the restricted maximum likelihood method [27, 28]. Consistency between direct and indirect evidence or between studies involving different sets of treatments for the same comparison was tested using the

design by treatment interaction model [29]. Inconsistency was assessed using the node-splitting method [30, 31].

Where outcomes demonstrated statistically significant differences between procedures, the ranking probabilities of each metabolic surgical procedure (RYGB was the reference) were calculated and presented as rankograms. The ranking (surface under the cumulative ranking curve, SUCRA) scores for each treatment for the most commonly reported effectiveness (percentage excess weight loss and remission of diabetes) and adverse (perioperative complication) outcomes were then combined by time point into clustered ranking plots, to enable a simultaneous comparison of benefits and risks. Sensitivity analyses were undertaken excluding trials where the risk of bias was considered to be high due to poor allocation concealment or randomisation processes.

The assessment of statistical heterogeneity in the entire network was based on the magnitude of the heterogeneity variance parameter (τ) estimated from the NMA models, which is the estimated standard deviation treatment effects. We applied a 0.5 zero-cell correction before meta-analysis. To investigate potential small-study effects, a comparison-adjusted funnel plot was constructed. Statistical analysis was performed in STATA 16.0 (StataCorp, College Station, TX, USA) using 'mvmeta' and 'network' commands and other routines as reported [32–34]. All statistical tests were two sided, with the threshold of significance set at a p value of less than 0.05.

Role of the Funding Source

There was no funding source for this study. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Following systematic searches in MEDLINE, EMBASE and trial registries, 2291 abstracts were identified, and following exclusions, 25 articles regarding 20 RCTs (1803 patients) were included [35–59] (Fig. 1). The characteristics of the included trials are shown in Table 1 and the risk-of-bias assessment shown in Fig. 2. The most commonly studied

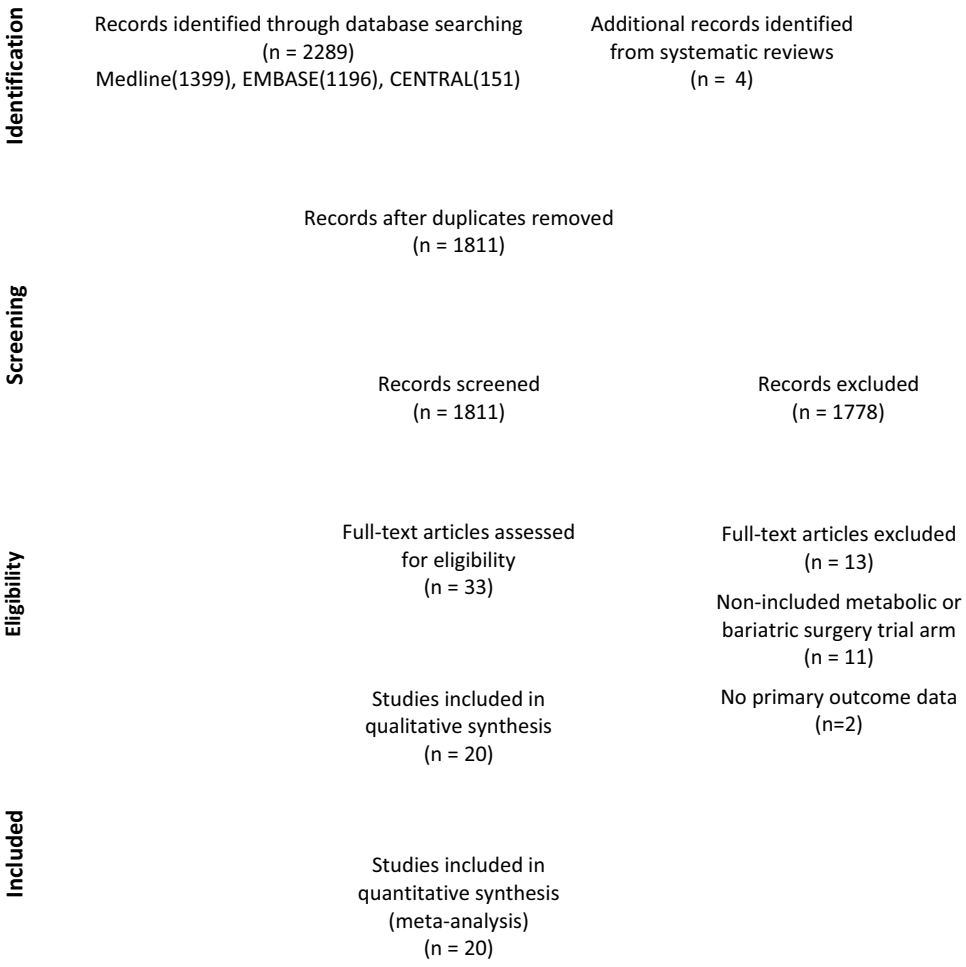

Fig. 1 PRISMA diagram for study inclusion

Table 1 Characteristics of the included studies

First author	Year of publication	Enrolment period	Country	Inclusion criteria	Criteria for T2DM remission	Complications definition	RYGB (*n*)	SG (*n*)	OAGB (*n*)
Lee	2005	2001–2003	Taiwan	BMI > 40 kg/m^2 or > 35 kg/m^2 with comorbidity	NR	NR	40	-	40
Karamanakos	2008	NR	Greece	NR	-	NR	16	16	-
Kehagias	2011	2005–2007	Greece	NR	Fasting plasma glucose < 126 mg/dL or 2-h plasma glucose < 200 mg/dL during OGTT or no pharmacologic therapy	NR	30	30	-
Lee	2011	2007–2008	Taiwan	BMI 25–35 kg/m^2 with DM	-	NR	-	30	30
Paluszkiewicz	2012	2008–2011	Poland	BMI > 40 kg/m^2 or > 35 kg/m^2 with comorbidity	Normal fasting glucose levels (< 100 mg/dL) and HbA1c < 6.0%	Major: death, reoperation or LOS > 7 days, blood transfusion of 4 units + . All others minor	35	34	-
Schauer*	2012	2007–2011	USA	BMI 27–43 kg/m^2 with DM	Glycated haemoglobin level ≤ 6.0% with or without the use of pharmacologic therapy	NR	50	49	-
Gras-Miralles	2014	NR	Spain	BMI > 40 kg/m^2 or > 35 kg/m^2 with comorbidity	NR	NR	7	7	-
Schauer*	2014	2007–2011	USA	BMI 27–43 kg/m^2 with DM	Glycated haemoglobin level ≤ 6.0% with or without the use of pharmacologic therapy	NR	48	49	-
Zhang	2014	2007–2008	China	BMI 32–50 kg/m^2		Major: death, reoperation or LOS > 7 days, or blood transfusion. All others minor	28	29	
Yang	2015	2009–2014	China	BMI 28–35 kg/m^2 with DM	HbA1c < 6.0% and fasting glucose < 7.0 mmol/L with no pharmacologic therapy	NR	27	28	-
Tang	2016	2011–2013	China	BMI > 28 kg/m^2 with DM	HbA1c < 6% and fasting glucose < 100 mg/dL (< 5.6 mmol/L) with no pharmacologic therapy for at least 1 year	NR	38	34	
Biter	2017	2013–2014	Netherlands	BMI > 40 kg/m^2 or > 35 kg/m^2 with comorbidity	-	NR	60	70	-
Casajoana	2017	2012–2014	Spain	BMI 35–43 kg/m^2 with DM	HbA1 < 6.0% for 1 year without medication	NR	15	14	-
Ignat	2017	2009–2012	France	BMI 40–60 kg/m^2	-	NR	44	48	-

Table 1 (continued)

First author	Year of publication	Enrolment period	Country	Inclusion criteria	Criteria for T2DM remission	Complications definition	RYGB (*n*)	SG (*n*)	OAGB (*n*)
Peterli*	2017	2007–2011	Switzerland	BMI > 40 kg/m^2 or > 35 kg/m^2 with comorbidity	HbA1c < 6% and fasting glucose < 100 mg/dL (< 5.6 mmol/L) with no pharmacologic therapy for at least 1 year	NR	106	105	-
Schauer*	2017	2007–2011	USA	BMI 27–43 kg/m^2 with DM	Glycated haemoglobin level ≤ 6.0% with or without the use of pharmacologic therapy	NR	49	47	-
Seetharamaiah*	2017	2013–2015	India	BMI > 35 kg/m^2 or > 30 kg/m^2 with comorbidity	Fasting plasma glucose level < 110 mg/dL or HbA1c level < 6.4% off medical treatment	NR	-	100	101
Peterli*	2018	2007–2011	Switzerland	BMI > 40 kg/m^2 or > 35 kg/m^2 with comorbidity	HbA1c < 6% and fasting glucose < 100 mg/dL (< 5.6 mmol/L) with no pharmacologic therapy for at least 1 year	NR	106	105	-
Salminen	2018	2008–2010	Finland	BMI > 40 kg/m^2 or > 35 kg/m^2 with comorbidity	5 years: HbA1c < 6% and fasting glucose < 100 mg/dL (< 5.6 mmol/L) with no pharmacologic therapy for at least 1 year	Major: death, reoperation or LOS > 7 days, blood transfusion of 4 units + . All others minor	40	41	-
Robert	2019	2014–2016	France	BMI > 40 or > 35 with at least 1 comorbidity	HbA1C < 6% and fasting glycaemia was less than 5.6 mmol/L without active pharmacological therapy or ongoing procedures	Serious: Death, life-threatening, requires hospital treatment or extension of hospital stay	117	-	117
Vix	2013	NR	France	BMI 40–60 kg/m^2	-	NR	44	48	-
Shivakumar*	2018	2012–2015	India	BMI > 35 and < 60	Fasting plasma glucose level < 110 mg/dL or HbA1c level < 6.4% off medical treatment	NR	-	100	101
Hofso	2019	2012–2015	Norway	BMI > 33 with HbA1c > 6.5 or BMI > 35 with HbA1c > 6.1	HbA1c ≤ 6% with no pharmacologic therapy	Graded according to the Contracted Accordion Classification	54	53	-
Jain*	2020	2013–2015	India	BMI > 35 kg/m^2 or > 30 kg/m^2 with comorbidity	-	NR	-	71	73

Table 1 (continued)

First author	Year of publication	Enrolment period	Country	Inclusion criteria	Criteria for T2DM remission	Complications definition	RYGB (*n*)	SG (*n*)	OAGB (*n*)
Level	2020	2012–2013	Venezuela	BMI > 40 kg/m^2 or > 35 kg/m^2 with comorbidity	Fasting blood glucose < 100 mg/dL, HbA1c < 6%, off medication	NR	19	-	9

NR definition not reported.
*Studies that are part of larger RCTs.

randomised comparison was between RYGB and SG (13 RCTs) for excess weight loss (EWL) (13 RCTs) and T2DM remission (12 RCTs) (Fig. 3). Whilst the overall risk of bias was low in the included articles, 8/25 had an unclear risk of bias related the randomisation process, and 4/25 had an unclear risk of bias regarding outcome reporting. No evidence of small-study effects on the network were identified on the comparison-adjusted funnel plot (Fig. 4).

Excess Weight Loss

At 1 year, 13 trials including 1270 randomised patients were included in the comparison of percentage excess weight loss [35, 37, 39–44, 46, 52, 54, 57, 58] (Table 2). For 1-year EWL, 8 RCTs compared RYGB with SG, 2 RCTs compared RYGB v OAGB and 3 RCTS compared SG with OAGB. In standard meta-analysis, no approach was favoured over another for EWL at 1 year. On network meta-analysis, RYGB and SG had similar EWL at 1 year, but OAGB had greater EWL at 1 year than both RYGB and SG. In the NMA, there was no inconsistency seen between the direct and network effect sizes ($\chi^2 = 8.56$, 3 d.f., $P = 0.0357$). No evidence of statistical heterogeneity was seen in the network ($\tau^2 < 0.001$).

At 2 years, 4 RCTs compared RYGB with SG, 2 RCTs compared RYGB v OAGB and 2 RCTs compared SG with OAGB [39, 41, 43, 46, 47, 53, 57, 59] (Table 2). In standard meta-analysis, no approach was favoured over another for EWL at 2-year follow-up. On network meta-analysis, RYGB and SG had similar EWL at 2 years, whereas OAGB has slightly greater EWL at 2 years when compared to RYGB. SG and OAGB had similar EWL at 2 years. In the NMA, there was no inconsistency seen between the direct and network effect sizes ($\chi^2 = 9.50$, 3 d.f., $P = 0.0187$). No evidence of statistical heterogeneity was seen in the network ($\tau^2 < 0.001$).

At 3–5 years, 7 RCTs compared RYGB with SG, 1 RCT compared RYGB v OAGB and 2 RCTS compared SG with OAGB [39, 41, 46, 48, 55–59] (Table 2). In standard meta-analysis, RYGB had greater EWL than SG at between 3 and 5 years postoperatively. No differences in EWL at this time point were noted in standard meta-analysis of the two trials of SG and OAGB. On network meta-analysis, RYGB had greater EWL than SG at 3–5 years, whereas RYGB and OAGB had similar EWL at this time point. SG and OAGB had similar EWL at 3–5 years. In the NMA, there was no inconsistency seen between the direct and network effect sizes ($\chi^2 = 10.16$, 3 d.f., $P = 0.0257$). No evidence of statistical heterogeneity was seen in the network ($\tau^2 < 0.001$).

Diabetes Remission

Fourteen trials including 697 randomised patients with T2DM were included in the comparison of diabetes

Fig. 2 Cochrane risk of bias—2 tool assessments of quality of included studies

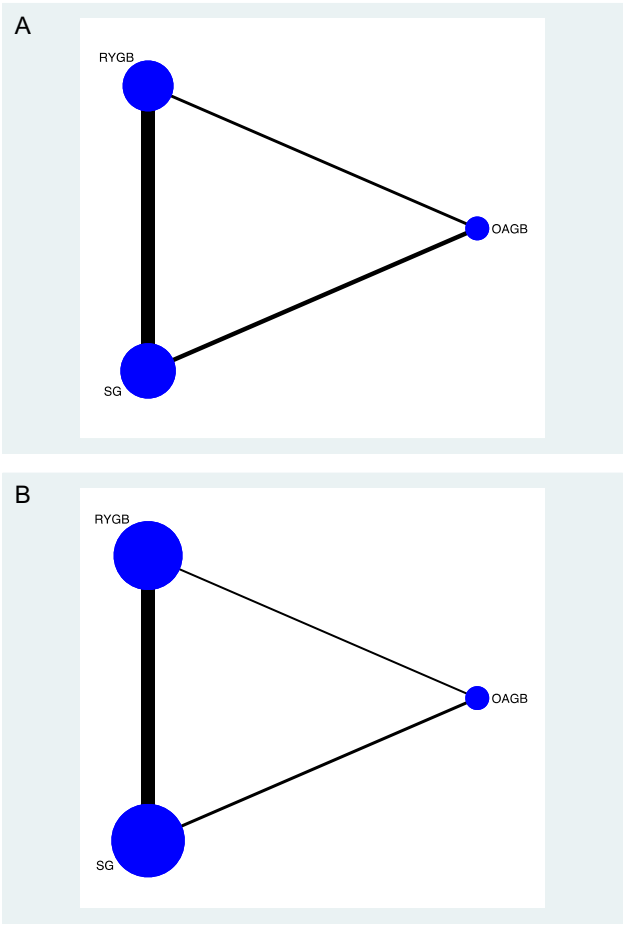

Fig. 3 Network plot for eligible comparisons in perioperative strategies for **a** excess weight loss (1 year) and **b** T2DM remission. The size of the nodes is proportional to the number of patients (*n*) randomised to receive the treatment. The width of the lines is proportional to the number of trials comparing the connected treatment strategies

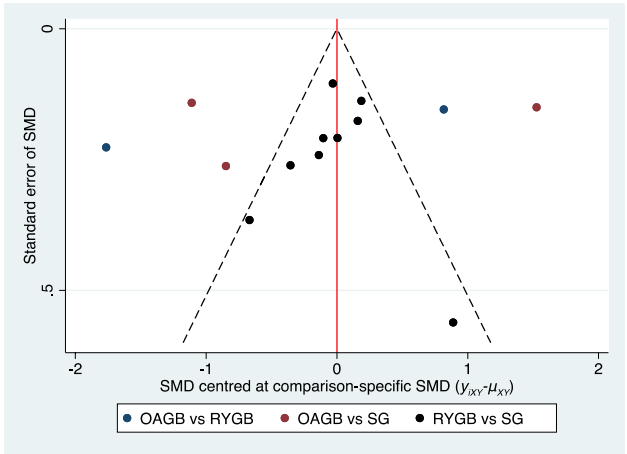

Fig. 4 Comparison-adjusted funnel plot for the outcome of excess weight loss (1 year). Comparisons are made comparing newer treatments against older treatments (RYGB being the oldest, followed by SG and then OAGB). The horizontal axis is the study-specific effect sizes centred to the respective comparison-specific pooled effect size, and the vertical axis is the inverted standard error of the effect sizes as used in a standard funnel plot. The solid red line represents the null hypothesis that the study-specific effect sizes do not differ from the respective comparison-specific pooled treatment effect estimates. Symmetrical distribution of this funnel plot suggests there is no small-study effect in this comparison. SMD standardised mean difference

remission [36–38, 41, 43–45, 47, 48, 50, 52, 53, 55, 58, 60] (Table 3). Ten RCTS compared RYGB with SG, 2 RCTs compared RYGB v OAGB and 2 RCTS compared SG with OAGB. In standard meta-analysis, RYGB was 20% more likely to result in remission of type 2 diabetes compared to SG. There was no difference in T2DM remission between OAGB and either RYGB or SG. On network meta-analysis, both RYGB and OAGB had increased postoperative remission of type 2 diabetes. There were no differences between RYGB and OAGB for remission of type 2 diabetes. In the NMA, there was no inconsistency seen between the direct and network effect sizes ($\chi^2 = 7.99$, 3 d.f., $P = 0.0397$). No evidence of statistical heterogeneity was seen in the network ($\tau^2 < 0.001$).

Perioperative Complications

Thirteen RCTs including 1593 randomised patients were included in the comparison of perioperative complications [35, 39–44, 46–48, 52, 55–58] (Table 4). Nine RCTs compared RYGB with SG, 2 RCTs compared RYGB v OAGB and 2 RCTS compared SG with OAGB. In standard meta-analysis, RYGB was more likely to result in perioperative complications compared to both SG and OAGB. There was no difference in perioperative complications between OAGB and SG. Similarly, on network meta-analysis, RYGB had increased perioperative complications compared to both SG and OAGB, and there were no differences between SG and OAGB for the development of perioperative complications. In the NMA, there was no inconsistency seen between the direct and network effect sizes ($\chi^2 = 1.92$, 3 d.f., $P = 0.0340$). No evidence of statistical heterogeneity was seen in the network ($\tau^2 < 0.001$).

Cluster Plots of Benefits and Risk

SUCRA clustered ranking plots are shown in Fig. 5. For all years, OAGB consistently ranked highest in terms of maximising EWL and T2DM remission whilst reducing the risk of perioperative complications.

Table 2 Standard pairwise meta-analysis and network meta-analysis of excess weight loss following metabolic surgery

Time point	Intervention	Comparator	No. of direct comparison studies	Pairwise meta-analysis (SMD)*	Between-study variance (MA)	Network meta-analysis (SMD)*	Between-study variance (NMA)
1 year	RYGB	SG	9	0.06 (−0.09, 0.22)	0.200	1.67 (−0.89, 4.24)	0.202
	RYGB	OAGB	2	1.76 (−0.77, 0.77)	0.210	4.35 (1.30, 7.40)	0.005
	SG	OAGB	2	1.21 (−0.64, 3.13)	0.233	2.68 (0.16, 5.21)	0.037
2 years	RYGB	SG	5	0.05 (−0.024, 0.14)	0.347	1.37 (−2.31, 5.06)	0.465
	RYGB	OAGB	3	1.00 (−0.63, 2.63)	0.222	3.84 (0.47, 7.22)	0.026
	SG	OAGB	2	1.26 (−1.01, 3.54)	0.309	2.47 (−0.85, 5.79)	0.144
3–5 years	RYGB	SG	7	−0.28 (−0.49, −0.07)	0.024	−7.19 (−10.88, −3.51)	<0.001
	RYGB	OAGB	1	N/A	-	0.85 (−3.24, 4.93)	0.685
	SG	OAGB	2	1.78 (−1.22, 4.78)	0.301	8.04 (3.98, 12.10)	<0.001

*Values in parentheses are 95% confidence intervals. A standardised mean difference (SMD) greater than 0.00 favours the comparator (more EWL with comparator than with intervention); a SMD of less than 0.00 favours intervention (less EWL with comparator than with intervention).

MA standard pairwise meta-analysis, *NMA* network meta-analysis.

Table 3 Standard pairwise meta-analysis and network meta-analysis of T2DM remission following metabolic surgery

Intervention	Comparator	No. of direct comparison studies	Pairwise meta-analysis (RR)*	Between-study variance (MA)	Network meta-analysis (RR)*	Between-study variance (NMA)
RYGB	SG	11	0.62 (0.29, 0.95)	0.011	0.55 (0.34, 0.90)	0.016
RYGB	OAGB	2	1.05 (0.95, 1.15)	0.411	1.82 (0.70, 4.71)	0.215
SG	OAGB	2	1.45 (0.90, 2.44)	0.101	3.31 (1.33, 8.23)	0.010

*Values in parentheses are 95% confidence intervals. A risk ratio (RR) greater than 1.00 favours the comparator (more desirable events with comparator than with intervention); a RR of less than 1.00 favours intervention (fewer desirable events with comparator than with intervention).

MA standard pairwise meta-analysis, *NMA* network meta-analysis.

Table 4 Standard pairwise meta-analysis and network meta-analysis of perioperative complications following metabolic surgery

Intervention	Comparator	No. of direct comparison studies	Pairwise meta-analysis (RR)*	Between-study variance (MA)	Network meta-analysis (RR)*	Between-study variance (NMA)
RYGB	SG	9	0.61 (0.32, 0.92)	0.033	0.53 (0.38–0.75)	<0.001
RYGB	OAGB	1	0.57	0.210	0.42 (0.24–0.72)	0.002
SG	OAGB	2	0.80 (0.44, 1.41)	0.345	0.78 (0.47, 1.32)	0.263

*Values in parentheses are 95% confidence intervals. A risk ratio (RR) greater than 1.00 favours the intervention (fewer events with intervention than with comparator); a RR of less than 1.00 favours comparator (fewer undesirable events with comparator than with intervention).

MA standard pairwise meta-analysis, *NMA* network meta-analysis.

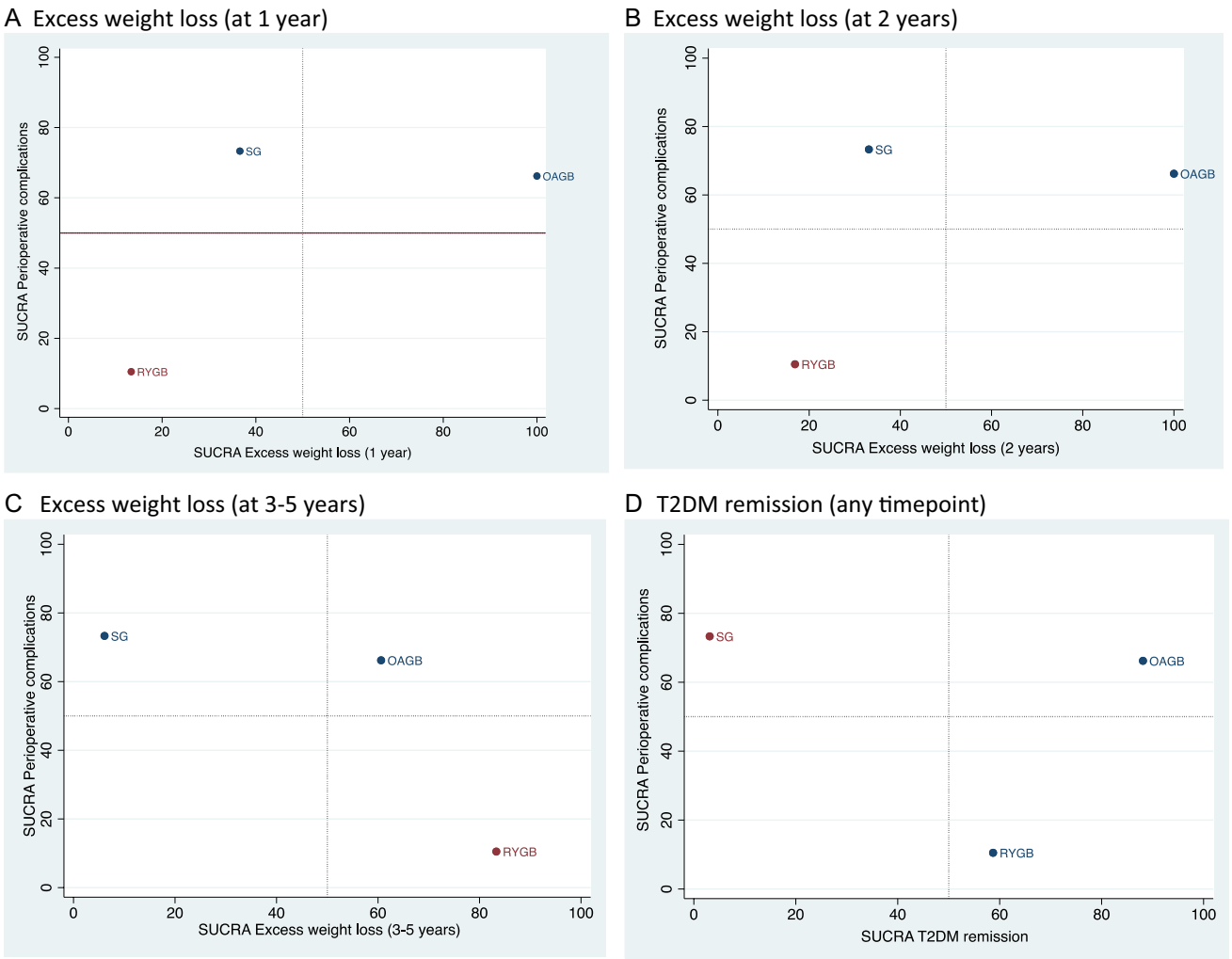

Fig. 5 Clustered ranking plots of the metabolic surgery network based on cluster analysis of SUCRA values for two sets of different outcomes: i) excess weight loss (EWL) and perioperative complications, and ii) type 2 diabetes (T2DM) remission and perioperative complications. Treatments lying in the upper right corner are more effective and carry less risk than the other treatments

Discussion

This network meta-analysis has uniquely summarised all RCTs to date comparing the most commonly performed current metabolic surgical procedures, i.e. RYGB, SG and OAGB. The EWL demonstrated minor differences at the 1-year and 2-year time points, but no differences between procedures at longer term follow-up. Remission of type 2 diabetes was more likely to occur with either RYGB or OAGB when compared to SG. The risk of perioperative complications was higher with RYGB when compared to either SG or OAGB. When the potential benefits of EWL and T2DM remission were considered against the risk of perioperative complications, OAGB appears to offer the optimal balance of these factors across all time points. The findings from this NMA suggest that OAGB offers comparable metabolic control through weight loss and T2DM remission to RYGB and SG whilst minimising perioperative complications. Therefore, OAGB should be considered more strongly as a primary metabolic surgical procedure.

Previously published NMA studies in bariatric surgery have reported conflicting results. Park and colleagues [61] found that RYGB, SG or biliopancreatic diversion procedures, but not OAGB, produced equally good short and long-term T2DM remission. They considered a larger number of randomised interventions in the formation of their network; however, not all would be currently considered reasonable metabolic surgery interventions. The premise of NMA is that the included interventions could be 'jointly randomisable' as though offered in a contemporary RCT [62]. Banded bypass, gastric plication and even adjustable gastric banding are not considered standard practice in many parts of the world. In comparison, the current NMA compares the three

most commonly performed metabolic surgical procedures worldwide.

According to the most recent IFSO registry report, the three most commonly performed procedures are RYGB, SG and OAGB [18]. IFSO endorses all of these procedures for use as metabolic surgical interventions [60, 63, 64]. RYGB is the acknowledged gold standard metabolic surgical intervention and has the most direct and indirect evidence supporting its use in this NMA. SG demonstrates excellent weight loss and metabolic control but is shown to be slightly inferior to RYGB when considering treatment of T2DM alone. This reason for the differences between bypass procedures and SG in metabolic control may be due to improved hepatic insulin sensitivity [38]. This is reflected in the increased use of RYGB, but also OAGB, compared to SG when considering metabolic surgery for T2DM in a recent IFSO report [65]. This NMA indicates that OAGB may offer acceptable weight loss and glycaemic control as a metabolic surgical procedure. However, there are concerns in the literature about the use of OAGB particularly with regard to risks of protein-calorie malnutrition and upper gastrointestinal malignancies related to bile reflux [66]. Whilst the rates of malnutrition reported in large multinational cohorts are low [67], a recent IFSO survey on OAGB recognised the potential serious risks of malnutrition, liver failure and bile reflux that may require surgical correction after OAGB [68]. Specifically relating to biliary reflux, there are case reports of biliary reflux associated cancers in the context of OAGB [69]. Whilst the overall risk of this complication is unclear, this should merit further investigation. There has been some debate that the limb length in OAGB may influence malnutrition [70], but there remains a lack of consensus on the optimal limb lengths in OAGB [68]. In the current NMA, the included trials had limb lengths from 200 to 350 cm [43, 47]. Some groups have found that reducing the limb length to 150 cm may obviate the risks of malnutrition [71], without a significant effect on the weight loss outcomes, whereas other groups have reported tailoring the limb length to one-third of the total bowel length offers the optimal metabolic outcome [72]. The latter approach may however be associated with higher risk of bowel injuries.

This NMA has identified comparative efficacies of RYGB, SG and OAGB to effect weight loss and induce remission of T2DM. Other studies have used data points in order to define which metabolic surgical procedures should be preferred for different indications. Aminian and colleagues, using data from 654 patients with diabetes who underwent RYGB or SG at the Cleveland Clinic, produced the Individualised Metabolic Surgical Score (IMSS) [73]. The IMSS incorporates the duration of T2DM, the number of preoperative antidiabetic medications, preoperative insulin use and glycated haemoglobin percentage (HbA1c (%)) to score patients into mild, moderate or severe categories. Patients with severe IMSS are proposed by the authors to undergo RYGB as it produces higher remission in this category on their validation set at a Spanish bariatric centre. No patients undergoing OAGB were included in that study, and there was minimal consideration of perioperative complications. Chiapetta and colleagues using data from the German register for obesity and metabolic surgery evaluated the risk of perioperative complications in patients with varying degree of obesity-related comorbidity using the Edmonton Obesity Staging System [74]. They found that patients with EOSS scores > 2 had a higher risk of morbidity which was reduced when either SG or OAGB was employed as the metabolic surgical procedure. The authors propose SG or OAGB is used to minimise risk in patients with severe obesity-related comorbidity. However, that study did not evaluate weight loss or T2DM remission outcomes. The current NMA extends these findings to suggest OAGB should be considered alongside RYGB and SG as an option for metabolic surgery in a patient presenting for treatment of obesity or obesity and T2DM.

This study has shown that both bypass procedures offer comparable weight loss and control of T2DM. The mechanism of action of RYGB is comparatively well characterised [75]. The pathways are likely to be multifactorial including changes in eating behaviour, humoral mediated through glucagon-like peptide 1 (GLP-1), gastroinhibitory peptide, glucagon and ghrelin signalling, bile acid kinetics and microbiome-associated effects. Conversely, the mechanism by which OAGB offers metabolic control comparable to RYGB remains to be established. Preliminary work indicates the mechanism of action of OAGB and RYGB may be similar [76]. Additional work in the experimental animal indicates the mechanism of metabolic improvement may be mediated by GLP-1 and bile acid pathways [77]. Overall, more work is required to characterise the mechanistic effect of OAGB in the human population.

Despite comprehensive reporting of all RCTS comparing RYGB, SG and OAGB, there are some limitations to this study that require consideration. By restricting the analysis to the three most commonly performed metabolic surgery procedures worldwide, some comparisons between techniques have limited direct comparative evidence—in particular, there are only two comparative trials of OAGB and RYGB at 1 and 2-year follow-up and only one at 3–5-year follow-up. Whilst this provides limited direct evidence, the strength of network meta-analysis is that the statistical technique permits use of indirect evidence to increase the precision of the treatment effect estimates. Indeed, by demonstrating consistency between direct and indirect treatment effects at all time points, this NMA analysis has shown the benefit of expanding the trial network beyond direct meta-analysis to maximise use of the randomised trial evidence in the area. However, more direct trials of OAGB and both RYGB and SG are needed to improve our understanding of their respective treatment effects. Whilst

this study has been able to make a comprehensive comparison of trialist-defined complications, there is limited standardisation of reporting and grading of complications which precludes a more in-depth assessment. By including only RCTs, this NMA has limited reporting of longer term data. This may mean that some aspects of outcomes following these particular metabolic procedures may not have been captured, such as weight regain and the need for revisional procedures. Both RYGB and OAGB are associated with a long-term risk of the development of internal hernias and chronic abdominal pain. SG is associated with a long-term risk of GERD [78], and there are reports of long-term gastro-oesophageal and bile reflux following OAGB [64, 69]. By comparison with other NMAs, this current study assessed fewer procedural types, and therefore the confidence interval estimates are wider as fewer patients overall are included. However, the strength of this NMA lies in the fact that it meets the requirement of joint randomisability of included interventions [62], which other reviews do not by including procedures that are either not practiced by contemporary surgeons or not endorsed by major societies.

In summary, the current NMA has provided a synthesis of the evidence on the three most commonly used metabolic surgical procedures at present. RYGB is associated with the highest rate of perioperative complications. Weight loss at 1 and 2 years appeared greatest with OAGB, but at longer follow-up the differences were less certain. Remission of T2DM was more common with RYGB or OAGB compared to SG. This study has confirmed that RYGB, OAGB or SG should be considered as primary metabolic surgical procedures, and individualised approaches would be reasonable with any of these operations.

Author Contribution ACC, AA, AF & KM were involved in research design. ACC, AA and AF were involved in data acquisition. ACC, AA, AF & KM were involved in data interpretation, production of the manuscript and critical revisions. All authors approved the final submitted manuscript.

Declarations

Ethics Approval This study was a systematic review of published research; therefore, no ethical or governance approvals were required.

Conflict of Interest ACC, AA and AF have no conflicts of interest or financial ties to disclose. KM has received honoraria from Ethicon, Medtronic, Olympus, Gore and various NHS Trusts for educational and mentoring activities related to the OAGB.

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