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Systematic Review

Mechanism of Diabetes Remission or Improvement in Glucose Control Following Roux-en-Y Gastric Bypass Versus Sleeve Gastrectomy: A Systematic Review and Meta-Analysis

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Abstract: Background: The mechanisms of diabetes remission following bariatric surgery independent of calorie restriction and weight loss remain unclear. Objectives: To undertake a systematic review and meta-analysis to investigate mechanisms underpinning diabetes remission. Methods: We included individuals with type 2 diabetes who have undergone RYGB, SG, and a very low-calorie diet (VLCD). In total, 234 studies were identified (N = 52 for qualitative; N = 40 for quantitative synthesis). Review Manager v5.4 and IBM SPSS for Windows (v28.0.1.1) were used for analysis. Results: Crude annualised diabetes relapse rates for RYGB and SG are as follows: -6.98 ± 16.19 ($p = 0.046$) and -2.75 ± 4.94 ($p = 0.08$); crude remission rates for RYGB and SG, respectively, are as follows: 39.59 ± 45.93 ($p = 0.000$) and 33.36 ± 33.87 SG ($p = 0.006$). Differences in other metabolic outcomes (standardised mean difference and 95% confidence intervals (CIs)) are BMI: ([RYGB:−2.73, 95%CI: −3.14 to −2.32, $p < 0.000001$) (SG: −2.82, 95%CI: −5.04 to −0.60, $p = 0.01$)]; HbA1c: [(RYGB:−1.58, 95%CI: −2.16 to −1.00, $p < 0.00001$) (SG:−1.42, 95%CI: −1.69 to −1.15, $p < 0.00001$)]; insulin: [(RYGB:0.16, 95%CI: −0.19 to −0.50, $p = 0.37$) (SG: −3.00, 95%CI: −3.17 to −2.82, $p = 0.75$)]; and fat mass [(RYGB: −2.56, 95%CI: −4.49 to −0.64, $p = 0.009$) (SG: −1.69, 95%CI: −4.58 to 1.21, $p = 0.25$)]. RYGB and SG produced a significant improvement in HOMA-B measurements. Adiponectin and the Matsuda index were significantly increased with RYGB. No difference was observed for other metabolic markers (RYGB: GLP-1, GIP, leptin, ghrelin, PYY) (SG: GLP-1 and FGF19) (VLCD: leptin, GLP-1, GIP, and ghrelin). Conclusions: Diabetes remission following RYGB and SG was primarily driven by improvement in beta-cell function, with improvement in insulin resistance markers also observed for RYGB, driven by reductions in fat mass. No other metabolic mechanism explaining diabetes remission was observed based on clinical studies.

Keywords: type 2 diabetes mellitus; bariatric surgery; VLCD; diabetes remission; mechanisms; obesity

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1. Introduction

The prevalence of obesity, defined as a body mass index (BMI) of greater than or equal to 30 kg/m^2, has nearly tripled in number since 1975 [1]. Obesity is now accepted

to be influenced by a complex interplay of hormones and a cascade of adaptive metabolic and physiological mechanisms that are central to the disease process [2]. An obesogenic environment with increasing per-capita food supplies, sedentary lifestyles, genetics [3] and the gut microbiome also contribute the rising epidemic.

Obesity and Type 2 Diabetes Mellitus (T2D) are intransigently associated with worsening morbidity and mortality [4], representing a significant metabolic challenge with increased risk of adverse long-term sequelae for both micro- and macrovascular complications [5]. Pathways to the development of overt T2D are broadly accepted to involve a progressive loss of beta-cell function, often in the background of insulin resistance [6]. Calorie restriction and associated weight loss have been shown to be effective treatment modalities to manage T2D, although sustaining calorie restriction can be challenging to many patients.

Bariatric surgery, meanwhile, is the term for a collective group of surgeries that make changes to the digestive system with the purpose of aiding weight loss alongside promoting improved cardiometabolic health. Increased evidence has emerged on the efficacy of bariatric surgery in inducing sustained diabetes remission. Remission rates of 24–95% for nearly two years, depending on the surgical choice [7,8], have been reported. The variation in reported remission rates is due to considerable heterogeneity between studies due to differing patient populations, differing surgical protocols, and even different definitions of remission [9]. Ongoing debate persists on the underlying mechanism for this, i.e., whether diabetes remission is driven primarily by loss of fat mass per se or whether there are some additional metabolic mechanisms independent of fat loss. Clarification to dissect fat loss-dependent or -independent mechanisms for diabetes remission is further complicated by the fact that integral to bariatric surgery is the routine enrolment of patients to a pre-operative 'liver shrinkage' diet (very low-calorie or low-calorie diets (VLCD and LCD)) [10,11]. A large liver size can impede or complicate the approach to the gastroesophageal junction and present an increased bleeding risk with surgical manipulation [12]. LCDs (1000–1200 kcal) and VLCDs (<800 kcal) are well recognised to improve glucose metabolism—a further suggested link with early post-operative remission of T2D alongside weight loss [13]. A previous study has shown that early improvements of RYGB in insulin sensitivity and beta-cell function are mimicked with a VLCD [14], indicating that at least in the short term, calorie restriction and subsequent weight loss are the predominant mechanisms for diabetes remission. A further series of studies have shown that caloric restriction and weight loss are the dominant mechanisms of improved glucose metabolism—the former responsible for the early postsurgical recovery of insulin sensitivity and secretion, while the latter determines final outcomes once weight is stable [15].

Data indicate that both RYGB and SG have a comparable impact on diabetes remission [16]. The mechanisms underpinning diabetes remission following bariatric surgery independent of fat loss remain unclarified. It is suggested that baseline beta-cell glucose sensitivity and restored GLP-1 response (by rapid delivery of nutrients to the distal small intestine following RYGB) are the chief determinants governing diabetes remission status [9,17]. Conversely, SG, often viewed as a restrictive/volume reduction surgery, is more nuanced, as SG causes a reduction in ghrelin levels [18,19]. Further, with respect to RYGB, enterohepatic pathways with bile acids, fibroblast growth factor 19 (FGF-19), and GLP-1 are also proposed to be mechanistic components [20,21]. This poses an important question with respect to the delineation between these often-combined mechanisms as to which is the fundamental cause of diabetes remission for different types of bariatric surgeries.

Research designed to review the mechanisms that underpin these improved glycaemic profiles will help optimise surgical choices alongside promoting individualised treatment and providing greater insight into decision processing for both the patient population and

medical community. This systematic review aims to explore underpinning mechanisms for glycaemic improvement, alongside reviewing differential anthropometric outcomes, between RYGB and SG and pre-surgery VLCD by collating and synthesising currently available clinical data. This work will produce a critical appraisal of the differential effects between these interventions and has the potential to address areas of uncertainty, as well as identify mechanistic factors that require further focussed research.

2. Methods

2.1. Protocol and Registration

The study protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42022312733), with registration following research question finalisation and an implementation of our agreed search strategy.

We ensured that the study protocol would be compliant with Cochrane research guidelines by adopting the participant, intervention, comparison and outcome (PICO) framework for research question formulation to ensure all involved within this study had clarity regarding the approach [22]. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines are included (Supplement S1) [23].

2.2. Eligibility Criteria

Inclusion criteria were adult human studies (>18 years of age). A minimum of one arm in each study was required to have a population group with a diagnosis of T2D. The population group had to be obese, defined as a body mass index (BMI) of greater than or equal to 30 kg/m^2. Interventions accepted were RYGB, SG, or hypocaloric diet. Outcomes were to include all mechanistic potentials underpinning glycaemic improvement/diabetes remission.

Eligible study designs were randomised clinical trials containing either the intervention or comparator in at least one arm, non-randomised clinical trials containing either the intervention or the comparator in at least one arm, retrospective analyses containing either the intervention or comparator in at least one arm, pilot trials containing either the intervention or comparator in at least one arm, review articles containing either the intervention or the comparator in at least one arm, and systematic reviews and meta-analyses containing either the intervention or comparator in at least one arm. Meta-analysis was utilised as means to cross-check for references that were suitable for inclusion. Case studies, abstracts only, and editorials were excluded. This systematic review and meta-analysis focused on sleeve gastrectomy and RYGB as the two most commonly performed procedures, with studies investigating the mechanism of diabetes remission mainly utilising these two procedures.

2.3. Information Sources and Searches

Sources searched include MEDLINE, Embase, PubMed, and Google Scholar (first ten pages only). The date of access and database search for each was 19 November 2021. An updated review of the literature up to 24 November 2023 was undertaken. Restrictions applied included for publication in English language and access to full text. Excluded were studies published in other languages, studies that were unpublished, economic evaluation studies/case studies, editorials, and study protocol/abstract publications only.

The search strategy included the use of Medical Subject Headings (MESH), which is a controlled vocabulary produced by the National Library of Medicine that is used for indexing and cataloguing biomedical and health-related information. Peer-agreed MESH terms for the research questions were then applied (Supplements S2 and S3).

2.4. Data Collection Process

Data extraction was initially performed by a single researcher within two Microsoft Excel spreadsheets where all outcomes of interest (clinical and/or mechanistic), intervention type, lead author, duration of intervention, reported data format, and numerical values (continuous data type) were inputted. These extracted data were then reviewed by two other researchers, where (i) individual studies were re-assessed for PICOS compliance, (ii) variable feasibility for forest plot implementation was considered, and (iii) inspection for data reporting standardisation occurred. Any required modifications or clarifications were relayed to initial single researcher for implementation and then confirmed with the subsequent two reviewers. Subsequently, all data were imported into a separate, reference Excel spreadsheet where all represented clinical and mechanistic variables were considered for eventual analysis.

2.5. Analysis of Results

A final Excel spreadsheet was then created for any relevant data conversion, reordering of studies (in order of increasing follow-up interval), and calculation of the standardised mean difference (SMD) with standard errors (SEs) for meta-analysis and sensitivity analysis. Additional details pertaining to the data handling procedures are provided (Supplement S4).

Individual studies were excluded if there were no data, the data format was not consistent with our proposed statistical analysis (such as a non-normal distribution reported data), there was no follow-up period identified, or there was any other contravention to PICOS. Datapoints on individual studies were excluded if there were no pre-intervention data to allow comparative assessments, and neither SD nor SE data were present.

It was determined that as a mixture of RCTs, single-arm and NRTs studies were used, pre-intervention and post-intervention values should be selected in place of controls and cases, respectively, for forest plot analysis. Any studies demonstrating only pre-intervention and MD data were removed. The data were then imported into a global datasheet.

Forest plot generation was carried out using Review Manager v5.4.1 (Accesssed August 2024 Review Manager (RevMan) [Windows version]. Version 5.4.1. The Cochrane Collaboration). The inverse-variance statistical method and random effects model were selected for all meta-analyses performed, with the effect measure being the SMD. Individual files for variable-specific and RYGB versus SG comparisons, in accordance with the PICO framework established previously, were created. Forest plots were generated if at least two datapoints were present for a particular subgroup and/or variable to facilitate a comparison.

2.6. Intra-Study Risk of Bias (RoB) Assessment

Studies that had reached the synthesis stage with a randomised intervention design were assessed using the Cochrane Risk of Bias (RoB2) tool. Two researchers (YA and RW) independently assessed all eligible studies using the ROB2 tool, with a third assessor (AA) for consensus if necessary. The Review Manager (RevMan) application for Windows (v.5.4.1) was used to present the individual domain and study results assessed. Decisions for ROB2 questions 1.1, 1.2, 2.1, 2.2 and 4.3 and author judgments for 3, 5 and 4 were, respectively, inputted into Revman questions 1–7.

All non-randomised trials were evaluated through the Newcastle Ottawa Scale (NOS) [24] (revman.cochrane.org). Only studies that had reached the quantitative synthesis stage were considered for RoB assessment. Assessment was performed by two independent researchers (YA and RW), with a third (AA) providing consensus. A resultant rank was determined by the summative count of stars. Assessment occurred within three subgroups:

comparability of cases and controls, selection of cases and controls and exposure. Each subgroup had 8 questions for which a single star could be inputted—aside from comparability, where 2 stars could be utilised. High quality was reflected with 7–9 stars, fair quality 4–6 stars and low quality 1–3 stars.

2.7. Inter-Study Risk of Bias Assessment and Sensitivity Analysis

The publication bias of continuous variables was assessed utilising meta-regression of the residuals of sample size, in accordance with Cochrane guidelines (use subsequent citation). STATA Standard Edition v16 was implemented to apply the published code, with a forest plot generated for visual inspection of missing data (2024).

An assessment of sensitivity based on the decision to incorporate studies with a wide follow-up interval was undertaken through the generated SMD data (utilising RevMan 5.4.1. with identical statistical procedures as described previously). Three clinical variables (weight, BMI and HbA1c) were identified, and datapoints were divided based on follow-up duration (less than or equal to 12 weeks versus 52 or more weeks for RYGB as the intervention with the most voluminous data produced). Following effect size and significance calculation, subgroup data for these variables were reported within a table with additional study characteristic data and a 95% CI, in accordance with Cochrane recommendations (https://handbook-5-1.cochrane.org/chapter_9/9_7_sensitivity_analyses.htm, accessed on 20 December 2024).

3. Results

Study Selection

There were 234 studies included that were identified across all databases (minus duplications). The Cohen K for doubly blinded inter-observer concordance was calculated at 0.515, which indicates moderate agreement following the application of PICOS, a structured framework to address the research question. In total, 52 of these studies were then determined suitable for qualitative synthesis and 40 of the same total were determined to be suitable for quantitative synthesis [8,14,17,21,25–70]. With regard to data selection, the following variables were excluded, insulin sensitivity index, liver fat mass, adipokine, Branched-Chain Amino Acids, circulating Amino Acids, Glucagon-like Peptide-2, bile acid, Exendin 9–39, oxyntomodulin, Stumyoll, First Phase Index, Pro-insulin, Acylcarnitine, interleukin-6, as there were insufficient data points regarding methods.

From thereon, data extraction was completed. Forest plots were composed for each clinical and mechanistic variable. Subgroups were delineated as per intervention type (i.e., RYGB vs. SG vs. VLCD).

4. Clinical Variables

4.1. BMI

In total, 23 studies were included with RYBG as the intervention type (Figure 1). The results revealed an SMD of −2.73 (95% −3.14 to −2.12, $p < 0.00001$) (Figure 1). Further, seven studies were included with SG as the intervention type; these results revealed an SMD of −2.82 with a 95% CI of −5.04 to −0.60 ($p < 0.05$), indicating a slightly larger effect size versus RYGB. Five studies were included for the VLCD intervention group, and these results revealed an SMD of −0.96 with a CI of −2.19 to 0.27, alongside a non-statistically significant result with $p = 0.12$.

Overall, combining these three intervention types for BMI, the results revealed an SMD of −2.34, with a CI of −2.96 to 1.72, with statistical significance, $p < 0.00001$. BMI is affected with significance for both RYBG and SG and RYBG/SG/VLCD combined but not for VLCD in isolation.

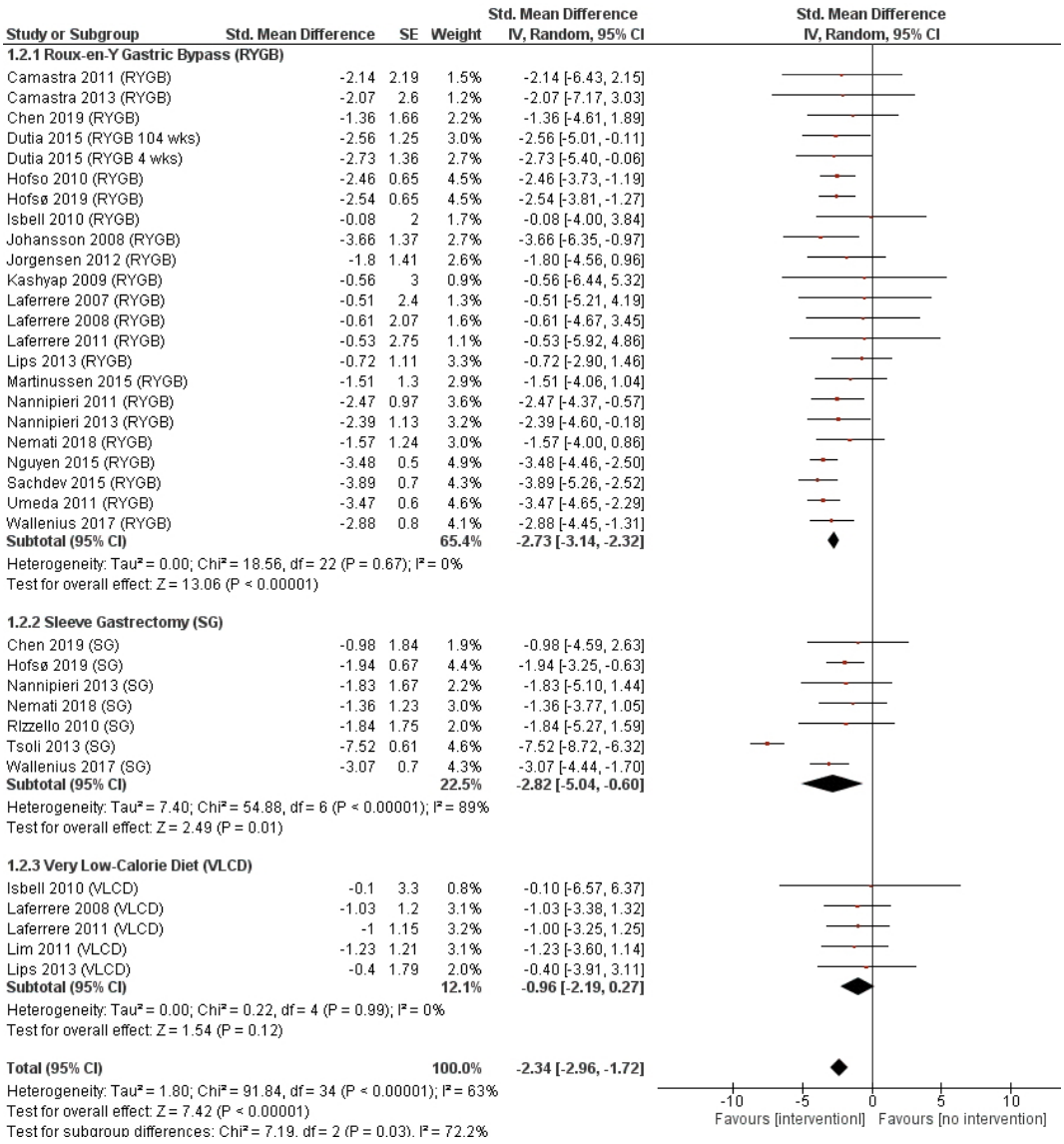

Figure 1. Clinical variable forest plot for BMI (kg/m^2): RYGB vs. SG vs. VLCD.

Heterogeneity was persistently observed across all three interventions, despite all individual effect sizes favouring intervention (Figure 1). A substantial number of datapoints presented with wide CIs associated with midpoint violation, indicative of commonplace clinical heterogeneity (Figure 1). Furthermore, measurement of statistical heterogeneity was considerable for SG (I^2 = 99%, $p < 0.00001$) but indeterminate for RYGB and VLCD ($p > 0.05$) (Figure 1).

4.2. Weight

In total, 27 studies were included for RYGB; the SMD was −1.69 (CI −3.22, −0.16) and there was a significant p value of 0.03. Seven studies were included for SG, and the SMD was −1.37 (CI −4.02, 1.28), with a non-significant p value of 0.31. For VLCD, five studies were included, with an SMD of −0.90 (CI −0.44, 2.63) and a non-significant p value of 0.62. Overall, with all three interventions combined, the SMD was −1.52 (CI −2.76, −0.28; p = 0.02), confirming that the pooled outcome of said interventions results in weight loss, which indirectly supports the VLCD non-significance being due to factors beyond effect size. Clinical heterogeneity was ubiquitous across all interventions for weight, with statistical heterogeneity assessment demonstrating equivocal results ($p > 0.05$) (Supplement S5A).

4.3. Fat Mass

Five studies were included for analysis for the RYGB intervention. Results revealed an SMD of −2.56 (CI −4.49 to −0.64; p = 0.009). Two datapoints were identified with SG, showing an SMD of −1.06 with a CI of −4.58 to 1.21 and a non-significant p value = 0.25. Analysis of VLCD was not possible due to an absence of data. Evidence of clinical heterogeneity is present in both interventions, with the statistical heterogeneity assessment being equivocal ($p > 0.05$) for both (Supplement S5B).

The overall results, when RYGB and SG are pooled, revealed an SMD of −2.30 (CI −3.90, −0.69), with a significant p value of 0.005. Overall, there was a significant result in fat mass (kg), although this was not delineated for the individual interventions included.

4.4. Fasting Glucose

Glucose (mmol/L) was also assessed in our study for each intervention as well as in the combined results. In total, 25 studies were included for RYGB assessment; the SMD was −1.01 (CI −1.25, −0.77), with a significant p value of <0.00001.

Five studies were included for SG, and the SMD was −0.82 (−1.29, −0.35), with a significant p value of 0.0007. VLCD, also represented by five trials, revealed an SMD of −1.49 (CI −2.34, v0.64), with a significant p value of 0.0006.

Clinical heterogeneity across all interventions was observed, with multiple trials exhibiting substantially wide Cis. Statistical heterogeneity was also inferred to potentially be substantial for VLCD (I^2 = 64%, p = 0.03). Assessments for RYGB and SG were equivocal ($p > 0.05$).

Altogether, the SMD for all interventions combined was −1.11 (CI −1.30, −0.91), with a significant p value < 0.00001. Therefore, all interventions, alone and in combination, showed significance in affecting the glucose measurements within these studies (Supplement S5C).

4.5. HBA1C

For HbA1c (mmol/mol), forest plots show for RYGB, for which there were 18 studies included, an SMD of −1.58 (CI −2.16, −1.00), with a significant $p < 0.00001$. There were five studies for SG, with an SMD of −1.42 (CI −1.69, v1.15) and significance $p < 0.00001$. Sufficient data for VLCD were not identified.

Considerable clinical heterogeneity is identified in 5 of the 18 trials identified for RYGB and 1 [36] for SG. Statistical heterogeneity is demonstrated to be considerable for RYGB (I^2 = 91%, $p < 0.00001$). The assessment was equivocal for SG (Figure 2).

Together, these interventions had an SMD of −1.52 (CI −1.98, −1.06), with a significance of $p < 0.00001$. We can thus determine that both bariatric surgery modalities produce greater glycaemic control in the population (Figure 2).

4.6. Insulin

IN total, 18 studies were included for RYGB analysis, and the SMD was 0.16 (CI −0.19, 0.50), with a non-significant p value of 0.37. There were four studies for SG included, with an SMD of −3.00 (CI −3.17, −2.82) and a non-significant p value of 0.75. Three studies were included for VLCD, with an SMD of −0.74 (CI −44.06, 42.59) and non-significance (p = 0.97). Clinical heterogeneity was relatively limited in SG compared to RYGB and, in particular, VLCD, as identified by the substantially wide CIs (S5D). Statistical heterogeneity determination was equivocal for all three interventions.

All three interventions combined revealed an SMD of −1.14 (CI −2.87, 0.59), with non-significance (p = 0.20).

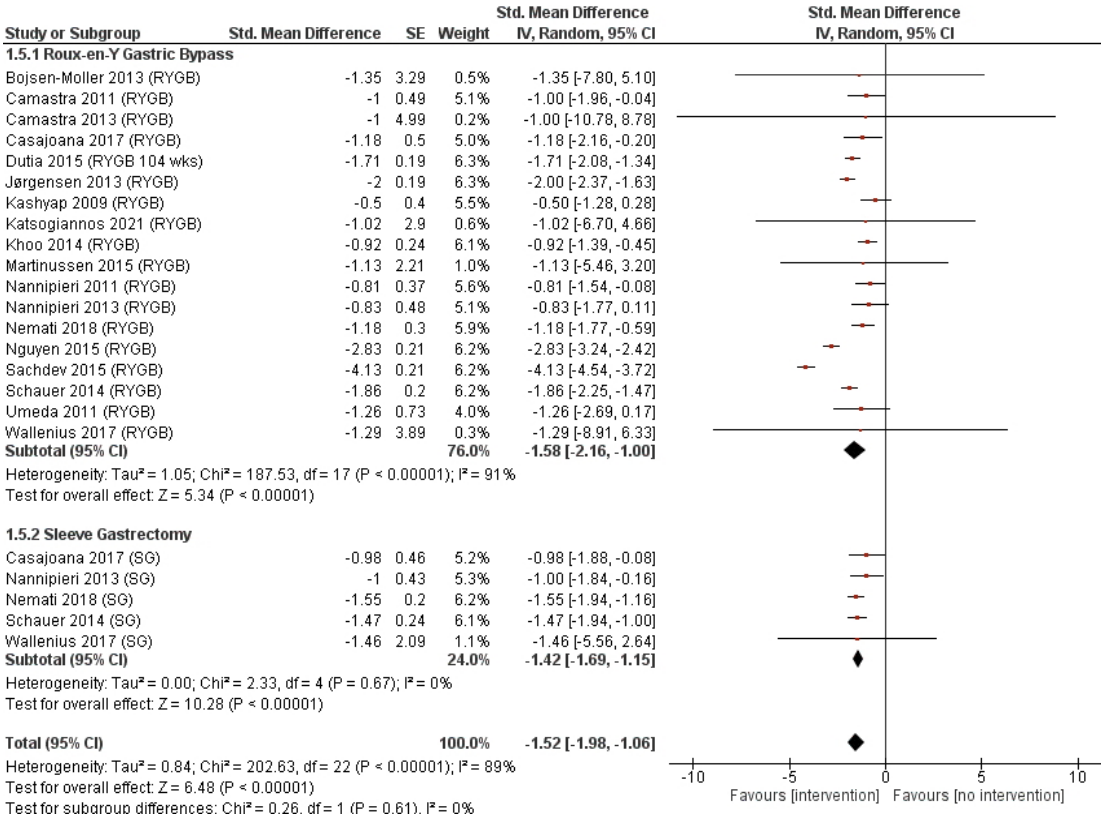

Figure 2. Clinical variable forest plot for HbA1c (mmol/mol): RYGB vs. SG.

5. Mechanistic Variables

5.1. FGF19

To being with, three studies were identified for FGF19 with RYGB being the intervention type. The results revealed an SMD of 1.29 (95% −11.64 to 14.21, $p = 0.85$). Further, two studies included assessing for FGF19 with SG as the intervention type; these results revealed an SMD of 2.18 (95% −10.55 to 14.91, $p = 0.74$). FGF19 is not affected with significance for either RYGB or SG. Heterogeneity was persistently observed across the two interventions. Furthermore, a statistical measurement for heterogeneity for RYGB and SG was indeterminate, $p > 0.05$ (Figure 3A).

5.2. GLP1

In total, 14 studies were included for the RYGB intervention. The results revealed an SMD of 0.68 (95% −0.39 to 1.76, $p = 0.21$). A further two studies were identified for the SG intervention, and these results revealed an SMD of −0.18 (95% −10.20 to 9.84, $p = 0.97$). Thus, GLP-1 has not demonstrated significance with either RYGB or SG (Figure 3B).

Heterogeneity was also observed across the two interventions; a statistical measurement for heterogeneity revealed an indeterminate result for both interventions ($p = 0.05$).

5.3. HOMA-B

Four studies were identified for HOMA-B for the RYGB intervention group (Figure 4). These results revealed an SMD of −0.67 (95% −0.77 to −0.57, $p < 0.00001$). Three studies for HOMA-B were identified for the SG intervention group, and these results revealed an SMD of −1.00 (95% −1.12 to −0.88, $p < 0.00001$). These results reveal that HOMA-B demonstrates statistical significance for effect in both the RYGB and SG intervention groups (Figure 3C).

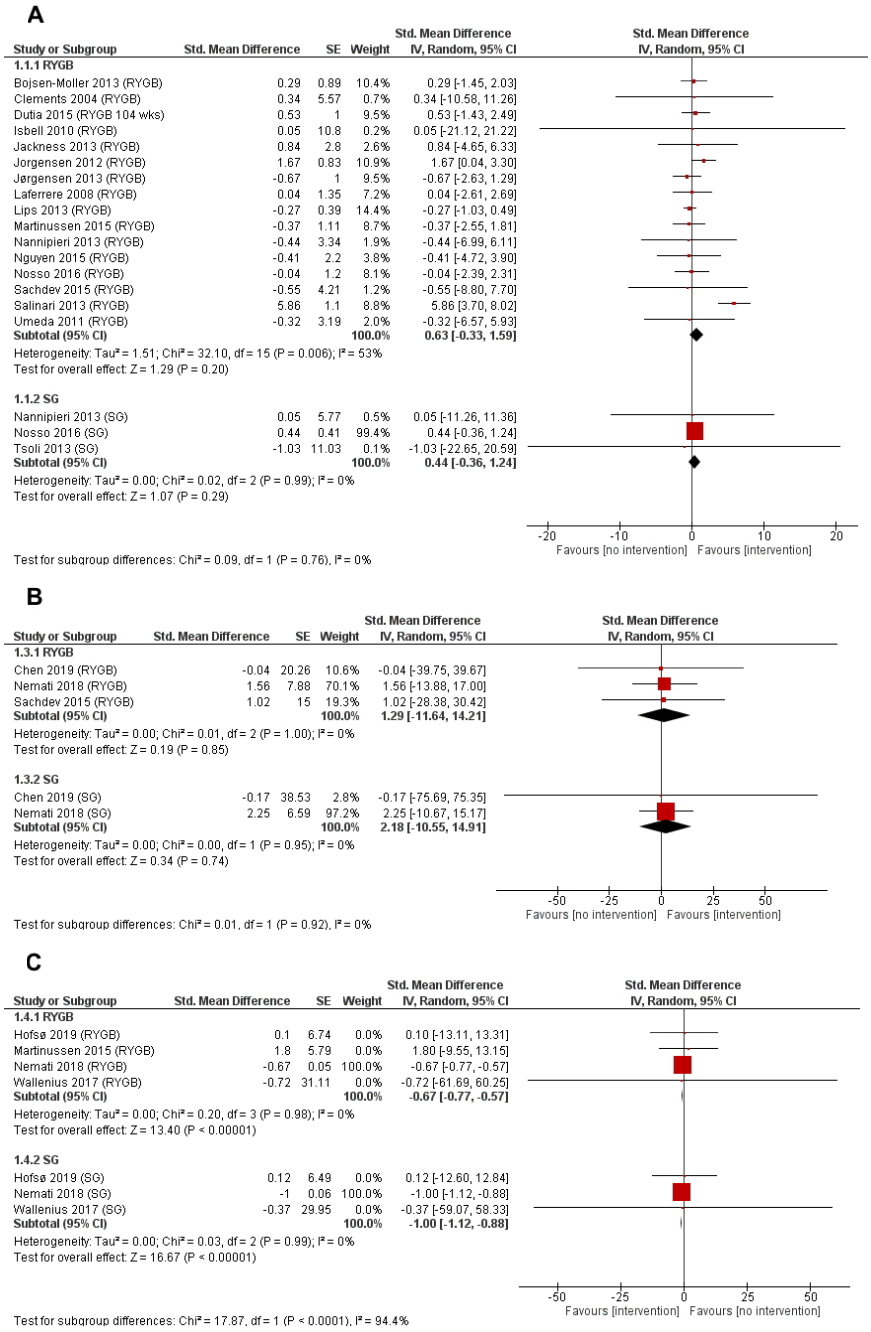

Figure 3. (**A**): Mechanistic variable forest plot for FGF19: RYGB vs. SG; (**B**): mechanistic variable forest plot for GLP 1: RYGB vs. SG; (**C**): mechanistic variable forest plot for HOMAB: RYGB vs. SG.

Further, heterogeneity is consistently observed for both intervention groups, with indeterminate significance ($p = 0.05$).

5.4. Adiponectin/Leptin/GIP/Ghrelin/Matsuda Index/Pyy

Individual mechanistic variables were also assessed if only one intervention provided sufficient data to explore outcomes to determine statistical significance. For the RYGB intervention group alone, results were as follows: five studies for adiponectin, with an SMD of 1.22 (95% 0.61 to 1.84, significant $p = 0.0001$); four studies for leptin, with an SMD of −1.40 (95% −7.37 to 4.58, non-significant $p = 0.65$); twelve studies for GIP, with an SMD of −0.12 (95% −1.31 to 1.06 with a non-significant $p = 0.84$); four studies for ghrelin revealed an SMD of −0.14 (95% −57.91 to 57.63, non-significant $p = 1.00$); four studies identified for the Matsuda index revealed an SMD of 3.00 (95% 0.77 to 5.23, significant $p = 0.008$); and

two studies for PYY, with an SMD of 0.48 (95% 7.86 to 8.82 with non-significant $p = 0.91$) (Figure 4).

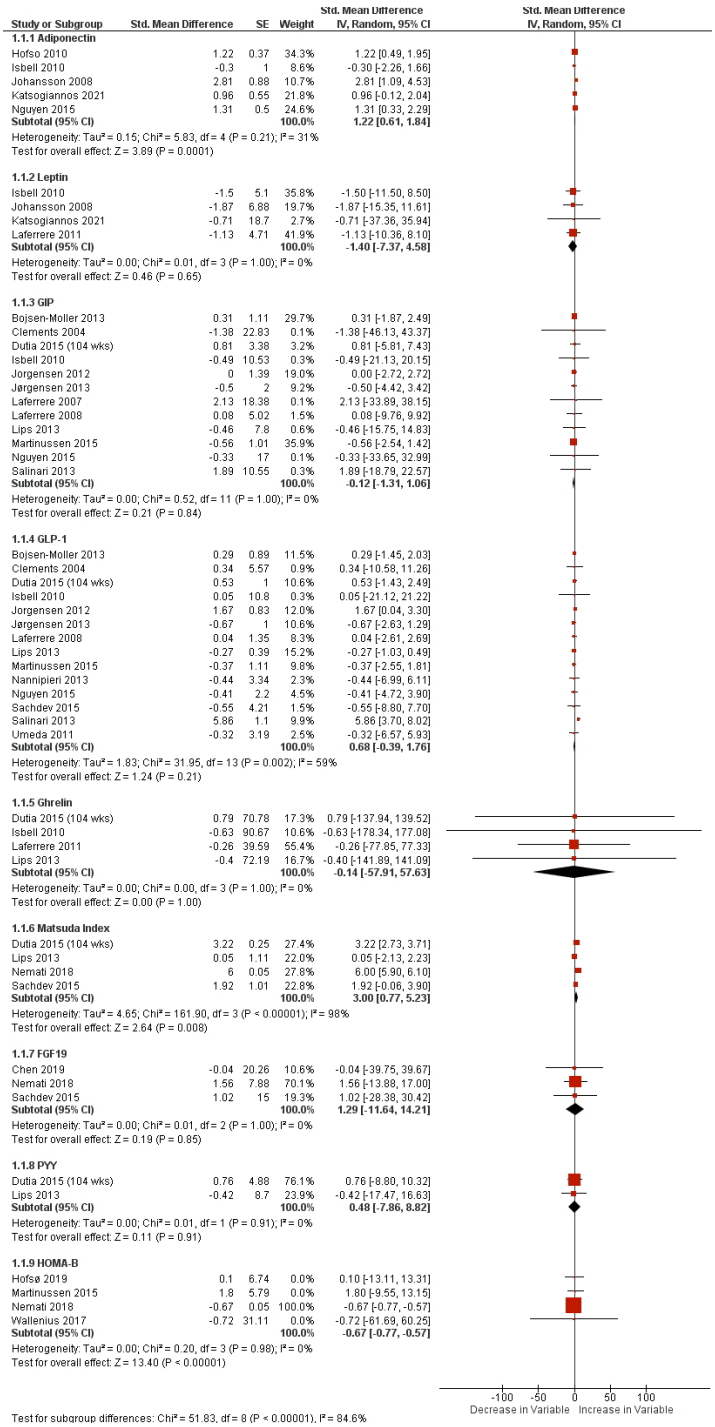

Figure 4. Mechanistic variable forest plot for RYGB.

For the SG intervention group, there were no additional mechanistic variables to be explored for statistical significance.

However, for the VLCD intervention group, there were additional mechanistic variables identified from our dataset, with results as follows (Figure 5): two studies for leptin, with an SMD of −0.92 (95% −6.91 to 5.06 with non-significant $p = 0.76$); three studies for GIP, with an SMD of −0.12 (95% −6.54 to 6.30 with a non-significant $p = 1.00$); three studies for GLP-1, with an SMD of −0.18 (95% −0.092 to 0.56 with a non-significant $p = 0.64$);

and three studies for Ghrelin, with an SMD of −0.11 (95% −91.01 to 90.79, non-significant $p = 1.00$).

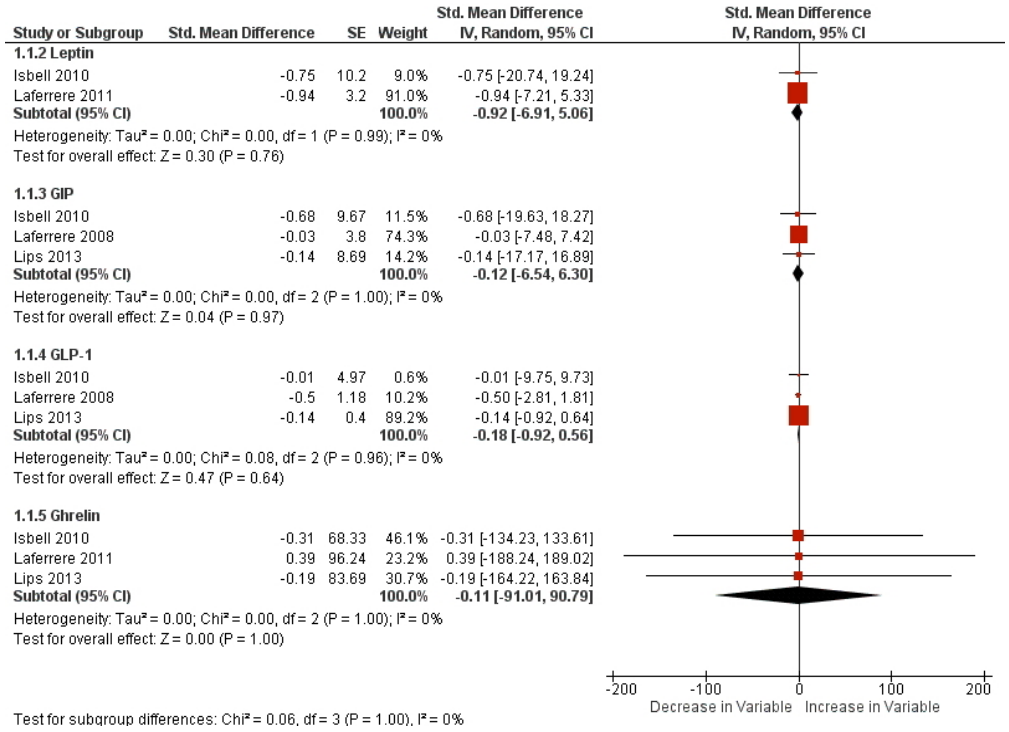

Figure 5. Mechanistic variable forest plot for VLCD.

5.5. Absolute Risk Reduction and Absolute Relapse Reduction (T2D)

We also determined the absolute risk reduction (ARR) for each of the assessed interventions. We counted the total number of individuals with diabetes for each intervention per study. Any entries that did not state both the follow-up period and absolute number of patients with diabetes were removed. This allowed a crude group-level ARR to be calculated (number of relapses per group/number of days follow up × 365.25). The study-based crude group-level ARRs were then divided by intervention type. An assessment of normality for each intervention was performed utilising the Shapiro–Wilk test using SPSS v28.0.1.1., which confirmed a normal distribution for each. A one-sample *t* test was undertaken, with a two-tailed significance threshold of $p < 0.05$ applied.

Crude ARR for relapse (Supplement S6) for the RYGB intervention group included 24 studies, with an SMD of −6.98 (95% −13.82 to −0.15) and a significant $p = 0.046$. SG included 12 studies, with an SMD of −2.75 (−5.88 to 0.39) and a $p = 0.080$. VLCD included three studies, with an SMD of −52.74 (95% −180.28 to 74.81 with $p = 0.217$).

For crude ARR (remission) for the RYGB intervention group, 24 studies were included, which revealed an SMD of 39.59 (95% 20.19 to 58.98 with $p = 0.000$). Then, for SG 12 studies were included, with an SMD of 33.36 (95% 11.85 to 54.88) and a p of 0.006. Then, VLCD had three studies included, with an SMD of 119.97 (05% −157.64 to 397.57, $p = 0.204$).

RYGB has a higher remission rate for DM than SG (both values < 0.05). VLCD lacked sufficient data. The normality assessments were then performed, which revealed parametric data justifying the single group *t* test that was selected for use.

6. Synthesis of Results

6.1. Risk of Bias Across Studies

Publication bias assessment was performed using weight as the selected variable, resulting in 26 studies represented by constituent datapoints.

On visual inspection, there is no evidence of missing data, particularly for negative results (Supplement S7). In addition, the distribution of data circumscribing the forest plot is approximately equal (14 and 12 for negatively and positively, respectively, valued meta-regression residuals) (Supplement S7) However, the calculated test for small-study effects was equivocal ($p = 0.25$). In addition, as the number of datapoints is less than 30, the statistical power to assess for publication bias utilising this approach is reduced (https://onlinelibrary.wiley.com/doi/full/10.1002/jrsm.1414#) (accessed 21 December 2024).

6.2. Sensitivity

The results from the sensitivity analysis for weight and HbA1c were equivocal, due to the absence of statistical significance for the ≤12-week subgroup ($p > 0.05$). However, BMI confirmed that a statistically significant difference existed between the intervention duration subgroups (Supplement S8). As such, the broad follow-up interval has potentially contributed to additional confounding of the presented results.

6.3. Risk of Intra-Study Study

There were 13 studies included for ROB2 assessment. The majority (10/13) were found to have an overall judgement of a high risk of bias, 2/13 returned some concerns for overall judgement and only 1 of the 13 returned with a global judgement of a low risk of bias.

RoB judgements performed on a domain-specific basis are presented within Supplementary Materials 6. Most trials were unblinded and therefore high risk predominated in the performance bias domain. Similarly, some trials did not conceal allocation or blind the outcome assessment, reflected, respectively, in the high risk of bias for both the selection bias and detection bias domains. The majority otherwise exhibited a low risk of bias for selection bias, attrition bias, reporting bias and other bias.

The aforementioned judgements were then reiterated into a study-specific format for ROB (Supplement S9). Hofso et al. [41] showed a low risk of bias across all seven domains. Schauer et al. had a high risk for four of the seven domains: selection bias, performance bias and detection bias. Of the 13 studies over a longer period included for this assessment, only 2 (Hofso et al. and Pournaras et al.) were of low/indeterminate risk for performance bias.

For the non-randomised manuscripts, the NOS tool was utilised. A total of 39 manuscripts were assessed using NOS, and 14 of these were deemed high-quality with a low risk of bias (7–9 stars), 24 were found to be fair quality (4–6 stars) and only 1 was found to be poor quality (1–3 stars). Broadly speaking, these results confirm that intra-study bias for the non-randomised manuscripts was not significant in terms of adverse implications.

7. Discussion

Our SRMA showed that both RYGB and SG were associated with comparable BMI, weight and HbA1c reduction, with associated improvement in beta-cell function as measured via HOMA-B. Intriguingly, fat mass loss was only significant for RYGB but not SG, while insulin measurements as well as levels of other metabolic hormone markers, e.g., GLP-1, GIP, ghrelin, FGF-19 and PYY, did not appear to be significantly changed after bariatric surgery. Markers of insulin resistance, such as adiponectin and the Matsuda index, were improved primarily in RYGB. Our data suggest that the primary mechanism for improved glucose metabolism contributing to diabetes remission is driven by BMI

loss with subsequent improvements in beta-cell function and insulin resistance. Therefore, at least in the early stages following bariatric surgery, no other metabolic mechanism to explain diabetes remission was observed based on this systematic review of clinical studies. Based on this, we would infer that at least in the early stages after bariatric surgery, caloric restriction inducing weight loss is the primary mechanism of improved glucose metabolism.

This conclusion is supported by previous studies, which have shown that the degree of caloric restriction and the amount of weight loss dictates the changes in glucostatic parameters. Wing et al. demonstrated that an 11% reduction in body weight with a 400 kcal/day diet resulted in a greater improvement in insulin sensitivity compared with the same weight reduction achieved over a longer period on a 1100 kcal/day diet [71]. Henry et al. [72] meanwhile demonstrated that on 330 kcal/day, most of the improvement in fasting plasma glucose occurred within the first 10 days of caloric restriction, preceding most of the weight loss. A subsequent study showed that improvement in beta-cell function is comparable between RYGB and calorie restriction, provided that the amount of calorie restriction is comparable with that of RYGB [14]. In a series of 204 patients whose marker of insulin sensitivity was measured after bariatric surgery, bariatric surgery was observed to improve the insulin resistance of T2D by ∼50% while at the same time causing a ∼30% decrease in BMI as early as 6 weeks after surgery [15]. This is explained by the fact that early after surgery, caloric restriction per se (whether achieved by lower intake as per restrictive procedures or reduced absorption as with malabsorptive operations) plays a major role in improving insulin action. The mechanisms beyond 2 years after surgery, however, are unclear. In a non-randomised study comparing gastric banding and RYGB in many non-diabetic patients [73], HOMA at 30 months post-surgery was similar, but RYGB induced a significantly larger weight loss than gastric banding.

The lack of evidence from this study linking metabolic hormones as important mediators of diabetes remission or improved glucose metabolism, while unexpected, based on the 'foregut' [74] and 'hind gut' [75] hypothesis, is in fact supported by other studies. Ghrelin levels after bariatric surgery, for example, have been inconsistent and unrelated to the ensuing changes in insulin sensitivity [76]. GLP-1 levels, meanwhile, while increased at 6 weeks post-surgery in normotolerant and impaired glucose-tolerant subjects, were not increased in T2D patients, despite similar improvements in insulin resistance and β-cell dysfunction [77]. Inconsistent levels of GIP hormones hae also been reported following gastric bypass operation in people with T2D [33,78]. The reasons for these inconsistencies in the effects of bariatric surgery on GLP-1 levels is unclear, but our systematic review indicates that these inconsistencies are likely to be partly driven by the heterogeneity of patient population, i.e., presence or absence of type 2 diabetes or impaired glucose tolerance, drug treatment, ethnic group and level of BMI and insulin resistance at baseline. Our study, however, did not identify an adequate number of studies investigating the role of bile acids (Pournaras, 2013) as a mediator of diabetes remission, nor did we find adequate evidence linking the role of any metabolic hormone as a mediator of diabetes remission beyond two years after bariatric surgery. Similarly, changes in gut microbiota following RYGB may influence host metabolism and may play a role in diabetes remission [79]. However, we did not explore this fully due to the limited number of mechanistic studies investigating its role in inducing diabetes remission. Further studies are clearly needed to investigate the role of gut microbiota changes as a mechanism of diabetes remission post-bariatric surgery.

We demonstrated that the crude annualised diabetes remission rate (ARR) was 6.98 ± 16.19 for RYGB ($p = 0.046$) vs. -2.75 ± 4.94 for SG ($p = 0.080$). Of particular importance is that RYGB was found to be superior for achieving a greater remission rate for diabetes mellitus as compared to SG, albeit both interventions were statistically signifi-

cant. VLCD did not generate enough data for this assessment and further research/review would be required for this. We also took the opportunity to perform an assessment of crude annualised diabetes relapse rate; statistically significant results were returned for RYGB (SD 16.19), illustrating that diabetes relapse can occur following bariatric surgery, which would be recognised as an adverse outcome, although we are unable to delineate why from these results. Results were not statistically significant for either SG or VLCD; in part, this will be due to the lack of data returned for these interventions. Our results are in concordance with preliminary data from a by-band sleeve study, which reported superior weight loss and HbA1c reduction with RYGB compared with SG or gastric banding [80]. Further, from reviewing the glucose (mmol/L) data we can see that all interventions both alone and pooled consistently demonstrate statistically significant results, supporting that glucose control is in indeed ameliorated through these interventions. Similarly, HbA1c (mmol/mol) also demonstrates statistically significant results for both RYGB and SG.

Throughout the literature, however, there were substantial sources of clinical and statistical heterogeneity; their magnitude was either considerable or identified as equivocal. There is a high risk in the overall judgements for the RoB2 assessments throughout the randomised-intervention manuscripts. High risk is especially noted within the performance bias, a direct reflection of studies not being blinded for participants and/or personnel. However, it must be noted that the interventions RYGB vs. SG could never be truly blinded by personnel as they are practitioners of the surgery, and similarly for consent purposes, one would expect participants to have awareness of which surgery modality they are listed for. Further, 38 of the 39 non-randomised manuscripts returned fair- to high-quality studies (i.e., lower risk of bias). As such, the certainty of the evidence needs to be considered within these caveats but should be considered as a fair assessment.

7.1. Study Limitations

The presented study of RCTs and NRS was undertaken in a systematic and formulaic approach as per Cochrane guidance. Despite this, limitations are still evident.

The number of identified trials at the synthesis stage is limited to 56, suitable for quantitative synthesis. Multiple sources of clinical heterogeneity within the published manuscripts are recognised, with non-uniformity of body composition variables: age, baseline BMI, baseline glycaemic control and other issues including pharmacotherapies, duration of follow-up, timepoint of performance of post-operative HbA1c. These factors may represent a contributory impact on the absence of statistical significance for some clinical and metabolic outcomes. Sensitivity analysis confirmed the impact of a large follow-up interval range (two or more weeks) on the effect size, and it should be considered as a potential confounder. It should be recognised that the broad follow-up period was agreed upon to attempt to retrieve as much available data as possible given the experimental outcomes that have been analysed.

Publication bias assessment utilising continuous variables returned equivocal results due to insufficient data. However, reassuringly the distribution across the graph is relatively even and one could infer that it would therefore be unlikely to be adversely affected by publication bias.

The representation of VLCD through a limited number of trials is a further limitation. Although when reviewing weight as an outcome, it is noted that RYGB is the only intervention demonstrating statistical significance, the three interventions pooled demonstrate statistical significance. This indirectly suggests that VLCD non-significance is due to factors beyond simply effect size/lack of data from the manuscripts studied.

Not included in the data extraction, as information was not readily provided throughout the manuscripts, is whether pharmaceutical agents were also prescribed during the

surgery recovery phase that may have influenced any glycaemic control outcome. In addition, our findings are conclusions that are limited to the short-term impact of bariatric surgery. Longer-term data are required to clarify which metabolic markers play an important role beyond weight loss in inducing diabetes remission.

7.2. Study Implications

The direct effects of RYGB, SG and VLCD with co-therapies on body composition and glycaemic control further supports the established knowledge on metabolic improvement following these interventions. There is potential to consider preferential application of RYGB as the intervention with the greatest evidence body for greater glycaemic control, as per our results. It must be noted that SG has a lower risk of complications, which was not assessed in this SRMA but would require it being a basis for clinical judgement for surgery selection.

Clinical recommendations could be considered using the Grade of Recommendations, Assessment, Development and Evaluation (GRADE) framework, a transparent framework for presenting evidence summaries.

Our results would support a stratified and individualised treatment approach to surgery selection amongst the bariatric population cohort with disordered glycaemic regulation.

7.3. Areas for Further Research and Recommendations

There was paucity of literature for pre-surgery VLCD or longer-term data after bariatric surgery at our synthesis stage. This requires further focus to delineate the impact that calorie restriction and metabolic hormone markers have both short and long term in these surgical candidates. As more experimental data are released with ongoing studies/trials, further SRMAs will be required to assess their wider influence.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/obesities5010014/s1, Supplement material S1–material S9. Supplement material S1: PRISMA checklist; Supplement material S2: MESH terms used for research question; Supplement material S3: Search strategy; Supplement material S4: Data Handling Procedures; Supplement material S5: Additional forest plots; Supplement material S6: Tables for Absolute Risk Relapse and Absolute Risk Remission; Supplement material S7: Funnel plot assessment for publication bias; Supplement material S8: Sensitivity analysis; Supplement material S9: Risk of Bias assessment.

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List of Abbreviations

ARR	Absolute risk reduction
BMI	Body mass index
CI	Confidence intervals
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
FGF-19	Fibroblast growth factor 19
GIP	Gastric Inhibitory Polypeptide
GLP-1	Glucagon-like peptide-1
HbA1c	Glycated Haemoglobin
HOMA-B	Homeostatic Model Assessment of Beta Cell Function
MESH	Medical Subject Headings
NOS	Newcastle Ottawa Scale
NRT	Non-randomised trial
PICOS	Population Intervention Comparator Outcome Study design(s)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PYY	Hormone peptide YY
RCT	Randomised controlled trial
ROB2	Risk of Bias 2
RYGB	Roux-en-Y Gastric Bypass
SE	Standard Error
SEM	Standard Error Mean
SG	Sleeve gastrectomy
SMD	Standard mean deviation
SRMA	Systematic Review and Meta-analysis
T2D	Type 2 diabetes
VLCD	Very Low-Calorie Diet
WHO	World Health Organization

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