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REVIEW

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Hypoglycemia rates and glycemic hormonal response after laparoscopic Roux-en-Y gastric bypass versus sleeve gastrectomy: a meta-analysis of comparative studies

Sotirios Artsitas[1,2*], Dimitrios Artsitas[3], Spyridon Smparounis[1,2], Dimitrios Theodorou[2,4] and George C. Zografos[2,4]

Abstract

Background This study aims to quantify the difference between Roux-en-Y gastric bypass (RYGB) and laparoscopic sleeve gastrectomy (LSG) concerning the incidence of post-bariatric surgery hypoglycemia (PBSH) and variations in glycemic homeostasis.

Main body of the abstract A literature search was conducted between July and August 2023. Inclusion criteria involved studies exclusively in the English language that comparatively investigated the occurrence of postoperative hypoglycemia in patients undergoing the above two bariatric approaches. A total of 16 studies, comprising data from 1806 patients, were identified and classified based on 39 primary and secondary outcomes pertaining to the period following the first postoperative semester. Our findings reveal that patients undergoing gastric bypass have a 50% higher risk of developing postoperative hypoglycemia compared to those undergoing sleeve gastrectomy. Moreover, this risk doubles when questionnaire data are taken into account. Lower glucose levels (MD = − 10.54 mg/dl, $CI_{95\%}$ = [− 16.63; − 4.45]) were observed in the RYGB group at 2 h after an oral glucose tolerance test (OGTT), which is considered a precursor to the development of PBSH. Higher zenith (MD = 49.11 mg/dl, $CI_{95\%}$ = [16.12; 82.10]) and lower nadir plasma glucose levels (MD = − 5.70 mg/dl, $CI_{95\%}$ = [− 10.03; − 1.37]) were also noted in the same group, with a wider glucose range (MD = 52.22 mg/dl, $CI_{95\%}$ = [18.25; 86.19]). Lastly, no differences were observed in insulin and C-peptide levels, glycosylated hemoglobin (HbA1c), as well as insulin sensitivity score (HOMA-IR).

Short conclusion Patients in the RYGB group are at least 50% more likely to develop postoperative hypoglycemia compared to those in the LSG group. Our analysis suggests a more unstable glycemic homeostasis mechanism, with a strong contribution from late dumping syndrome.

Keywords Roux-en-Y gastric bypass, Laparoscopic sleeve gastrectomy, Bariatric surgery, Hypoglycemia, Meta-analysis

*Correspondence:
Sotirios Artsitas
sotbike@hotmail.com
Full list of author information is available at the end of the article

Background

Bariatric surgery (BS) has gained prominence in recent years amidst the global obesity epidemic, with Roux-en-Y gastric bypass (RYGB) and laparoscopic sleeve gastrectomy (LSG) being among the most popular approaches (Roslin et al. 2014). However, as their utilization has surged, so too has the recognition of specific postoperative complications, particularly post-bariatric surgery hypoglycemia (PBSH) (Nannipieri et al. 2016). This condition, which is becoming increasingly acknowledged as a late complication primarily after RYGB, affects a significant proportion of patients within one to three years post-surgery. While the exact mechanisms behind PBSH remain complex and multifaceted, they are intrinsically tied to alterations in gastrointestinal anatomy and gastric innervation brought about by the surgical procedure. These alterations can accelerate gastric emptying, leading to rapid glucose absorption, hyperglycemia, and excessive insulin secretion, ultimately culminating in late hypoglycemia (HG). The role of incretin hormones such as glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) in the development of hypoglycemia remains a topic of controversy and ongoing research (Lee et al. 2022; Salehi 2023). It is crucial to note that severe HG can have perilous consequences, while even mild-to-moderate HG can significantly impact patients' health. Moreover, with the increasing number of women of childbearing age undergoing bariatric surgery, concerns regarding the potential repercussions of postoperative complications, including PBSH, are emerging (Rottenstreich et al. 2018). Additionally, the impact of BS on glucose regulation and insulin sensitivity is a subject of scrutiny, particularly as new surgical techniques like vertical sleeve gastrectomy (VSG), single anastomosis duodeno-ileal bypass (SADI-S), and duodenal switch (DS) come into focus (Roslin et al. 2014; Colquitt et al. 2014; Guimarães et al. 2023). As the landscape of BS evolves, understanding the complexities surrounding postoperative HG and its implications for patients becomes increasingly paramount (Lee et al. 2022, 2015; Varma et al. 2017). The primary objective of this systematic review and meta-analysis was to investigate the incidence of PBSH when comparing RYGB to LSG. The rationale for comparing these two approaches is associated with the greater availability of data, as they pertain to the two most frequently adopted BS procedures. From a methodological perspective, we conducted a comparative examination of fluctuations in glycemia, glycosylated hemoglobin (HbA1c), as well as hormonal responses related to postoperative insulin and C-peptide levels. Finally, we assessed the comparative effects between RYGB and LSG on weight loss (WL), body mass index (BMI), somatometric parameters, and insulin resistance.

Main text

Materials and methods

Literature search and study selection

Between July and August 2023, a comprehensive literature search was conducted for all published comparative studies between RYGB and LSG that contained data on the incidence of PBSH. The literature search was carried out across multiple databases, including "Medline—Pubmed", "Scopus", "ScienceDirect", "CENTRAL", and "Google Scholar". The protocol for conducting this systematic review was predefined and registered on the Prospero website (https://www.crd.york.ac.uk/prospero) under the identification number (ID): CRD42023461268 (Schiavo and "PROSPERO 2019). No modifications were made to the structure and content of the above protocol, as it was recently formulated.

The search strategy (SS) involved querying key terms such as "hypoglycemia", "gastric bypass", and "sleeve gastrectomy" in titles and abstracts, without any restrictions on publication year. Following the implementation of SS across each of the aforementioned databases, respective sets of studies were exported in ".ris" format to the Sysrev electronic platform (https://sysrev.com) (Bozada et al. 2021). The search strategy protocol is publicly available through PROSPERO at the URL: https://www.crd.york.ac.uk/PROSPEROFILES/461268_STRATEGY_20230906.pdf.

Inclusion criteria encompassed randomized or non-randomized studies, exclusively in the English language, non-duplicate publications, with available full text and comparative data between RYGB and LSG. The latter was required to pertain to the frequency of hypoglycemic episodes, the comparative analysis of plasma glucose concentrations, or similar investigations into insulin levels at least six months post-BS. Permissible methods for determining HG included specialized questionnaires (Q), oral glucose tolerance test (OGTT), mixed-meal tolerance test (MMTT), and continuous glucose monitoring (CGM). Questionnaires were allowed to adopt or not adopt the Whipple's triad, which includes symptoms of hypoglycemia, low plasma sugar levels, and symptom relief after glucose administration (Cifuentes et al. 2022). Conversely, non-comparative analyses, studies lacking available text or data, as well as studies describing outcomes from a single BS approach, were excluded at this stage.

Evidence acquisition and quality assessment

The process of applying the inclusion criteria was carried out independently by two investigators (SA and DA) within the integrated environment of Sysrev, and the relevant project is available at the URL: https://sysrev.com/p/123461. In summary, this process involved evaluating

each study resulting from the initial literature search against a set of predefined parameters, with the aim of making the final decision regarding inclusion. However, the set of analyses resulting from the above process was not homogeneous in terms of reported outcomes. Consequently, two members of the authoring team (DA and SS) undertook the task of categorizing the studies based on a series of primary and secondary variables, as described below. The final tabulation of the isolated records was done in ".csv" files based on the outcome of interest. Missing data pertained to a total of 25 patients, with 15 belonging to the experimental group (RYGB) and 10 to the control group (LSG).

Subsequently, the extraction of necessary data for the upcoming analysis was performed without the use of automation tools. In parallel with tabulating numerical data into appropriate ".xlsx" files, metadata was also recorded, including the author's name, publication year, method of hypoglycemic episodes detection, study design, implementation of a patient matching protocol, the number of referral centers involved, study durations, deviations in baseline characteristics, and other pertinent information. The recording of the aforementioned data was carried out by three reviewers (SA, DA, SS) collaboratively. These same members of the writing team were also entrusted with the process of qualitative assessment of the final set of studies incorporated, utilizing both the Newcastle–Ottawa Scale (NOS) and the ROBINS-I tool. The adoption of two methods of qualitative assessment was undertaken to mitigate confounding in terms of risk of bias (ROB) stratification, as these two scaling modalities complement each other.

Outcomes

As primary outcomes, the following were considered: the number of patients who experienced at least one hypoglycemic event after 6 months following BS, for each of the four diagnostic modalities that were incorporated (OGTT, MMTT, CGM, Q). Within the same group of variables, fasting glucose (mg/dl) and insulin levels (pmol/l) were analyzed, along with changes from baseline values in each case. Additionally, within the framework of OGTT, glycemia and insulin levels were also investigated at one and two hours after oral glucose loading, along with the corresponding changes from baseline levels. As for the secondary outcomes, comparative analyses were conducted on changes in body weight (Kg) and BMI (Kg/m^2), as well as variables including the proportion of males (n), 10-day average of hypoglycemic events, glycosylated hemoglobin (%), waist circumference (cm), and excess body weight loss (%). Furthermore, values for maximum (peak) and minimum (nadir) glycemia (mg/dl) and the time to peak glycemia (min) were also examined. Subsequently, a comparison concerning insulin resistance was performed using the HOMA-IR (Homeostasis Model Assessment-Insulin Resistance) index, along with changes from baseline for each surgical approach. In accordance with the above, postoperative C-peptide levels (ng/ml) were analyzed for the period following the first postoperative semester after BS, along with their respective changes from baseline. Finally, a comparative investigation of glucose and insulin ratios concerning 1-h/fasting and 1-h/2-h concentrations was conducted.

To transform the original data into a suitable format for analysis, a series of unit conversions and assumptions were made. Initially, in cases where data were available in the form of "median–interquartile range (IQR)", the rule of thumb was used to convert it into the form of "mean–standard deviation (SD)", in order to facilitate the subsequent meta-analysis process. Lastly, for the determination of the mean differences from baseline, the relevant equations for expected value and variance were employed, as described by Cheng and Peace in their book "Applied Meta-analysis with R" on pages 128–129 (Chen and Peace 2013). With the assistance of these transformations and assumptions, the analysis of the entire dataset that was isolated was made possible, appropriately shaping study groups for each outcome under investigation.

Statistical analysis

For the purpose of the present study, an array of variables was analyzed, as previously mentioned, and categorized into primary and secondary outcomes based on their relevance to hypoglycemic events and glycemic hormonal control. Within the scope of primary outcomes, a comparative investigation was carried out concerning the incidence of PBSH at the patient population level when comparing RYGB versus LSG. The diagnostic methods for hypoglycemic events that were included encompassed OGTT, MMTT, CGM, and the application of questionnaires (Q). Generally, the threshold for hypoglycemia detection for quantitative methods was set at 40–50 mg/dl, whereas for questionnaires, diagnosis relied on the presence of typical glycopenic (i.e., weakness, fatigue, sensation of warmth), neuroglycopenic (i.e., confusion, cognitive failure, seizure, coma), and vasomotor (i.e., hypotension, palpitations, syncope) symptoms (Michaels et al. 2017).

Relative risk (RR) was selected as the effect size for the aforementioned individual analyses, determined using the Mantel–Haenszel (MH) method (Kaya et al. 2021). The second group of parameters investigated as primary outcomes included only continuous variables. Specifically, a comparative assessment was made regarding fasting glucose and insulin levels, as well as the change in each from baseline, utilizing mean difference (MD) as the

effect size. To determine and extract the overall effect, the Hartung–Knapp (HK) adjustment was adopted (Siemens et al. 2021). Lastly, remaining within the framework of primary outcomes investigation, plasma glucose and insulin levels during the OGTT were comparatively analyzed. The time points for determining the corresponding concentrations were at one and two hours after oral glucose intake. In this case, the respective differences from baseline levels for each time point and individual parameter were examined. It is worth noting that, for determining the overall effect size, MD was once again employed, with its calculation being modified according to the HK adjustment.

On the other hand, as secondary outcomes, changes in body weight (WL), BMI, the percentage of glycated hemoglobin (HbA1c), and waist circumference (WC) were investigated. As with all continuous variables, MD was employed as the effect size when comparing between RYGB and LSG. Furthermore, a comparative analysis was conducted for the number of male patients for each surgical approach using the odds ratio (OR) according to the MH method (Smolinsky 2019). Additionally, the incidence of hypoglycemic episodes over a 10-day period was assessed, utilizing RR as the effect size in this case. The remaining parameters analyzed were continuous variables, and thus, MD was used as the effect size, with its estimation being modified according to HK adjustment as above.

To assess heterogeneity, statistical parameters including Higgins I^2, H-statistic, and Cochran's Q were determined. In case of detecting statistically significant heterogeneity, a prior decision was made to adopt a random effects model (DerSimonian–Laird random effects pooling method) to account for inter-study variation (τ^2), estimated via the restricted maximum likelihood method (REML) (Oskolkov 2020). Beyond meta-analysis (MA) of pooled data, subgroup analysis (SGA) or sensitivity analysis (SA) followed, in cases of forming appropriate study groups or excluding individual studies, respectively. Subgroups were defined based on publication year with a cutoff point in the year 2018, the application of a patient matching protocol, the inclusion or exclusion of patients with type 2 diabetes mellitus (DM2), and in accordance with the risk of bias (ROB) category based on the ROBINS-I tool. In addition to the above, it was predetermined to apply meta-regression analysis (MRA) if the number of studies exceeded 8, to facilitate the extraction of a robust regression line, adequately representing the comparative effect. The two moderators used in MRA pertained to the publication year and the number of quality stars derived from the NOS scale during the relevant assessment. In this case as well, the model adopted for estimating the effect in MRA was that of the REML. Finally, concerning the assessment of publication bias (PB), appropriate radial plots were generated with concomitant application of the Egger's test to evaluate its statistical significance (Mathur and VanderWeele 2021).

The composition of the present meta-analysis adhered to the relevant guidelines provided on the PRISMA website at the URL: http://prisma-statement.org/Extensions/Protocols, in order to ensure compliance with the PRISMA 2020 Checklist (Sohrabi et al. Apr 2021). The study results are presented as the respective effect size accompanied by the 95% confidence interval ($CI_{95\%}$), utilizing a confidence level of $\alpha = 0.05$. Data analysis was conducted using the R programming language in version 4.3.1 (Berry et al. 2021). The results of the analysis are appropriately presented in the form of forest plots and summary tables. To ensure the required transparency for the reproducibility of the above, the complete dataset pertaining to both primary and secondary outcomes is provided in ".csv" format, while the corresponding analytical code is available in ".txt" files within a GitHub repository, accessible via the URL: https://github.com/sotbike/SILENUS.git (Batoun et al. 2023).

Results

Study retrieval

Based on the literature search process and the application of inclusion criteria within the Prospero framework, the PRISMA flowchart depicted in Fig. 1 was developed. Initially, by applying the criteria comprising the SS presented above, a total of 276 studies were identified. Among these, 19 were retrieved from the Google Scholar database, 52 from Medline (Pubmed), 10 from the Cochrane database (CENTRAL), 175 from Scopus, and 20 from ScienceDirect. Seven of them were not in English and were therefore excluded, while 82 were eliminated as duplicate studies, and 153 due to inappropriate titles, abstracts, or content. Subsequently, 34 records were screened for available text or data. Out of these, ten were excluded as it was not feasible to retrieve their text. Of the remaining 24, two did not provide data in a suitable format for statistical analysis. Ultimately, among the 22 studies examined, two were excluded as systematic reviews or meta-analyses, and another four were also excluded as they did not contain comparative data, resulting in a final set of 16 studies. From these, after initially extracting metadata regarding their title, author, publication year, and design, a qualitative assessment followed based on the NOS scale and the ROBINS-I tool. Subsequently, the initially extracted studies were grouped based on the primary and secondary variables described earlier in the "Outcomes" subsection of the "Materials and methods" section. During this process, it was permissible for each study to belong to more than

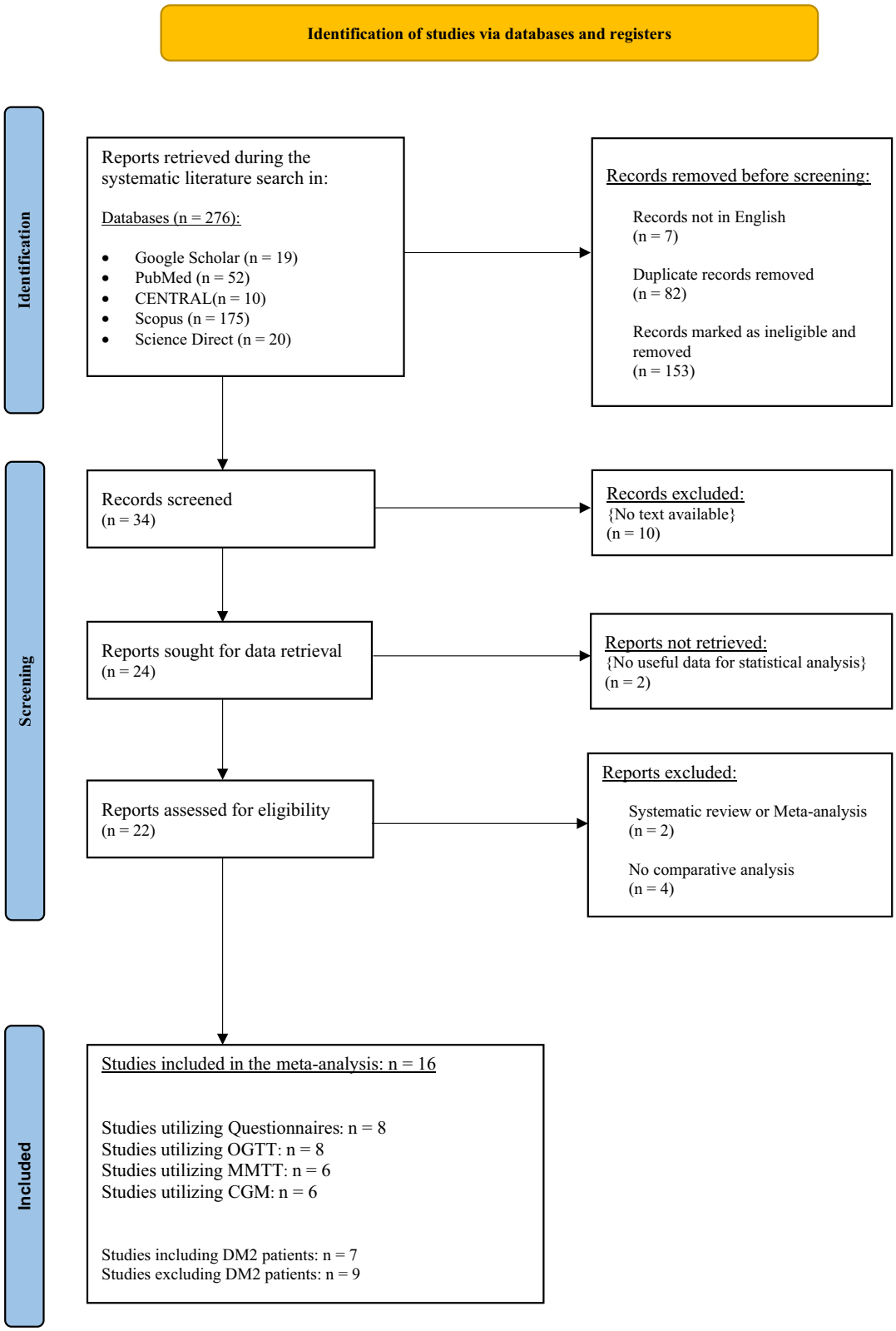

Fig. 1 Flow chart of studies according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Abbreviations: CENTRAL: Cochrane Central Register of Controlled Trials, OGTT: oral glucose tolerance test, MMTT: mixed-meal tolerance test, CGM: continuous glucose monitoring, DM2: type 2 diabetes mellitus

one outcome-driven study group. In the 16 records that formed the core of the analysis we conducted, data for a total of 1806 patients were included, of which 1237 belonged to the experimental group (RYGB) and 569 to the control group (LSG).

Study demographics

In this subsection, we will present the analysis of the metadata that were captured for the entire set of 16 isolated studies. Regarding the qualitative assessment according to the ROBINS-I tool, the presentation of results was conducted using the statistical package "Robvis" for R (McGuinness and Higgins 2021). Figure 2 displays the relevant traffic light plot for the evaluation of the 16 studies in each of the seven domains of the tool. In Fig. 3, the summary plot presents the percentages of analyses falling into each category of ROB (ROBINS-I: Low, Moderate, Serious, and Critical) and within each domain (i.e., confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported results). From this diagram, it is evident that approximately 5% of the studies belong to the "ROBINS-I: Low" cluster, 35% to "ROBINS-I: Moderate", another 35% to "ROBINS-I: Serious", and lastly, 25% to "ROBINS-I: Critical". The optimal quality performance of the included studies was found to be in the domain of ROB due to deviations from intended interventions, where it was observed that the original surgical treatment protocol was mostly followed across all analyses. On the other hand, the lowest performance was noted in the domain of ROB due to confounding, which was attributed to the availability and inclusion of mostly non-patient-matched studies and a single randomized controlled trial (RCT) (Capristo et al. 2018). The identification of qualitative differences among studies was also carried out at the subgroup level based on the publication year, the application of patient matching, and the inclusion or exclusion of patients with DM2. Additional file 1: Figures S1, S2, S4, S5, S7, S8, and Additional file 1: Figures S3, S6, S9 present the corresponding traffic light plots and summary plots, respectively. From the analysis of the above diagrams, a better-quality profile emerged for studies published before 2018, those adopting patient matching, as well as

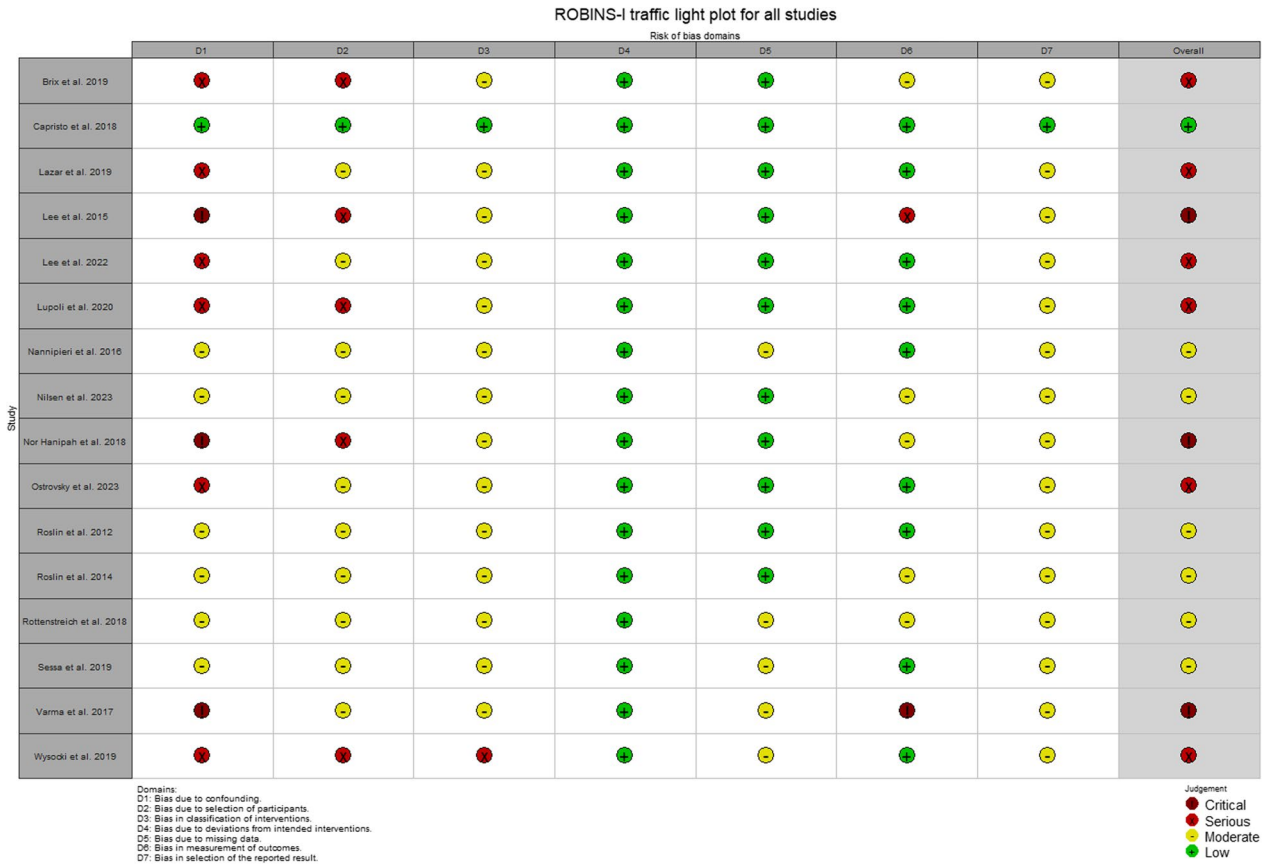

Fig. 2 ROBINS-I traffic light plot for the pooled set of studies that were isolated, where their risk of bias class is cited for each of the 7 domains of the tool. Abbreviations: ROBINS-I: Risk of Bias in Non-randomized Studies of Interventions

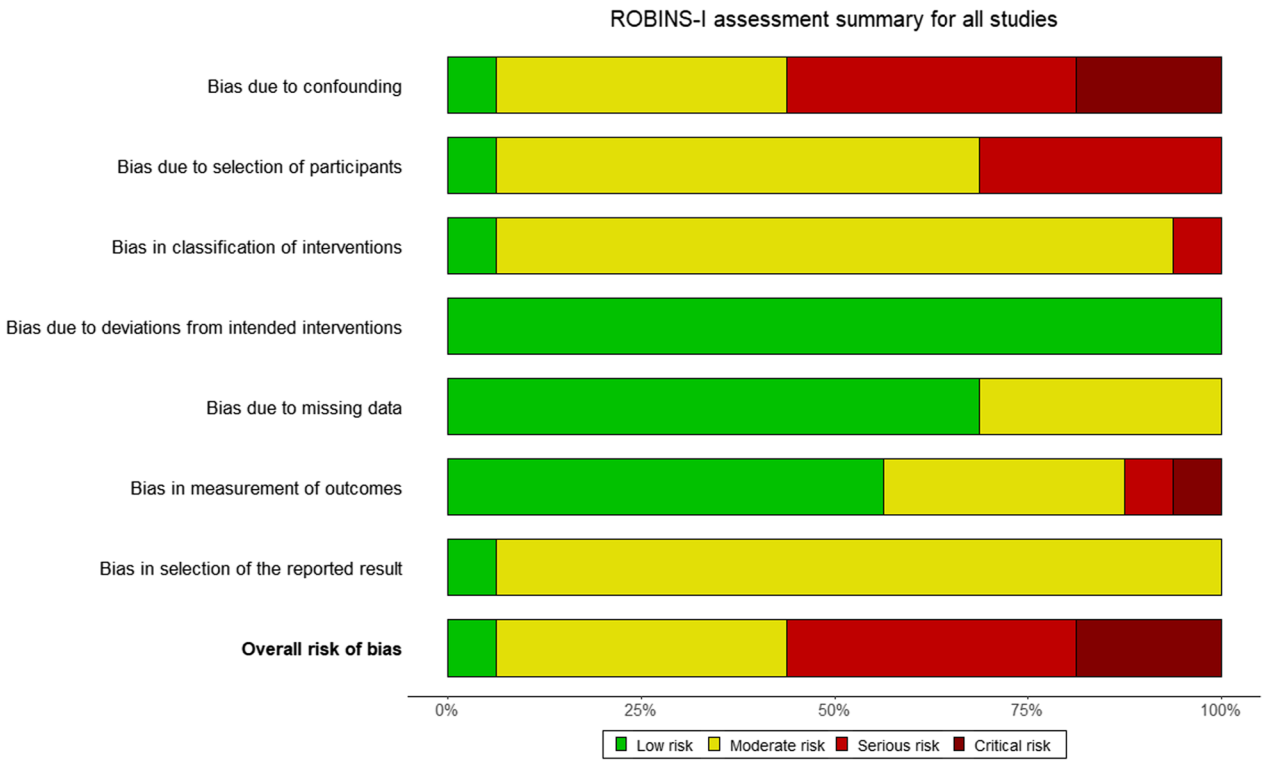

Fig. 3 ROBINS-I summary plot showing the percentages of studies for different risk of bias levels across the 7 domains of the tool, based on all available records. Abbreviations: ROBINS-I: Risk of Bias in Non-randomized Studies of Interventions

those that did not include diabetic patients. Finally, the relevant ROBINS-I assessment forms for the entire study set are available as supplementary material (Additional file 2: ROBINS-I forms).

Furthermore, regarding the country of origin of the utilized data, Fig. 4 presents the related pie charts highlighting the proportional distributions, both at the study level and within the population of patients corresponding to each record. From these diagrams, it is evident that the majority of the available data primarily originated from the USA and continental Europe. The same data are visually represented in a more illustrative manner in the form of map charts in Additional file 1: Figure S10.

Additionally, concerning the subgroups we defined earlier, Figs. 5 and 6 present the respective percentages belonging to each category, both at the study level and within the patient populations. In Fig. 5a, it becomes evident that the data were uniformly distributed at the study level between publications before and after 2018. On the other hand, 74% of the patient-level data were derived from studies published before 2018. Figure 5b reveals that 88% of the data at the study level and 93% at the patient level originated from studies without patient matching. Subsequently, from the interpretation of Fig. 6a, it emerges that the total number of studies was almost uniformly distributed among those that included or did not include diabetic patients in their populations. At the patient level, the majority of the analyzed data (63%) came from studies that included DM2 patients. Figure 6b presents pie charts corresponding to the data utilized at the study-patient levels according to the ROB class. More specifically, in both levels, data concerning studies classified as "ROBINS-I: Low" account for approximately 6% of the total. On the other hand, the "ROBINS-I: Critical" class concerned 18.5% of the studies, which, however, corresponds to 55% of the total patient population.

Finally, Additional file 1: Figures S11, S12, and S13 depict the timelines of activity concerning all the included analyses, according to the previously described subgroups. Through careful examination of the above charts, we can draw the conclusion of consistent representation of the period from 2010 and onwards, without significant deviations among the different subgroups examined in each case. Hence, it is reasonable to assume the adequate coverage of the last decade from the perspective of the available data utilized for conducting the present analysis.

With regard to the surgical technique, the interventions in the entirety of the studies that were isolated were generally standardized. More specifically, RYGB involved

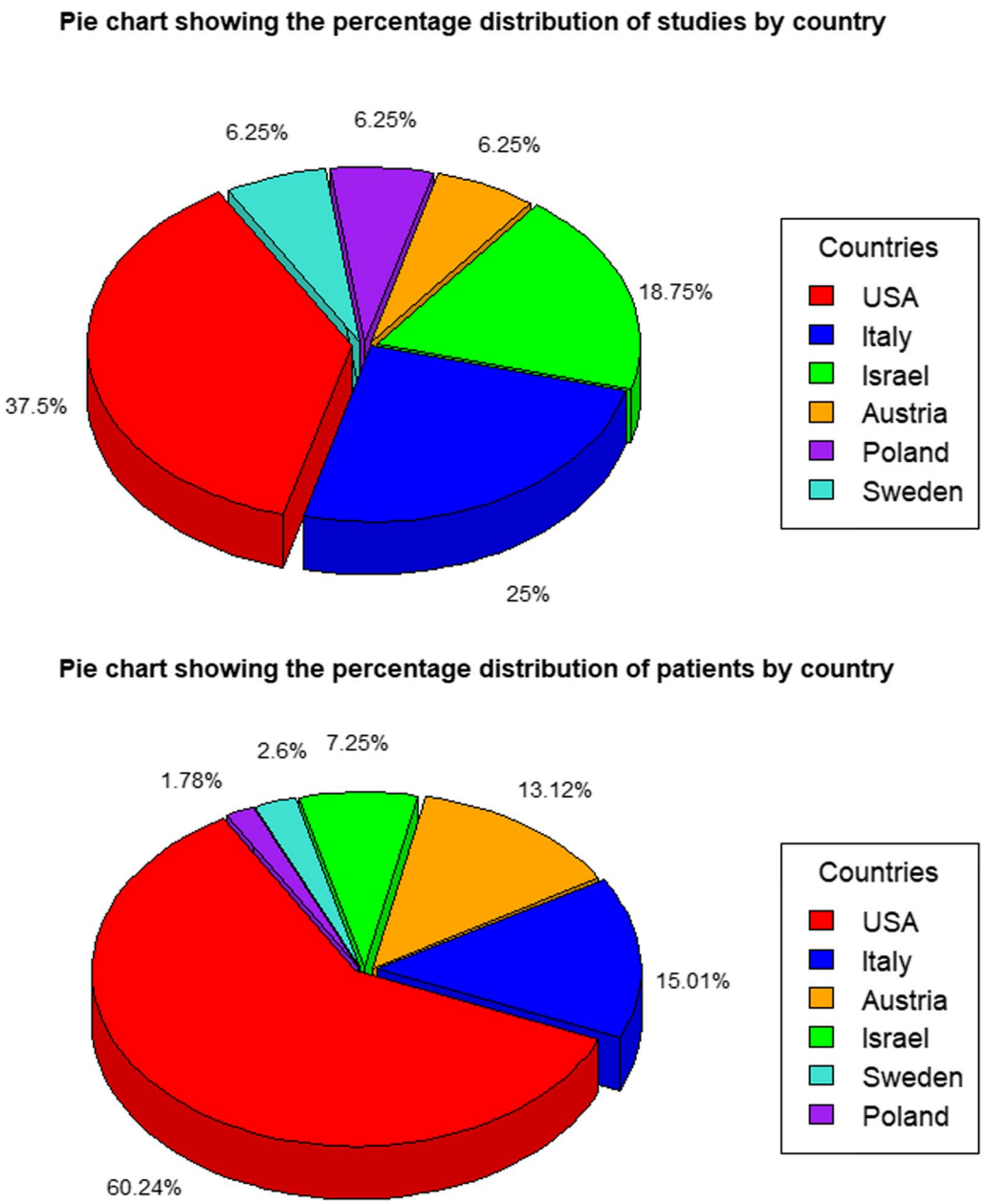

Fig. 4 Pie charts illustrating the percentage distribution of data at the study and patient levels based on the country of origin

the formation of a gastric pouch of 20–25 cc, an alimentary (Roux) limb of 150 cm, and a biliopancreatic limb of 75–100 cm. The sequence of steps in RYGB generally varied among the different studies. On the other hand, LSG included the use of a bougie with a diameter of 34–40 Fr, with the starting position of the gastrectomy located 3–6 cm proximally to the pylorus, and the residual gastric volume was approximately 100 cc. In this case, the sequence of LSG steps was relatively uniform across the various investigations. With regard to the standardization of PBSH diagnosis, in OGTT glucose loading involved 75–100 g, with measurements conducted over a period of 2–3 h. On the other hand, in MMTT oral loading was performed using regimens of 350 kcal, consisting of 50 g of carbohydrates, 12–13 g of proteins, and 11 g of fats, with measurements taken within a time frame of 2–4 h. Moreover, CGM was conventionally carried out using certified equipment for the precise recording of sugar levels in the interstitial fluid of subcutaneous tissue, subsequently allowing for the estimation of plasma

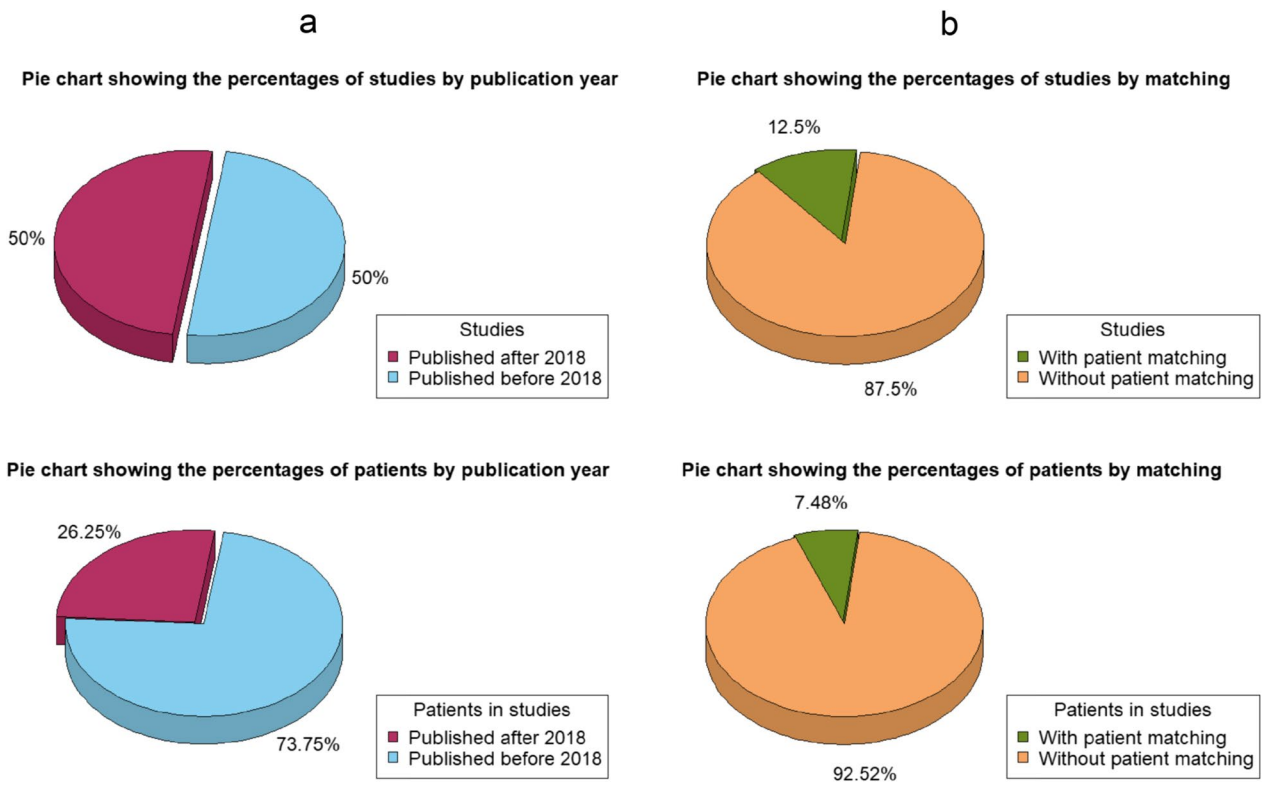

Fig. 5 Pie charts depicting the percentage distribution of available data in study and patient levels, stratified by publication year (**a**) and the implementation of patient matching (**b**)

glucose concentrations through the utilization of specialized algorithms. These measurements were conducted over a span of 5–10 days, with the threshold for detecting PBSH set at 40–50 mg/dl. Lastly, the questionnaires (Q) analyzed were primarily derived from the Edinburgh Hypoglycemia Symptom Scale (EHSS), with or without the incorporation of Whipple's triad. Table 1 provides an overview of the final study set, accompanied by essential metadata, including author names, publication year, country of origin, study design based on patient matching, number of referral centers involved, duration of activity, quality rating based on NOS and ROBINS-I tool, as well as any discrepancies in baseline characteristics between the compared patient populations.

Meta-analysis of primary outcomes

At this point, we are going to present the results of the MA pertaining to the primary outcomes as defined in the relevant "Outcomes" subsection of the "Materials and methods" section. The first group of these variables essentially involves frequentist data concerning the number of patients who developed at least one episode of PBSH after the first postoperative semester. Individual subanalyses are associated with the method of hypoglycemic event detection during the RYGB vs. LSG comparison. Figure 7 presents the corresponding forest plots under a random effects model with the application of the MH method to determine the RR. During the application of the OGTT for the above comparison, the following result emerged: RR = 1.50 with a $CI_{95\%} = [1.20; 1.87]$, as depicted in Fig. 7a. Regarding heterogeneity, it was: $I^2 = 0\%$ with a $CI_{95\%} = [0.0\%; 79.2\%]$, $\tau^2 = 0$ with a $CI_{95\%} = [0.0000; 0.3278]$, $H = 1.00$ with a $CI_{95\%} = [1.00; 2.19]$, $Q = 1.49$ with degrees of freedom: $df = 4$, and p value = 0.8276, indicating the absence of a significant impact. The aforementioned finding demonstrates a statistically significant 50% increase in the relative risk of developing PBSH after RYGB compared to LSG. Figure 7b displays the forest plot corresponding to the MMTT method, where the result was: RR = 1.26 with a $CI_{95\%} = [0.86; 1.85]$ (heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $H = 1.00$, $Q = 0.32$, $df = 1$, p value = 0.5737). In Fig. 7c, the corresponding forest plot for the CGM method is presented, with the result being: RR = 1.29 with a $CI_{95\%} = [0.55; 3.02]$ (heterogeneity: $I^2 = 75.4\%$ with $CI_{95\%} = [32.0\%; 91.1\%]$, $\tau^2 = 0.609$ with $CI_{95\%} = [0.065; 13.741]$, $H = 2.02$ with $CI_{95\%} = [1.21; 3.35]$, $Q = 12.20$, $df = 3$, p value = 0.0067). The analysis of the MMTT and CGM methods suggests a trend toward an increased risk (an additional 20–30%) of postoperative hypoglycemic events with the adoption of RYGB over

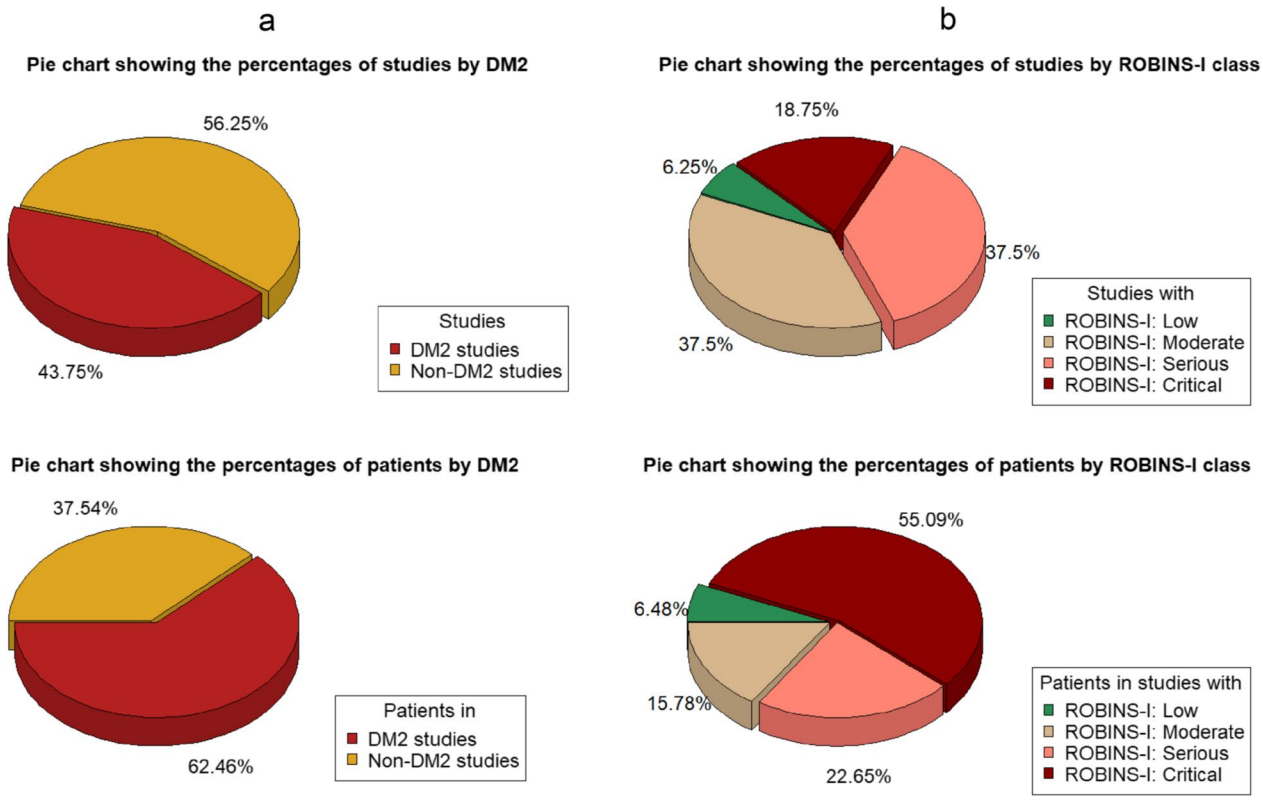

Fig. 6 Pie charts depicting the percentage distribution of available data in study and patient levels, categorized by the involvement of DM2 patients (**a**) and ROBINS-I class (**b**). Abbreviations: DM2: type 2 diabetes mellitus

LSG, albeit without achieving statistical significance. The last method utilized for HG event detection involves the use of questionnaires (with or without the Whipple triad adoption), and the corresponding forest plot is presented in Fig. 7d. The analysis yielded the following result: RR = 1.99 with a $CI_{95\%}$ = [1.38; 2.86] (heterogeneity: I^2 = 42.2% with $CI_{95\%}$ = [0.0%; 78.7%], τ^2 = 0.071 with $CI_{95\%}$ = [0.000; 2.614], H = 1.32 with $CI_{95\%}$ = [1.00; 2.17], Q = 6.92, df = 4, p value = 0.1403). From the above, it becomes evident that there is a twofold higher risk of developing PBSH after RYGB compared to LSG, and this finding is statistically significant. The assessment of PB was based on the radial plots depicted in Additional file 1: Figure S14 for each diagnostic modality, highlighting a significant impact when CGM data were utilized. Additional file 1: Figure S15 presents the SGA and SA for OGTT. Sub-analyses revealed that the main drivers for the previously described results were studies published before 2018, those without patient matching, those excluding DM2 patients, and those of "ROBINS-I: Moderate" class. In Additional file 1: Figure S16, individual analyses for the CGM method are highlighted, with no statistical significance observed in any of the examined cases. Finally, in Additional file 1: Figure S17, the above process for questionnaire application in PBSH detection is presented. In this case, a statistically significant higher relative risk (RR = 2.31 with a $CI_{95\%}$ = [1.75; 3.05]) for postoperative HG events with RYGB compared to LSG was evident from studies published before 2018. To assess the PB, appropriate radial plots were generated for each method (i.e., OGTT, MMTT, CGM, Q). The corresponding plots are presented in Additional file 1: Figure S18. In cases where fewer than 10 studies were included, the evaluation was performed visually by comparing the deviation of the dashed regression line corresponding to the data with the solid line representing the Egger's test application, as integrated into each diagram. Therefore, when assessing the emerging diagrams, significant deviation is observed only for the OGTT method, a finding that should be considered when striving to arrive at secure conclusions.

The second group of primary variables includes plasma glucose and insulin concentrations, as well as their corresponding changes from the respective baseline values. Figure 8 presents the forest plots corresponding to fasting glucose levels (mg/dl) and the change from baseline, as well as fasting insulin levels (pmol/l) along with their corresponding changes. However, from the review of the

Table 1 Table of included studies, detailing title, author's name, publication year, country of origin, methodology and design, duration of activity, quality assessment, patient population in each arm of the comparison, and baseline differences between populations

Title	Author	Type	Design	Population	Duration	Quality	Baseline
Frequency of hypoglycemia after different bariatric surgical procedures	Brix et al. (2019) (Austria)	Single center without patient matching	OGTT, Q, MMTT no DM2 pts included	$N_{exp}=175$ $N_{ctrl}=62$ (Total: 237)	729 days (1/1/2017–31/12/2018)	NOS: 5 ROBINS-I: Serious	RYGB: higher BMI
Incidence of hypoglycemia after gastric bypass vs. sleeve gastrectomy: A randomized trial	Capristo et al. (2018) (Italy)	Single center with patient matching	CGM, OGTT, MMTT, Q no DM2 pts included	$N_{exp}=59$ $N_{ctrl}=58$ (Total: 117)	760 days (1/12/2012–31/12/2014)	NOS: 9 ROBINS-I: Low	No baseline differences
Symptomatic and asymptomatic hypoglycemia after three different bariatric procedures: A common and severe complication	Lazar et al. (2019) (Israel)	Single center without patient matching	MMTT, Q, CGM no DM2 pts included	$N_{exp}=16$ $N_{ctrl}=15$ (Total: 31)	364 days (1/8/2017–31/7/2018)	NOS: 5 ROBINS-I: Serious	RYGB: pts with more education years
Prevalence of and risk factors for hypoglycemic symptoms after gastric bypass and sleeve gastrectomy	Lee et al. (2015) (USA)	Single center without patient matching	Q DM2 pts included	$N_{exp}=355$ $N_{ctrl}=95$ (Total: 450)	1491 days (1/8/2008–31/8/2012)	NOS: 4 ROBINS-I: Critical	RYGB: 78.9% of pts
Comparison of hormonal response to a mixed-meal challenge in hypoglycemia after sleeve gastrectomy vs. gastric bypass	Lee et al. (2022) (USA)	Single center without patient matching	MMTT no DM2 pts included	$N_{exp}=20$ $N_{ctrl}=23$ (Total: 43)	2190 days (1/1/2009–31/12/2014)	NOS: 6 ROBINS-I: Serious	RYGB: older pts, less time since surgery
Continuous glucose monitoring in subjects undergoing bariatric surgery: Diurnal and nocturnal glycemic patterns	Lupoli et al. (2020) (Italy)	Single center without patient matching	CGM DM2 pts included	$N_{exp}=22$ $N_{ctrl}=29$ (Total: 51)	364 days (1/1/2019–31/12/2019)	NOS: 5 ROBINS-I: Serious	No baseline differences
Risk factors for spontaneously self-reported postprandial hypoglycemia after bariatric surgery	Nannipieri et al. (2016) (Italy)	Single center without patient matching	OGTT, Q no DM2 pts included	$N_{exp}=34$ $N_{ctrl}=51$ (Total: 85)	729 days (1/1/2013–31/12/2014)	NOS: 6 ROBINS-I: Moderate	LSG: older pts, more obese pts

Table 1 (continued)

Title	Author	Type	Design	Population	Duration	Quality	Baseline
Glycemic variability and hypoglycemia before and after Roux-en-Y gastric bypass and sleeve gastrectomy: A cohort study of females without diabetes	Nilsen et al. (2023) (Sweden)	Single center without patient matching	CGM, Q no DM2 pts included	$N_{exp} = 28$ $N_{ctrl} = 19$ (Total: 47)	364 days (1/1/2022–31/12/2022)	NOS: 6 ROBINS-I: Moderate	Female pts RYGB: higher BMI
Clinical features of symptomatic hypoglycemia observed after bariatric surgery	Nor Hanipah et al. (2018) (USA)	Single center without patient matching	OGTT, MMTT DM2 pts included	$N_{exp} = 104$ $N_{ctrl} = 13$ (Total: 117)	5112 days (1/1/2002–31/12/2015)	NOS: 4 ROBINS-I: Critical	No baseline differences
Persistent post-bariatric surgery hypoglycemia: A long-term follow-up reassessment	Ostrovsky et al. (2023) (Israel)	Single center without patient matching	CGM, MMTT, Q no DM2 pts included	$N_{exp} = 10$ $N_{ctrl} = 5$ (Total: 15)	333 days (1/6/2020–30/4/2021)	NOS: 5 ROBINS-I: Serious	LSG: older pts RYGB: greater weight regains
Comparison between RYGB, DS, and VSG effect on glucose homeostasis	Roslin et al. (2012) (USA)	Single center without patient matching	OGTT, HOMA-IR DM2 pts included	$N_{exp} = 12$ $N_{ctrl} = 13$ (Total: 25)	365 days (1/1/2012–31/12/2012)	NOS: 6 ROBINS-I: Moderate	No baseline differences
Response to glucose tolerance testing and solid high carbohydrate challenge: Comparison between Roux-en-Y gastric bypass, vertical sleeve gastrectomy, and duodenal switch	Roslin et al. (2014) (USA)	Single center without patient matching	OGTT DM2 pts included	$N_{exp} = 13$ $N_{ctrl} = 12$ (Total: 25)	364 days (1/1/2013–31/12/2013)	NOS: 6 ROBINS-I: Moderate	No baseline differences
Hypoglycemia during oral glucose tolerance test among post-bariatric surgery pregnant patients: Incidence and perinatal significance	Rottenstreich et al. (2018) (Israel)	Single center without patient matching	OGTT no DM2 pts included	$N_{exp} = 30$ $N_{ctrl} = 55$ (Total: 85)	4017 days (1/1/2006–31/12/2016)	NOS: 6 ROBINS-I: Moderate	Pregnant pts No baseline differences
Effect of single anastomosis duodenal-ileal bypass with sleeve gastrectomy on glucose tolerance test: Comparison with other bariatric procedures	Sessa et al. 2019 (Sessa et al. 2019)	Single center with patient matching	OGTT no DM2 pts included	$N_{exp} = 11$ $N_{ctrl} = 7$ (Total: 18)	637 days (1/6/2016–28/2/2018)	NOS: 6 ROBINS-I: Moderate	No baseline differences

Table 1 (continued)

Title	Author	Type	Design	Population	Duration	Quality	Baseline
Weight regain in patients with symptoms of post-bariatric surgery hypoglycemia	Varma et al. (2017) (USA)	Single center without patient matching	Q DM2 pts included	$N_{exp} = 334$ $N_{ctrl} = 94$ (Total: 428)	272 days (1/8/2013–30/4/2014)	NOS: 4 ROBINS-I: Critical	RYGB: 78% of pts
Continuous glucose monitoring in bariatric patients undergoing laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass	Wysocki et al. (2019) (Poland)	Single center without patient matching	CGM DM2 pts included	$N_{exp} = 14$ $N_{ctrl} = 18$ (Total: 32)	364 days (1/1/2018–31/12/2018)	NOS: 5 ROBINS-I: Serious	RYGB: more pts with DM2, higher proportion of females DM2: higher ASA score, older pts

RYGB Roux-en-Y gastric bypass, *LSG* laparoscopic sleeve gastrectomy, *NOS* Newcastle–Ottawa scale, *ROBINS-I* risk of bias in non-randomized studies of interventions, N_{exp} patient population in experimental arm (RYGB), N_{ctrl} patient population in control arm (LSG), *OGTT* oral glucose tolerance test, *MMTT* mixed-meal tolerance test, *CGM* continuous glucose monitoring, *Q* questionnaires, *DM2* type 2 diabetes mellitus, *ASA* American Society of Anesthesiologists, *BMI* body mass index, *pts* patients

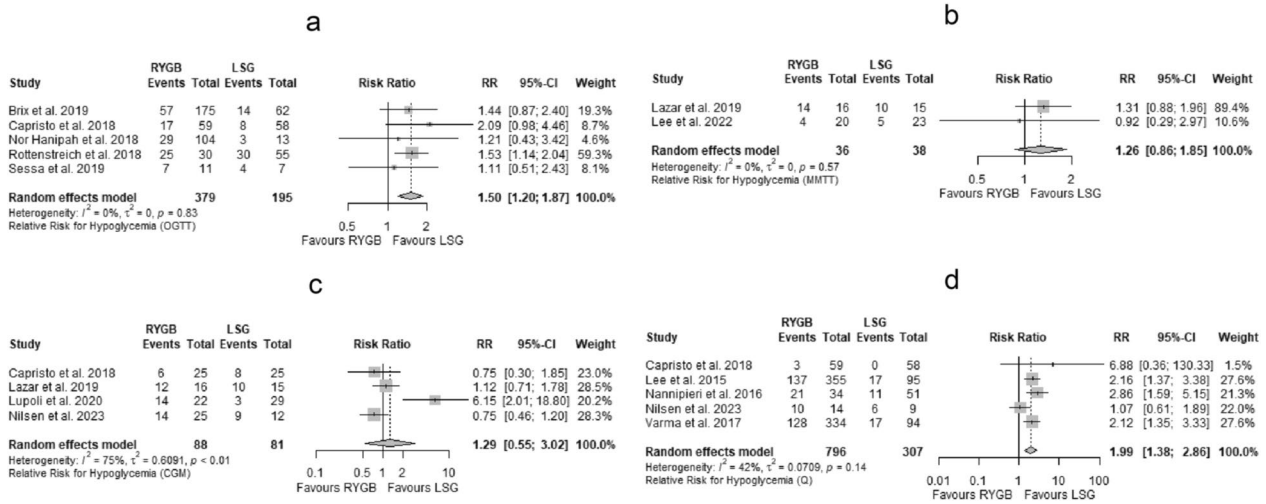

Fig. 7 Forest plots under a random effects model using the MH method in the estimation of the overall RR for PBSH after RYGB vs. LSG during OGTT (**a**), MMTT (**b**), CGM (**c**), and the application of questionnaires (**d**). Abbreviations: MH: Mantel–Haenszel, RR: relative risk, PBSH: post-bariatric surgery hypoglycemia, RYGB: Roux-en-Y gastric bypass, LSG: laparoscopic sleeve gastrectomy, OGTT: oral glucose tolerance test, MMTT: mixed-meal tolerance test, CGM: continuous glucose monitoring

above diagrams, no statistically significant difference was observed in any of the individual analyses. Additional file 1: Figure S19 displays the SGA and SA for fasting blood glucose levels, with no statistically significant MD observed for any of the examined subgroups. Similarly, in Additional file 1: Figure S20, the respective diagrams for the change in fasting-blood glucose concentration from baseline are provided, and in this case as well, no significant MD was found within the spectrum of subgroups. Furthermore, Additional file 1: Figures S21 and S22 also do not indicate statistical significance regarding the MD for fasting insulin levels and their change from baseline across all subgroups, with no apparent advantage observed for RYGB or LSG. During the assessment of PB through the examination of the relevant radial plots, in Additional file 1: Figure S23, significant deviation is observed only for the difference in fasting-insulin levels from baseline.

Subsequently, in Fig. 9, forest plots are presented for the MD in plasma glucose levels at one and two hours after the start of the OGTT, as well as the corresponding changes from baseline concentrations. Regarding the findings after one hour, no statistically significant MD was observed, except for a trend toward a higher increase in glucose levels compared to baseline in patients who underwent RYGB (MD = 9.58 mg/dl, $CI_{95\%}$ = [−4.96; 24.12]). On the other hand, after two hours, plasma glucose concentration was significantly lower in patients who underwent RYGB compared to those in the LSG group. The difference was determined as: MD = −10.54 mg/dl, $CI_{95\%}$ = [−16.63; −4.45], with heterogeneity as follows: I^2 = 0.0% with $CI_{95\%}$ = [0.0%; 79.2%], τ^2 = 0, H = 1.00 with $CI_{95\%}$ = [1.00; 2.19], Q = 1.43, df = 4, p value = 0.8384 (not statistically significant). The corresponding difference from baseline was not statistically significant; however, a trend toward a greater reduction in glucose levels in the RYGB group (MD = −12.67 mg/dl, $CI_{95\%}$ = [−39.66; 14.33]) was evident. Additional file 1: Figure S24 provides the SGA and SA for these outcomes. No significant differences were found in any subgroup, but a trend toward higher one-hour plasma glucose levels was more apparent in patients who underwent RYGB. This finding, in combination with the above, suggests a more variable glycemic profile in RYGB patients compared to those in the LSG group, which may predispose to HG events if considered as clinically significant manifestations of nadir glycemia. Additional file 1: Figure S25 presents the SGA and SA for the change in one-hour plasma glucose concentrations from baseline. In this case as well, no statistically significant differences were found in any of the MDs of the subgroups. However, a consistent finding could be described as the trend toward a smaller reduction in glucose levels from baseline for the RYGB group compared to LSG. In Additional file 1: Figure S26, SGA and SA are provided for the MD of two-hour plasma glucose levels during the OGTT. The main drivers of the results presented above, regarding the statistically significant MD between RYGB and LSG, were studies published before 2018, those without patient matching, studies that did not include diabetic patients, and those classified as "ROBINS-I: Moderate". Finally, Additional file 1: Figure S27 includes

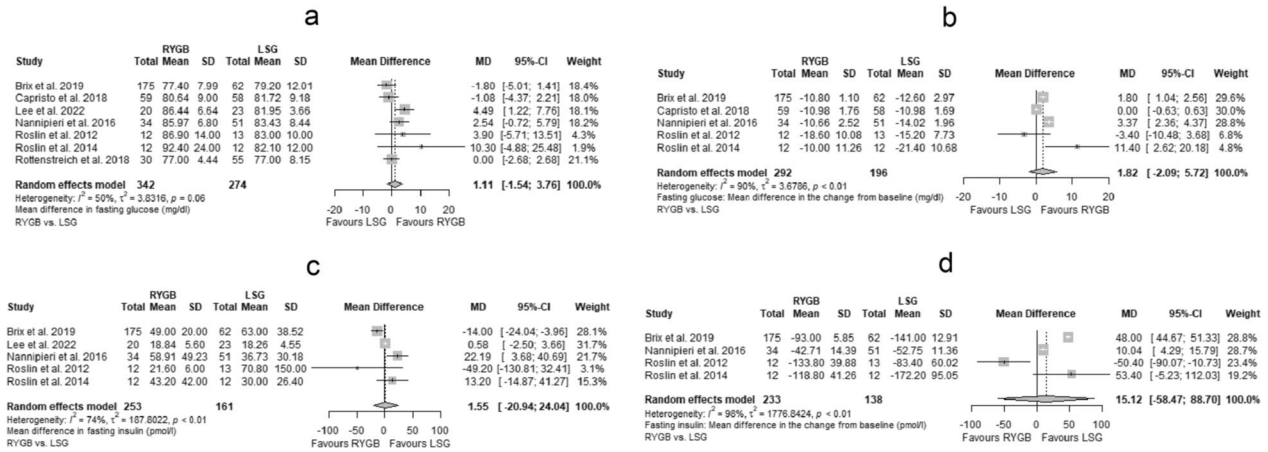

Fig. 8 Forest plots under a random effects model with the HK adjustment for the estimation of the overall MD in postoperative fasting glucose (**a**) and insulin levels (**b**), and the change from baseline in fasting glucose (**c**) and insulin (**d**). Abbreviations: HK: Hartung–Knapp, MD: mean difference

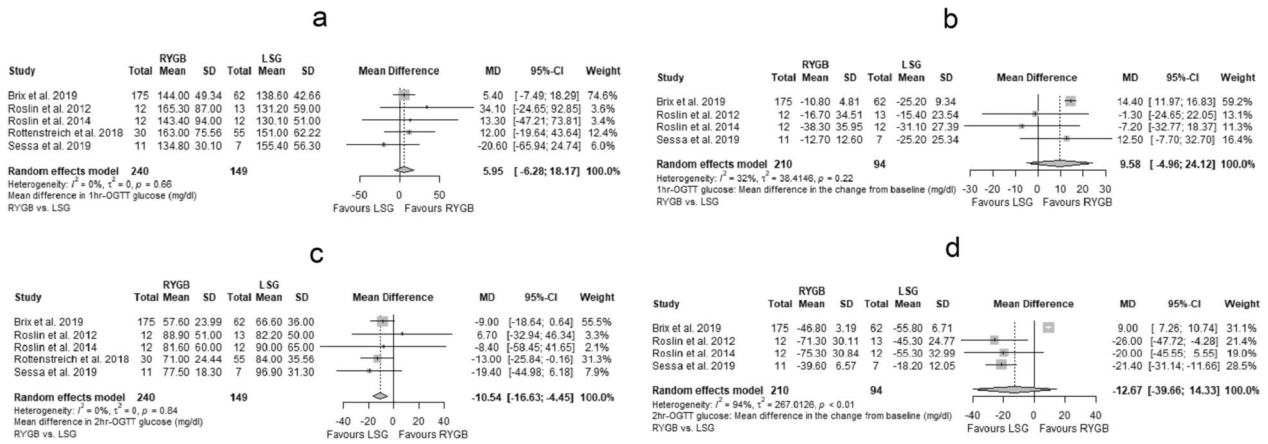

Fig. 9 Forest plots under a random effects model with the HK adjustment for the estimation of the overall MD in 1-h OGTT glucose (**a**) and its change from baseline (**b**) & 2-h OGTT glucose (**c**) and its change from baseline (**d**). Abbreviations: HK: Hartung–Knapp, MD: mean difference, OGTT: oral glucose tolerance test

forest plots corresponding to the same sub-analyses for the change in two-hour plasma glucose levels from baseline. The results for the individual subgroups were not found to be statistically significant. However, in shaping the trend described earlier regarding the greater reduction in glucose levels in the RYGB group, the maximum contribution came from studies published before 2018, a single study with patient matching (RCT) (Capristo et al. 2018), studies that included DM2 patients, and those classified as "ROBINS-I: Moderate".

Figure 10 displays the corresponding forest plots for insulin levels at one and two hours during the OGTT, as well as the respective changes from baseline levels. Also in this case, the results did not emerge as statistically significant. However, it is worth noting the emergence of a trend toward lower plasma insulin levels and smaller reductions in insulin levels from baseline in the RYGB group. From this finding, one could hypothesize that early postprandial insulin levels may not be the primary cause of the observed differences between RYGB and LSG in the incidence of PBSH. Additional file 1: Figure S28 presents the corresponding radial plots for assessing the impact of PB, which appears to be significant for this primary outcome group. Additional file 1: Figure S29 provides the SGA and SA for one-hour plasma insulin levels. Overall, no significant differences are observed between RYGB and LSG in the respective diagrams, while the main drivers of the aggregate results appear to be studies published after 2018, those without patient matching, those excluding DM2 patients, and those

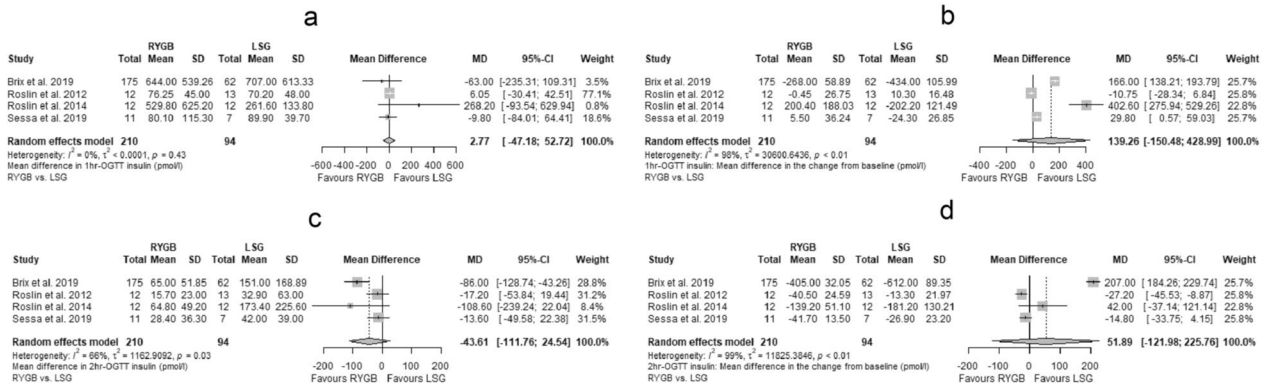

Fig. 10 Forest plots under a random effects model with the HK adjustment for the estimation of the overall MD in 1-h OGTT insulin (**a**) and its change from baseline (**b**) & 2-h OGTT insulin (**c**) and its change from baseline (**d**). Abbreviations: HK: Hartung–Knapp, MD: mean difference, OGTT: oral glucose tolerance test

classified as "ROBINS-I: Moderate". Additional file 1: Figure S30 displays the same diagrams for the change in one-hour insulin levels from baseline, also without statistically significant differences between the two surgical approaches. Finally, Additional file 1: Figures S31 and S32 provide comparative data for two-hour insulin levels and their changes from baseline in terms of SGA and SA, again without statistically significant differences between the individual subgroups. The entirety of the results presented above regarding the primary outcomes is summarized in Table 2.

Meta-analysis of secondary outcomes

In this subsection, we are going to present the results that emerged during the analysis of secondary outcomes. Additional file 1: Figure S33a displays a comparison regarding the number of male patients undergoing RYGB vs. LSG. The corresponding forest plot revealed only a trend, indicating that overweight male patients are more likely to undergo LSG (OR = 0.63, $CI_{95\%}$ = [0.28; 1.41]). Subsequently, in Additional file 1: Figure S33b, the forest plot depicts the difference in weight loss (WL) following six months after BS. This finding was statistically significant, with the maximum benefit provided by RYGB: MD = − 3.84 kg, $CI_{95\%}$ = [− 7.06; − 0.63] (heterogeneity: I^2 = 71.4% with $CI_{95\%}$ = [27.7%; 88.7%], τ^2 = 2.9087 with $CI_{95\%}$ = [0.1055; > 100.0000], H = 1.87 with $CI_{95\%}$ = [1.18; 2.98], Q = 14.00, df = 4, p value = 0.0073). Furthermore, Additional file 1: Figure S33c provides a corresponding diagram for estimating the MD in BMI change (ΔBMI). In this case as well, the finding was statistically significant, with RYGB offering a greater reduction compared to LSG: MD = − 1.49 kg/m^2, $CI_{95\%}$ = [− 1.86; − 1.12] (heterogeneity: I^2 = 50.2% with $CI_{95\%}$ = [0.0%; 76.7%], τ^2 = 0.0089 with $CI_{95\%}$ = [0.0000; 4.8690], H = 1.42 with $CI_{95\%}$ = [1.00; 2.07], Q = 16.06, df = 8, p value = 0.0415).

Table 2 Table displaying the results of the data analysis pertaining to the primary outcomes

Outcome	Pooled comparative effect	95% Confidence interval ($CI_{95\%}$)
PBSH (OGTT)	**RR = 1.50**	**[1.20; 1.87]**
PBSH (MMTT)	RR = 1.26	[0.86; 1.85]
PBSH (CGM)	RR = 1.29	[0.55; 3.02]
PBSH (Q)	**RR = 1.99**	**[1.38; 2.86]**
Fasting Glucose (mg/dl)	MD = 1.11	[− 1.54; 3.76]
Δ[Fasting Glucose] (mg/dl)	MD = 1.82	[− 2.09; 5.72]
Fasting Insulin (pmol/l)	MD = 1.55	[− 20.94; 24.04]
Δ[Fasting Insulin] (pmol/l)	MD = 15.12	[− 58.47; 88.70]
1-h OGTT Glucose (mg/dl)	MD = 5.95	[− 6.28; 18.17]
Δ[1-h OGTT Glucose] (mg/dl)	MD = 9.58	[− 4.96; 24.12]
2-h OGTT Glucose (mg/dl)	**MD = − 10.54**	**[− 16.63; − 4.45]**
Δ[2-h OGTT Glucose] (mg/dl)	MD = − 12.67	[− 39.66; 14.33]
1-h OGTT Insulin (pmol/l)	MD = 2.77	[− 47.18; 52.72]
Δ[1-h OGTT Insulin] (pmol/l)	MD = 139.26	[− 150.48; 428.99]
2-h OGTT Insulin (pmol/l)	MD = − 43.61	[− 111.76; 24.54]
Δ[2-h OGTT Insulin] (pmol/l)	MD = 51.89	[− 121.98; 225.76]

The related findings are presented as the comparative effect between RYGB and LSG, along with the corresponding 95% confidence interval ($CI_{95\%}$).

RYGB Roux-en-Y gastric bypass, *LSG* laparoscopic sleeve gastrectomy, *PBSH* post-bariatric surgery hypoglycemia, *OGTT* oral glucose tolerance test, *MMTT* mixed-meal tolerance test, *CGM* continuous glucose monitoring, *Q* questionnaires. Note that the symbol "Δ" indicates the change from baseline levels, while statistically significant findings are indicated in bold

Complementarily, Additional file 1: Figure S33d presents the forest plot for the reduction in excessive body weight (EBW). In this case, however, no significant differences were observed between the two BS approaches. In Additional file 1: Figure S34, radial plots are displayed for estimating the PB regarding the variables previously presented. Substantial deviations indicating significant

bias were found in WL and EBWL after the sixth postoperative month. Additional file 1: Figure S35 provides the SGA—SA for the estimation of OR concerning the distribution of males between RYGB and LSG. Upon interpreting the results, no statistically significant differences were observed in any of the examined subgroups, except perhaps a tendency for the treatment of non-diabetic males with LSG (OR = 0.63, CI 95% = [0.32; 1.27]). Additional file 1: Figure S36 illustrates the SGA—SA results for estimating the MD in weight loss (WL) after the first postoperative semester. Notably, the main contributing factors to the statistically significant outcome in the pooled analysis included studies published before 2018, those without patient matching, those without patients with type 2 diabetes (DM2), and those categorized as 'ROBINS-I: Moderate. In Additional file 1: Figure S37, we delve into the results from the SGA – SA, aiming to determine the comparative impact on BMI drop. Once again, the same categories of studies played a pivotal role in driving the effect within this sub-analysis. From the last two outcome-oriented analyses conducted, an intriguing hypothesis emerges, in terms of whether the presence of type 2 diabetes (DM2) diminishes the advantage of RYGB over LSG in achieving the maximum desired weight loss (WL). This hypothesis is supported by the observation that the differences in WL and BMI reduction, from studies that included diabetic patients, were not statistically significant ($MD_{WL} = -1.75$ kg, $CI_{95\%} = [-105.94; 102.44]$ and $MD_{\Delta BMI} = -1.05$ kg/m^2, $CI_{95\%} = [-2.71; 0.61]$, respectively). Nevertheless, it is imperative to emphasize that the exploration of the above hypothesis does not represent the primary focus of the present study. Additional file 1: Figure S38 illustrates the meta-regression analysis (MRA) for the BMI change, with moderators being the publication year of each study and the number of quality stars assigned during the assessment using the NOS scale. When assessing the above diagrams, a consistent comparative effect is observed both over the years and across the full spectrum of study quality. This finding demonstrates the overall superiority of RYGB over LSG in reducing BMI after the first postoperative semester. Finally, Additional file 1: Figure S39 displays the forest plots for the SGA—SA regarding the mean difference in EBWL (MD_{EBWL}). Similar to the cumulative data, in all subgroups, no statistically significant differences were observed.

Further, for the second group of secondary outcomes, Additional file 1: Figure S40 presents forest plots for the change from baseline in waist circumference ($MD_{\Delta WC}$), the mean difference in glycosylated hemoglobin (MD_{HbA1c}), and insulin sensitivity ($MD_{HOMA\text{-}IR}$) following 6 months post-BS, as well as the change from baseline in the latter. Upon reviewing the above data, no statistically significant differences emerge, except for a trend toward a higher level of HbA1c in patients who underwent RYGB (MD = 0.15, $CI_{95\%} = [-0.12; 0.42]$). As evident in the radial plot of Additional file 1: Figure S41, the aforementioned finding is subject to significant publication bias. In Additional file 1: Figure S42, the subgroup analysis (SGA—SA) is presented for the mean difference in HbA1c. Interpretation of the relevant diagrams suggests that the above description as a trend is further supported by studies published before 2018, those without patient matching, and those that included DM2 patients. Subsequently, Additional file 1: Figure S43a presents the forest plots for the mean incidence of hypoglycemic (HG) episodes within a ten-day period from the start of the OGTT, with no statistically significant differences between the two BS techniques. In Additional file 1: Figure S43b, a comparison of peak glucose concentration during OGTT is made, with the difference being significantly higher in favor of RYGB, specifically: MD = 49.11 mg/dl, $CI_{95\%} = [16.12; 82.10]$ (heterogeneity: $I^2 = 63.4\%$ with $CI_{95\%} = [0.0\%; 87.6\%]$, $\tau^2 = 237.2226$ with $CI_{95\%} = [0.0000; > 2372.2263]$, $H = 1.65$ with $CI_{95\%} = [1.00; 2.84]$, $Q = 8.19$, $df = 3$, p value = 0.0423). In Additional file 1: Figure S43c, the time in minutes (min) to achieve maximum blood sugar levels is compared between RYGB and LSG, with no statistically significant difference being observed. In Additional file 1: Figure S43d, a comparison of the two surgical approaches regarding the nadir plasma glucose levels during OGTT is presented. In this case, the RYGB group showed statistically significantly lower minimum glucose levels: MD = −5.70 mg/dl, $CI_{95\%} = [-10.03; -1.37]$ (heterogeneity: $I^2 = 0.0\%$ with $CI_{95\%} = [0.0\%; 84.7\%]$, $\tau^2 = 0$ with $CI_{95\%} = [0.0000; 81.5916]$, $H = 1.00$ with $CI_{95\%} = [1.00; 2.56]$, $Q = 2.03$, $df = 3$, p value = 0.5660). The above findings support the earlier hypothesis (made in the previous subsection) that patients undergoing RYGB are more susceptible to PBSH than those undergoing LSG during the period after the first postoperative semester, entering a pattern of wider glycemic fluctuations, with higher zenith and lower nadir plasma concentrations, predisposing them to clinically significant hypoglycemic symptoms. The corresponding radial plots for the assessment of the effect of PB in the study of MD for peak and nadir glycemia are presented in Additional file 1: Figure S44, where the most significant deviations are observed regarding the latter outcome. In Additional file 1: Figure S45, the subgroup analysis (SGA—SA) is presented for the MD in peak glycemia. The main drivers of the statistically significant result were studies published after 2018, those without patient matching, a single study including diabetic patients (Lupoli et al. 2020), as well as studies evaluated as "ROBINS-I: Serious". Similarly, in Additional file 1:

Figure S46, the sub-analysis related to nadir glycemia is explored, with the same categories of studies directing the overall comparative effect. Additional file 1: Figure S47a investigates the MD of the range of zenith minus nadir plasma glucose (i.e., glycemia range). The forest plot shows that in patients who underwent RYGB, this range is statistically significantly wider, specifically: MD = 52.22 mg/dl, $CI_{95\%}$ = [18.25; 86.19] (heterogeneity: I^2 = 98.6% with $CI_{95\%}$ = [97.8%; 99.1%], τ^2 = 448.2242 with $CI_{95\%}$ = [139.2920; > 4482.2421], H = 8.51 with $CI_{95\%}$ = [6.80; 10.67], Q = 217.48, df = 3, p-value < 0.0001). This constitutes a third finding that supports the existence of a pattern of wider glycemic variability in the RYGB group compared to those undergoing LSG. In Additional file 1: Figures S47b and c, the MDs are presented regarding C-peptide levels and their change from baseline, with no statistically significant differences being identified between RYGB and LSG. In Additional file 1: Figure S47d, the radial plot for the assessment of PB concerning the glycemic range is presented, with no significant deviation indicating a substantial effect. Additional file 1: Figure S48 presents the subgroup analysis (SGA–SA) for the MD in the range of "maximum–minimum" plasma glucose concentrations. In this case as well, the main drivers for the formation of the overall comparative effect were studies published after 2018, those without patient matching, a single study including DM2 patients (Lupoli et al. 2020), and studies evaluated as "ROBINS-I: Serious".

Finally, in the last part of the analysis of secondary outcomes, we examined the 1-h to fasting and 1–2-h ratios of glucose and insulin levels after the start of the OGTT. In Additional file 1: Figures S49a and S49b, forest plots are presented for comparing the 1-h/fasting ratio of glucose levels and its respective change from baseline, with no statistically significant differences observed. In Additional file 1: Figures S49c and d, the corresponding diagrams are provided for the 1-h/2-h plasma glucose ratio, also showing no differences between the two BS approaches. Similarly, no statistically significant findings were observed from the interpretation of the corresponding diagrams that emerged for plasma insulin levels, which are presented in Additional file 1: Figure S50. Table 3 succinctly provides the complete set of results pertaining to both primary and secondary outcomes, along with the findings during the SGA and SA procedures.

Discussion

Discussion of findings

The occurrence of clinically significant hypoglycemic (HG) episodes represents a relatively uncommon yet noteworthy complication during the late postoperative period following bariatric surgery (BS) (Oca et al. 2021; Collazo-Clavell and Shah 2020). This clinical entity, increasingly recognized over the past decade, is described as post-bariatric surgery hypoglycemia (PBSH) (Tayar et al. 2021; Brix et al. 2019). The spectrum of clinical manifestations includes typical HG symptoms (i.e., sweating, hunger, restlessness), along with neuroglycopenic events (i.e., dizziness, difficulty in concentrating, headaches), as well as manifestations from the cardiovascular system (i.e., tachycardia, palpitations, syncope) (Ritz et al. 2016). These clinical events have been associated with an increased risk of further adverse events, such as traffic accidents, severe physical injury from falls, and an increased incidence of suicidal ideation (Courcoulas 2017). The clinical implications of PBSH in obese patients who have undergone surgical treatment necessitate the development of protocols for timely diagnosis and the establishment of a rigorous and more comprehensive follow-up assessment of adequate duration. Nevertheless, despite the crucial necessity for the prompt diagnosis and effective management of PBSH, there exists a dearth of comparative data in the international literature regarding the frequency of its occurrence among the various BS approaches currently being implemented (Nor Hanipah et al. 2018). In this study, we aimed to compare the two most commonly used bariatric interventions, specifically RYGB and LSG, to arrive at an estimation of the comparative incidence of PBSH. Additionally, we sought to investigate hormonal responses following oral glucose loading. It is well documented in the literature that patients undergoing RYGB exhibit an increased susceptibility to postoperative hypoglycemic episodes. On this basis, we aimed to quantify the relative risk (RR) compared to LSG, which represents a more recent and increasingly applied BS technique (McGlone et al. 2020).

In the international literature, PBSH is defined as the manifestation of late hypoglycemic episodes that occur more frequently following approximately one year from the surgical intervention (Athavale and Ganipisetti 2023). The most widely used diagnostic methods for confirmation include OGTT, MMTT, CGM, as well as the use of broadly accepted questionnaires. Historically, the main pathogenic mechanism proposed for PBSH has been the removal of the pyloric sphincter, which occurs especially after RYGB and predisposes to the development of late dumping syndrome (Palermo and Gagner 2020). This mechanism involves the rapid elevation of plasma glucose levels following early gastric emptying and the increased absorption of carbohydrates in the jejunum, resulting in a simultaneous increase in insulin levels. After achieving transient euglycemia, the delay in restoring plasma insulin levels leads to an increased

Table 3 Table displaying the results of the data analysis pertaining to primary & secondary outcomes

Outcome	Units	Pooled analysis	Post-2018	Pre-2018	Pt. matching	No pt. matching	DM2 pts included	DM2 pts excluded	ROBINS-I: Low	ROBINS-I: Moderate	ROBINS-I: Serious	ROBINS-I: Critical
PBSH (OGTT)	–	**RR = 1.50 [1.20; 1.87]**	RR = 1.34 [0.87; 2.05]	**RR = 1.56 [1.20; 2.03]**	RR = 1.54 [0.83; 2.85]	**RR = 1.49 [1.17; 1.90]**	*RR = 1.21 [0.43; 3.42]*	**RR = 1.51 [1.20; 1.90]**	*RR = 2.09 [0.98; 4.46]*	**RR = 1.47 [1.12; 1.93]**	*RR = 1.44 [0.87; 2.40]*	*RR = 1.21 [0.43; 3.42]*
PBSH (CGM)	–	RR = 1.29 [0.55; 3.02]	RR = 1.57 [0.49; 5.02]	*RR = 0.75 [0.30; 1.85]*	*RR = 0.75 [0.30; 1.85]*	RR = 1.57 [0.49; 5.02]	***RR = 6.15 [2.01; 18.80]***	RR = 0.90 [0.65; 1.25]	*RR = 0.75 [0.30; 1.85]*	*RR = 0.75 [0.46; 1.20]*	RR = 2.43 [0.46; 12.75]	–
PBSH (Q)	–	**RR = 1.99 [1.38; 2.86]**	*RR = 1.07 [0.61; 1.89]*	**RR = 2.31 [1.75; 3.05]**	*RR = 6.88 [0.36; 130.33]*	**RR = 1.95 [1.35; 2.82]**	**RR = 2.14 [1.55; 2.94]**	RR = 1.95 [0.80; 4.74]	*RR = 6.88 [0.36; 130.33]*	RR = 1.75 [0.67; 4.58]	–	**RR = 2.14 [1.55; 2.94]**
Fasting Glucose	mg/dl	MD = 1.11 [−1.54; 3.76]	MD = 1.34 [−38.64; 41.33]	MD = 0.71 [−1.98; 3.41]	MD = −1.08 [−4.37; 2.21]	MD = 1.63 [−1.51; 4.77]	MD = 5.73 [−31.01; 42.47]	MD = 0.80 [−2.42; 4.02]	MD = −1.08 [−4.37; 2.21]	MD = 1.48 [−2.10; 5.07]	MD = 1.34 [−38.64; 41.31]	–
Δ[Fasting Glucose]	mg/dl	MD = 1.82 [−2.09; 5.72]	***MD = 1.80 [1.04; 2.56]***	MD = 2.13 [−5.96; 10.22]	*MD = 0.00 [−0.63; 0.63]*	MD = 2.56 [−1.70; 6.82]	MD = 3.76 [−90.21; 97.74]	MD = 1.69 [−2.49; 5.87]	*MD = 0.00 [−0.63; 0.63]*	MD = 3.42 [−13.52; 20.36]	***MD = 1.80 [1.04; 2.56]***	MD = 1.11 [−1.54; 3.76]
Fasting Insulin	pmol/l	MD = 1.55 [−20.94; 24.04]	MD = −5.89 [−97.96; 86.17]	MD = 17.09 [−23.04; 57.21]	–	MD = 1.55 [−20.94; 24.04]	MD = −5.75 [−370.35; 358.85]	MD = 1.60 [−41.69; 44.90]	–	MD = 17.09 [−23.04; 57.21]	MD = −5.89 [−97.96; 86.17]	–
Δ[Fasting Insulin]	pmol/l	MD = 15.12 [−58.47; 88.70]	***MD = 48.00 [44.67; 51.33]***	MD = 1.95 [−121.64; 125.54]	–	MD = 15.12 [−58.47; 88.70]	MD = −0.84 [−659.62; 657.95]	MD = 29.10 [−212.07; 270.26]	–	MD = 1.95 [−121.64; 125.54]	***MD = 48.00 [−44.67; 51.33]***	–
1-h OGTT Glucose	mg/dl	MD = 5.95 [−6.28; 18.17]	MD = 1.86 [−111.44; 115.16]	MD = 16.33 [−9.52; 42.18]	*MD = −20.60 [−65.94; 24.74]*	MD = 7.65 [−3.13; 18.43]	MD = 24.01 [−108.08; 156.09]	MD = 4.59 [−16.70; 25.88]	–	MD = 7.56 [−24.37; 39.49]	*MD = 5.40 [−7.49; 18.29]*	–
Δ[1-h OGTT Glucose]	mg/dl	MD = 9.58 [−4.96; 24.12]	**MD = 14.37 [11.51; 17.24]**	MD = −3.98 [−41.31; 33.35]	*MD = 12.50 [−7.70; 32.70]*	MD = 6.40 [−6.28; 18.17]	MD = −3.98 [−41.31; 33.35]	**MD = 14.37 [11.51; 17.24]**	–	MD = 2.97 [−22.71; 28.64]	***MD = 14.40 [11.97; 16.83]***	–
2-h OGTT Glucose	mg/dl	**MD = −10.54 [−16.63; −4.45]**	MD = −10.29 [−53.89; 33.31]	MD = −10.98 [−28.15; 6.20]	*MD = −19.40 [−44.98; 6.18]*	**MD = −9.79 [−16.56; −3.01]**	MD = 0.88 [−92.50; 94.26]	**MD = −11.19 [−20.57; −1.81]**	–	**MD = −12.47 [−23.58; −1.36]**	*MD = −9.00 [−18.64; 0.64]*	–
Δ[2-h OGTT Glucose]	mg/dl	MD = −12.67 [−39.66; 14.33]	MD = −5.81 [−198.88; 187.26]	MD = −23.48 [−61.10; 14.14]	***MD = −21.40 [−31.14; −11.66]***	MD = −9.80 [−58.49; 38.90]	MD = −23.48 [−61.10; 14.14]	MD = −5.81 [−198.88; 187.26]	–	**MD = −21.94 [−27.28; −16.59]**	***MD = 9.00 [7.26; 10.74]***	–
1-h OGTT Insulin	pmol/l	MD = 2.77 [−47.18; 52.72]	MD = −18.12 [−263.70; 227.46]	MD = 72.81 [−1378.40; 1524.03]	*MD = −9.80 [−84.01; 64.41]*	MD = 5.64 [−83.77; 95.06]	MD = 72.81 [−1378.40; 1524.03]	MD = −18.12 [−263.70; 227.46]	–	MD = 5.12 [−69.73; 79.97]	*MD = −63.00 [−235.31; 109.31]*	
Δ[1-h OGTT Insulin]	pmol/l	MD = 139.26 [−150.48; 428.99]	MD = 97.98 [−767.31; 963.27]	MD = 190.97 [−2434.33; 2816.27]	*MD = 29.80 [0.57; 59.03]*	MD = 179.04 [−330.72; 688.79]	MD = 190.97 [−2434.33; 2816.27]	MD = 97.98 [−767.31; 963.27]	–	MD = 133.58 [−424.63; 691.78]	MD = 166.00 [138.21; 193.79]	–
2-h OGTT Insulin	pmol/l	MD = −43.61 [−111.76; 24.54]	MD = −48.84 [−508.65; 410.96]	MD = −40.51 [−546.69; 465.67]	*MD = −13.60 [−49.58; 22.38]*	MD = −58.69 [−173.51; 56.13]	MD = −40.51 [−546.69; 465.67]	MD = −48.84 [−508.65; 410.96]	–	MD = −18.83 [−72.77; 35.10]	***MD = −86.00 [−128.74; −43.26]***	–

Table 3 (continued)

Outcome	Units	Pooled analysis	Post-2018	Pre-2018	Pt. matching	No pt. matching	DM2 pts included	DM2 pts excluded	ROBINS-I: Low	ROBINS-I: Moderate	ROBINS-I: Serious	ROBINS-I: Critical
Δ[2-h OGTT Insulin]	pmol/l	MD = 51.89 [−121.98; 225.76]	MD = 96.01 [−1313.11; 1505.12]	MD = −3.75 [−419.93; 412.44]	*MD = −14.80 [−33.75; 4.15]*	MD = 74.83 [−228.23; 377.88]	MD = −3.75 [−419.93; 412.44]	MD = 96.01 [−1313.11; 1505.12]	-	MD = −19.50 [−55.78; 16.78]	***MD = 207.00 [184.26; 229.74]***	–
Male pts	–	OR = 0.63 [0.28; 1.41]	–	–	–	–	–	–	–	–	–	–
WL	Kg	**MD = −3.84 [−7.06; -0.63]**	MD = −2.93 [−8.82; 2.96]	**MD = −5.51 [−7.72; -3.29]**	MD = −3.99 [−36.27; 28.29]	**MD = −2.99 [−5.32; -0.66]**	MD = −1.75 [−105.94; 102.44]	MD = −3.92 [−9.15; 1.32]	***MD = −5.53 [−6.53; -4.53]***	MD = −0.34 [−13.82; 13.14]	***MD = −3.00 [−4.14; -1.86]***	–
Δ[BMI]	Kg/m^2	**MD = −1.49 [−1.86; -1.12]**	MD = −1.08 [−2.85; 0.69]	MD = −1.45 [−1.81; -1.10]	MD = −0.68 [−12.95; 11.58]	**MD = −1.62 [−2.12; -1.13]**	MD = −1.05 [−2.71; 0.61]	**MD = −1.53 [−2.04; -1.02]**	***MD = −1.41 [−1.68; -1.14]***	MD = −1.07 [−3.10; 0.97]	MD = −1.40 [−3.44; 0.64]	–
EBWL	%	MD = −3.15 [−12.05; 5.74]	MD = −3.15 [−12.05; 5.74]	–	*MD = −0.60 [−19.97; 18.77]*	MD = −3.37 [−18.55; 11.81]	*MD = 3.30 [−2.28; 8.88]*	**MD = −7.71 [−10.55; -4.86]**	–	MD = −0.60 [−19.97; 18.77]	MD = −3.37 [−18.55; 11.81]	–
Δ[WC]	cm	MD = −0.75 [−61.49; 59.98]	–	–	–	–	–	–	–	–	–	–
HbA1c	%	MD = 0.15 [−0.12; 0.42]	MD = 0.03 [−0.93; 1.00]	MD = 0.28 [−0.43; 1.00]	*MD = 0.03 [−0.10; 0.16]*	MD = 0.23 [−0.17; 0.63]	MD = 0.35 [−0.10; 0.81]	MD = 0.01 [−0.17; 0.19]	*MD = 0.03 [−0.10; 0.16]*	MD = 0.50 [0.50; 0.50]	MD = 0.03 [−0.93; 1.00]	–
HOMA-IR	–	MD = −0.09 [−1.23; 1.05]	–	–	–	–	–	–	–	–	–	–
Δ[HOMA-IR]	–	MD = 1.82 [−6.51; 10.15]	–	–	–	–	–	–	–	–	–	–
HG events	10-d average	MD = 2.59 [−24.68; 29.85]	–	–	–	–	–	–	–	–	–	–
Peak Glucose (OGTT)	mg/dl	**MD = 49.11 [16.12; 82.10]**	**MD = 53.22 [27.83; 78.61]**	MD = 38.13 [−267.82; 344.08]	–	**MD = 49.11 [16.12; 82.10]**	***MD = 62.00 [28.26; 95.74]***	MD = 45.14 [−14.42; 104.69]	-	MD = 38.13 [−267.82; 344.08]	**MD = 53.22 [27.83; 78.61]**	–
Time to Peak Glucose (OGTT)	min	MD = 6.27 [−20.98; 33.51]	–	–	–	–	–	–	–	–	-	–
Nadir Glucose (OGTT)	mg/dl	**MD = −5.70 [−10.03; -1.37]**	MD = −3.90 [−17.30; 9.49]	MD = −7.26 [−33.23; 18.71]	-	**MD = 5.70 [−10.03; −1.37]**	*MD = −5.00 [−11.86; 1.86]*	MD = −5.88 [−13.90; 2.13]	–	MD = −7.26 [−33.23; 18.71]	MD = −3.90 [−17.30; 9.49]	–
Peak–Nadir glycemic range	mg/dl	**MD = 52.22 [18.25; 86.19]**	MD = 60.82 [−10.98; 132.63]	MD = 43.15 [−237.51; 323.82]	-	**MD = 52.22 [18.25; 86.19]**	***MD = 67.00 [60.02; 73.98]***	MD = 47.37 [−10.28; 105.03]	–	MD = 43.15 [−237.51; 323.82]	MD = 60.82 [−10.98; 132.63]	–

Table 3 (continued)

Outcome	Units	Pooled analysis	Post-2018	Pre-2018	Pt. matching	No pt. matching	DM2 pts included	DM2 pts excluded	ROBINS-I: Low	ROBINS-I: Moderate	ROBINS-I: Serious	ROBINS-I: Critical
C-peptide	ng/ml	MD = −0.80 [−15.57; 13.97]	–	–	–	–	–	–	–	–	–	–
Δ[C-peptide]	ng/ml	MD = 1.34 [−36.78; 39.45]	–	–	–	–	–	–	–	–	–	–
1 h/fasting Glucose Ratio	–	MD = 0.12 [−1.75; 2.00]	–	–	–	–	–	–	–	–	–	–
Δ[1 h/fasting Glucose Ratio]	–	MD = 0.04 [−0.59; 0.67]	–	–	–	–	–	–	–	–	–	–
1 h/2 h Glucose Ratio	–	MD = 0.24 [−1.36; 1.84]	–	–	–	–	–	–	–	–	–	–
Δ[1 h/2 h Glucose Ratio]	–	MD = 0.33 [−1.70; 2.37]	–	–	–	–	–	–	–	–	–	–
1 h/fasting Insulin Ratio	–	MD = 5.97 [−37.77; 49.70]	–	–	–	–	–	–	–	–	–	–
Δ[1 h/fasting Insulin Ratio]	–	MD = 8.43 [−21.39; 38.25]	–	–	–	–	–	–	–	–	–	–
1 h/2 h Insulin Ratio	–	MD = 4.08 [−23.87; 32.03]	–	–	–	–	–	–	–	–	–	–
Δ[1 h/2 h Insulin Ratio]	–	MD = 4.70 [−23.26; 32.65]	–	–	–	–	–	–	–	–	–	–

The related findings are presented as the comparative effect between RYGB and LSG, along with the corresponding 95% confidence interval ($CI_{95\%}$).

RYGB Roux-en-Y gastric bypass, *LSG* laparoscopic sleeve gastrectomy, *PBSH* post-bariatric surgery hypoglycemia, *OGTT* oral glucose tolerance test, *MMTT* mixed-meal tolerance test, *CGM* continuous glucose monitoring, *Q* questionnaires, *pts* patients, *WL* weight loss, *BMI* body mass index, *EBWL* excess body weight loss, *WC* waist circumference, *HbA1c* glycosylated hemoglobin, *HOMA-IR* homeostatic model assessment for insulin resistance, *HG events* hypoglycemic events. Note that the symbol "Δ" indicates the change from baseline levels. The statistically significant findings are indicated in bold, while estimates from individual studies are presented in italics

susceptibility to postprandial hypoglycemia due to relative hyperinsulinemia, essentially defining an insulin-dependent mechanism (Oca et al. 2021; Furth et al. 2020; Camastra et al. 2022). Recent studies, however, have highlighted the critical role of other gastrointestinal hormones such as glucagon and incretins, which are involved in a specialized hormonal homeostasis and contribute to insulin level regulation. The most significant incretins include glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide or gastric inhibitory peptide (GIP) (Lee et al. 2022; Salehi 2023). Regarding LSG, the mechanism has been described as being related to the restriction of gastric volume and faster gastric emptying. However, data for this specific BS approach are limited due to the fact that its broader adoption as a separate procedure from the original biliopancreatic diversion (BPD) has practically occurred within the last decade (Sandoval and Patti 2023). Postoperatively, changes in insulin sensitivity, as well as hormonal impacts of BS on insulin, glucagon, C-peptide, and incretins (GLP-1, GIP), are additional parameters that further complicate the glycemic profile of patients (Tripyla et al. 2023). As changes in plasma insulin levels are not always recognized in patients experiencing PBSH events, the mechanisms underlying the development of this clinical entity can be categorized into those that are insulin-mediated and those that are insulin-independent. The latter have been the subject of intensive study over the last decade. One intriguing mechanism related to the insulin-mediated category is referred to as nesidioblastosis or non-insulinoma pancreatogenous hypoglycemia syndrome (NIPHS) (Dar et al. 2020; Terryn and Majerus 2022). This syndrome involves the development of postprandial hyperinsulinemic hypoglycemia (PHH) in BS patients after approximately one year from the intervention, due to the hyperplasia of pancreatic β-cells on the basis of a relatively consistent state of preoperative hyperglycemia (Hu et al. 2020). In the treatment of PBSH, conservative measures are primarily adopted, focusing on dietary modifications to avoid late dumping syndrome (i.e., limiting carbohydrate intake, following a diet comprising multiple small meals, avoiding the simultaneous intake of liquids and solid foods) (Michaels et al. 2017; Nor Hanipah et al. 2018). However, in clinically complicated cases with multiple adverse events and refractory hypoglycemia, most commonly observed in patients who have undergone RYGB, options such as conversion to LSG or distal pancreatectomy have been described as feasible definitive measures (Terryn and Majerus 2022; Macedo et al. 2016).

For this analysis, we categorized the outcomes from the original studies into two groups related to the occurrence of post-bariatric surgery hypoglycemia (PBSH) when comparing RYGB to LSG. In the first category, we compared the patient populations who experienced hypoglycemic events using the various diagnostic methods employed in the respective subset of the literature. Specifically, after at least 6 months post-bariatric surgery, there was a 50% increase in the relative risk for PBSH in patients who underwent RYGB compared to the LSG group. The highest relative risk increase was 56%, as indicated in studies published before 2018 (RR = 1.56, $CI_{95\%}$ = [1.20; 2.03]), while the lowest was 47%, as observed in "ROBINS-I: Moderate" studies. On the other hand, the use of questionnaires revealed that the relative risk for RYGB patients was nearly double (RR = 1.99, $CI_{95\%}$ = [1.38; 2.86]). In the corresponding SGA, the highest relative risk was found in studies published before 2018 (RR = 2.31, $CI_{95\%}$ = [1.75; 3.05]), while the lowest was in studies without patient matching (RR = 1.95, $CI_{95\%}$ = [1.35; 2.82]). In reference to the diagnostic modalities of CGM and MMTT, we exclusively identified a propensity for an elevated risk of PBSH among RYGB patients in comparison with their LSG counterparts (RR = 1.29, $CI_{95\%}$ = [0.55; 3.02] and RR = 1.26, $CI_{95\%}$ = [0.86; 1.85], respectively). Regardless of the moderate quality of the studies and the limited availability of data, it is evident that there is a significant increase in the risk of PBSH in the RYGB group compared to those who underwent LSG, estimated to be an additional 30% to 50%. This finding quantifies the prevailing opinion about the heightened predisposition to hypoglycemic events in RYGB patients, which is supported by a significant portion of the literature (Tripyla et al. 2023; Vilallonga et al. 2021). Regarding potential differences in fasting glucose and insulin levels and their changes from baseline plasma concentrations, no substantial differences were identified. Additionally, there was no significant difference between RYGB and LSG in terms of one-hour glucose levels during the OGTT. However, for the two-hour blood sugar levels (in OGTT), a statistically significant difference was observed between the two approaches, with lower levels in the RYGB group (MD = − 10.54 mg/dl, $CI_{95\%}$ = [− 16.63; − 4.45]). In the SGA, the maximum absolute difference was observed in the "ROBINS-I: Moderate" studies (MD = − 12.47 mg/dl, $CI_{95\%}$ = [− 23.58; − 1.36]), while the minimum was from studies that did not apply patient matching (MD = − 9.79 mg/dl, $CI_{95\%}$ = [− 16.56; − 3.01]). Concerning the changes in two-hour glucose levels from baseline, we observed a trend toward greater reduction in the RYGB group (MD = − 12.67 mg/dl, $CI_{95\%}$ = [− 39.66; 14.33]). However, a statistically significant greater reduction in RYGB compared to LSG was observed in the subgroup of "ROBINS-I: Moderate" studies. Therefore, the data suggest at least a trend toward a reduction in glucose levels two hours after

a glucose load in patients undergoing RYGB. This finding supports the involvement of late dumping syndrome in the development of postprandial hypoglycemia, with the highest risk pertaining to patients undergoing gastric bypass compared to those who receive LSG, possibly due to the more extensive anatomical rearrangement associated with the former procedure.

The comparative investigation of plasma insulin levels after the first postoperative semester followed a similar pattern. Concerning one-hour insulin levels (during OGTT), no statistically significant differences were observed between the two BS approaches. However, there was a trend toward a greater increase from baseline through RYGB (MD = 139.26 pmol/l, $CI_{95\%}$ = [− 150.48; 428.29]). Additionally, for the two-hour plasma insulin change from baseline, an analogous trend emerged with a somewhat narrower range of variation (MD = 51.89 pmol/l, $CI_{95\%}$ = [− 121.98; 225.76]). Although the data utilized may not have been of optimal quality, these findings potentially suggest a more rapid increase in plasma insulin concentration in the RYGB group following oral glucose loading over a two-hour period. In this observation, there may be an underlying propensity for the development of postprandial hypoglycemic episodes beyond the 2-h mark after increased carbohydrate intake following RYGB. This observation once again highlights the involvement of late dumping as a significant pathophysiological mechanism in the development of postprandial hypoglycemia (Malik et al. 2016). Furthermore, certain studies have also indicated the possible involvement of impaired incretin homeostasis as an additional pathogenetic factor in the aforementioned context (Smith et al. 2018). However, our currently available data do not allow for further exploration of the aforementioned hypothesis.

Among the secondary outcomes, an analysis of the distribution of male patients between RYGB and LSG revealed a tendency for male obese patients to be more frequently treated with the latter (OR = 0.63, $CI_{95\%}$ = [0.28; 1.41]). Weight loss (WL) after the first six months following BS showed a greater reduction in the RYGB group (MD = -3.84 kg, $CI_{95\%}$ = [− 7.06; − 0.63]). In the subgroup analysis (SGA), the maximum difference in WL was observed in studies published before 2018 (MD = − 5.51 kg, $CI_{95\%}$ = [− 7.72; − 3.29]), while the minimum mean difference was in studies without patient matching (MD = − 2.99 kg, $CI_{95\%}$ = [− 5.32; − 0.66]). Furthermore, concerning the reduction in BMI, RYGB demonstrated a comparative advantage (MD = -1.49 kg/m^2, $CI_{95\%}$ = [− 1.86; − 1.12]), indicating the overall superiority of RYGB over LSG in achieving absolute weight loss six months post-BS. In the SGA, the maximum difference in BMI reduction was described in studies without patient matching (MD = − 1.62 kg/m^2, $CI_{95\%}$ = [− 2.12; − 1.13]), while the minimum was in those published before 2018 (MD = − 1.45 kg/m^2, $CI_{95\%}$ = [− 1.81; − 1.10]). Based on the above, a compelling advantage emerges for RYGB over LSG, both in terms of body weight loss and BMI reduction six months after bariatric surgery. This finding aligns with the comparative literature between the two BS procedures (Svanevik et al. 2023; Debs et al. 2020). However, during the examination of subgroups involving the inclusion or exclusion of diabetic patients, the elimination of the aforementioned advantage by RYGB was observed in studies that included DM2 populations. This finding warrants further investigation by specialized studies in the future to explore the impact of type 2 diabetes on the provided advantage of RYGB over LSG in overall weight loss. Regarding excessive body weight loss (EBWL) and waist circumference (WC) reduction, no substantial differences were observed between the compared BS approaches. Moving on to postoperative levels of glycosylated hemoglobin (HbA1c), there was a trend toward higher values in patients who underwent RYGB (MD = 0.15%, $CI_{95\%}$ = [− 0.12; 0.42]), with the mean difference being maximized (as a trend) in studies that included DM2 patients (MD = 0.35%, $CI_{95\%}$ = [− 0.10; 0.81]).

The maximum plasma glucose concentration during the OGTT was found to be significantly higher in patients of the RYGB group (MD = 49.11 mg/dl, $CI_{95\%}$ = [16.12; 82.10]). Conversely, the minimum glucose levels were also observed in patients who underwent the same BS approach (MD = − 5.70 mg/dl, $CI_{95\%}$ = [− 10.03; − 1.37]). These findings align with the relevant literature, which employs the OGTT for comparing RYGB versus LSG in terms of glycemic response to oral glucose loading (Lee et al. 2022; Salehi et al. 2022). Furthermore, in the analysis of the zenith minus nadir (i.e., maximum–minimum) difference of plasma glucose concentration, a statistically significant wider range was similarly observed in patients who underwent RYGB compared to those in the LSG group (MD = 52.22 mg/dl, $CI_{95\%}$ = [18.25; 86.19]). These findings clearly indicate that the variation in glucose levels in patients undergoing RYGB, as opposed to those receiving LSG, is significantly greater after the first postoperative semester. This higher peak glucose concentration is accompanied by lower trough levels, predisposing patients to the development of clinical hypoglycemia due to broader glycemic fluctuations (Nilsen et al. 2023). These fluctuations are attributed in the literature to a more extensively impaired counter-regulatory response to hypoglycemia (Salehi et al. 2022, 2023; Nilsen et al. 2023). Notably, patients with type 2 diabetes mellitus (DM2) may be at a significantly higher

risk of hypoglycemic events (Azim and Kashyap 2016). In the SGA, only one study with diabetic patients was included in the investigation of the glycemic range, but a significant mean difference was observed between the two surgical approaches, with the wider range applying to RYGB also in this case (MD = 67.00 mg/dl, $CI_{95\%}$ = [60.02; 73.98]). On the contrary, in the studies that did not include diabetic patients, the corresponding difference between RYGB and LSG emerged only as a trend and was not statistically significant (MD = 47.37 mg/dl, $CI_{95\%}$ = [− 10.28; 105.03]). This position finds support from a significant portion of the international literature, which highlights the increased susceptibility of diabetic patients to hypoglycemic episodes, in the case of delayed recognition of the need for downscaling or discontinuation of their anti-diabetic medication after bariatric surgery, especially following RYGB (Kassem et al. 2017; Wirunsawanya et al. 2021). However, the hormonal responses investigated in this analysis were not sufficient to explain the broader variations in plasma glucose levels observed after RYGB compared to LSG. One possible reason may lie in the fact that our data cover only a 2-h period after oral glucose loading during the OGTT, which may not be adequate to fully explore the broad spectrum of these responses. On the side of RYGB, it could be hypothesized that a more unstable hormonal mechanism in glycemic homeostasis contributes to the observed difference in the range of glycemia when compared to LSG (Salehi et al. 2022). Therefore, particular attention is needed to appropriately and promptly curtail anti-diabetic medications for DM2 patients treated with RYGB.

In summary, the significantly increased risk of developing post-bariatric surgery hypoglycemia (PBSH) after RYGB compared to LSG can possibly be explained by a two-stage mechanism. Initially, the more rapid passage of carbohydrates to the jejunum appears to induce a state of early relative insulin deficiency, resulting in higher 1-h plasma glucose levels compared to LSG. Subsequently, after at least a 2-h interval, the insulin secretion response seems to be faster and more intense, leading to late relative hyperinsulinemia and the clinical onset of PBSH. This composite mechanism likely underlies the broader glycemic range observed in the RYGB group, with lower nadir glucose levels (in relation to LSG) corresponding to the first phase and higher zenith levels to the second. Additionally, the role of incretins, such as GLP-1 and GIP, in these responses appears to be crucial. Therefore, further studies will be necessary in the future to investigate the involvement of GLP-1, GIP, and glucagon in the glycemic regulation of all bariatric surgery patients, with the aim of providing a more comprehensive understanding of the pathophysiological aspects related to the wider variability in glucose levels observed after RYGB.

Discussion in the body of literature

Numerous studies have extensively investigated PBSH and its clinical implications. One such study, conducted by Capristo et al. (Capristo et al. 2018), compared the outcomes of RYGB and SG, focusing on the incidence of PBSH in a cohort of 175 patients. After one year, the findings revealed that HG occurred in 14% of LSG patients and 29% of RYGB patients during OGTT. Interestingly, the incidence of daily HG episodes and hospitalizations for hypoglycemia did not significantly differ between the two surgical groups. Both BS procedures resulted in improved insulin sensitivity, but LSG demonstrated a more significant impact on β-cell glucose sensitivity. Conversely, RYGB was associated with more severe HG events, attributed to unchanged β-cell sensitivity to glucose changes. However, despite these differences, the authors did not identify any statistically significant discrepancy in the risk of PBSH between LSG and RYGB. In another study conducted by Lazar et al. (2019), an observational cohort design aimed to investigate PBSH in patients who underwent various bariatric procedures, including RYGB, omega-loop gastric bypass (OLGB), and LSG, over a year before the evaluation of the outcomes. Additionally, a control group of obese individuals awaiting surgery was included for comparison. The study assessed HG events using questionnaires, MMTT, and CGM. The results underscored the prevalence of PBSH, particularly following bypass procedures such as RYGB and OLGB, with occurrences of fasting hypoglycemia in addition to postprandial episodes. It is noteworthy that many cases of PBSH were asymptomatic, which could potentially lead to an underestimation of its true incidence. Lee et al. (2022) contributed to the understanding of PBSH by comparing MMTT hormonal responses in individuals experiencing HG after RYGB and LSG. Among those with PBSH, LSG patients exhibited lower peak glucose levels and reduced responses in glucagon and GLP-1 compared to RYGB patients. However, their insulin and GIP responses were similar. This finding suggests differences in meal-stimulated hormonal responses between LSG and RYGB in cases of PBSH, highlighting the need for further research to comprehend the underlying mechanisms. Nor Hanipah et al. (2018) took a comprehensive approach by investigating PBSH over a 13-year period at an academic center in the USA, among a large cohort of 6024 BS patients, with 1.4% presenting with symptomatic hypoglycemia. The study identified various causes of symptomatic HG, including postprandial hyperinsulinemic hypoglycemia (PHH), infections, diabetic medications, and poor carbohydrate intake.

Notably, most patients with symptoms achieved resolution without the need for revisional surgery or pancreatic resection. Effective management primarily involved dietary adjustments and, in some instances, individualized pharmacotherapy. Overall, the study revealed relatively low rates of PBSH, which could be effectively managed through non-surgical interventions. Additional insights from Lee et al. (2015) were focused on the clinical implications of PBSH. Their research indicated that HG symptoms could affect up to 34% of BS patients, with potential underreporting of asymptomatic cases. The study identified that preoperative symptoms of hypoglycemia were strongly associated with the occurrence of PBSH, irrespective of preoperative diabetes status. Additional factors linked to HG events included undergoing RYGB, female gender, and more time elapsed since surgery. The study highlighted RYGB patients as particularly vulnerable to this complication, underscoring the importance of systematic preoperative screening for hypoglycemic disorders among BS candidates, to recognize and effectively manage post-surgery symptoms. Although not conclusive, the study suggested that screening could aid in identifying individuals at risk of PBSH and enable targeted interventions, such as dietary modifications. Nilsen et al. in their relevant study (Nilsen et al. 2023) investigated post-BS glycemic variability (GV) in female patients without diabetes. Their findings indicated a significant increase in GV at six and twelve months postoperatively. Interestingly, while GV increased, the mean 24-h interstitial glucose (IG) concentration remained lower than preoperative levels. The study also noted an elevated proportion of patients experiencing HG events following surgery, with approximately 70% reporting moderate to severe hypoglycemic symptoms at twelve months post-surgery. This high prevalence of HG contrasted with some previous meta-analyses (Lupoli et al. 2022; Kabir et al. 2019), suggesting that PBSH might occur earlier than previously thought, potentially due to increased GV combined with lower mean glucose concentrations. Another study by Brix et al. (Brix et al. 2019) prospectively examined the prevalence and risk factors associated with PBSH. The study found that 25.6% of patients experienced HG after BS, with gastric bypass patients having the highest incidence at 32.6%. Factors such as a younger age at surgery and lower preoperative 2-h OGTT blood glucose were associated with a higher risk of PBSH. Hypoglycemia was linked to lower fasting and 2-h OGTT but higher 1-h OGTT plasma insulin levels postoperatively, in accordance with our findings. Concluding, the authors recommended routine OGTT follow-up post-BS and emphasized the importance of patient training for hypoglycemia management. Varma et al. (2017) conducted an investigation into the relationship between PBSH and weight regain (WR) in patients who underwent RYGB or LSG. The primary finding suggested that patients reporting PBSH symptoms had higher odds of experiencing WR of at least 10%. This association was more pronounced among RYGB patients, whereas the LSG group showed no significant relationship, potentially due to a smaller sample size and shorter follow-up duration. Long-term adherence to nutritional guidelines and time since surgery were also correlated with WR. The study postulated that PBSH, characterized by inappropriate insulin secretion and hormonal responses, might lead to behavioral modifications aimed at preventing HG, essentially contributing to WR. More specifically, the authors supported that insulin-induced HG could stimulate appetite and caloric intake through various physiological mechanisms, potentially exacerbating WR, ultimately underscoring the importance of systematic assessments of PBSH and the need for postoperative nutritional adherence to standardized dietary protocols.

In summary, recent literature suggests a higher incidence of PBSH compared to historical data. RYGB appears to have a more complex impact on insulin homeostasis, and a significant number of individuals with PBSH remain asymptomatic, underscoring the need for rigorous diagnostic protocols to detect latent cases. Furthermore, RYGB patients often experience wider fluctuations in plasma glucose levels, indicating compromised glycemic control and an elevated risk of hypoglycemic episodes. The presence of DM2 further complicates our understanding of PBSH, and patients with preoperative HG are at an increased risk of developing PBSH, with RYGB representing a notable risk factor in this regard as well. Therefore, comprehensive postoperative assessments, including OGTT, are crucial, especially for high-risk individuals. Effective management of PBSH involves adhering to standardized yet adaptable dietary protocols for at least two years following surgery. These findings, consistent with our main body of research, collectively highlight the multifaceted nature of PBSH, its varying prevalence, and the urgent need for further research to gain a comprehensive understanding of the underlying mechanisms and its clinical implications in the context of BS.

Strengths and limitations

The present study exhibits several notable strengths. Firstly, it conducts a comprehensive comparison between the two most commonly performed BS procedures, RYGB and LSG, concerning the occurrence of PBSH. In contrast to previous research, it employs a variety of diagnostic methods, including OGTT, MMTT, CGM, and questionnaires, ensuring a thorough examination of the comparative incidence. Moreover, the analysis doesn't

solely focus on the frequency of HG episodes but also considers glucose levels and hormonal responses during oral glucose loading. This multifaceted analysis contributes to a deeper understanding of how these surgical procedures impact glucose control and hormonal dynamics. Regarding statistical methodology, the study utilizes a robust random effects model, which is particularly valuable in cases of significant heterogeneity. Additionally, it conducts subgroup analyses and sensitivity analyses based on various criteria, further enhancing the reliability of findings.

On the other hand, it is essential to acknowledge the several limitations of this study that should be considered when interpreting its findings. Firstly, the study had to work with a relatively limited pool of available research, potentially affecting the precision of the conclusions drawn about comparative outcomes. Secondly, the majority of the studies included in the analysis were non-randomized, with only one randomized controlled trial (RCT) in the final study set (Capristo et al. 2018), which theoretically could introduce bias and affect the overall reliability of the findings. Additionally, many of the studies did not employ patient matching, a critical step in ensuring truly comparable groups, potentially introducing confounding variables that challenge the clarity and accuracy of comparisons. It is noteworthy that most of the studies analyzed were published before 2018, which may not fully represent the current state of surgical techniques and patient care practices. Furthermore, most subsets used to determine comparative effects were categorized as studies with an intermediate ROB level, indicating moderate data quality, and the presence of "ROBINS-I: Serious" records introduced inconsistency in the quality of evidence across different outcomes. Moreover, the study did not incorporate more specialized hormonal parameters, such as glucagon and incretins (GLP-1, GIP), due to a lack of relevant comparative data in the existing literature, limiting the comprehensiveness of the comparative analysis on hormonal homeostasis. Concerning data transformations, in addition to converting individual parameters into the "mean–SD" format, alterations were applied to the measurement units for glucose, insulin, and C-peptide concentrations, which have the potential to introduce measurement errors impacting result accuracy. Lastly, the use of varying cutoff points by different studies to define hypoglycemia (ranging from 40 to 50 mg/dl) and inconsistent utilization of questionnaires added variability to the results, potentially influencing the overall study conclusions.

Despite the array of limitations, we consider the contribution of this study to be substantial in quantifying the differences between RYGB and LSG concerning late glycemic homoeostasis. To the best of our knowledge, the analysis we presented is the first to incorporate nearly all available, albeit limited, comparative literature on PBSH. It explores a broad spectrum of outcomes and lays the groundwork for further research in this field.

Future potential

Looking forward, there is a clear need for additional original research and meta-analyses to bolster the reliability of estimations concerning the comparative impact of RYGB vs. LSG on the incidence of PBSH. To gain deeper insights, the inclusion of more data regarding hormonal responses following OGTT is imperative. This will help elucidate the roles of insulin, glucagon, and incretins in postoperative physiology. Furthermore, the investigation of these hormonal responses should extend beyond the initial two hours after meals, potentially covering the first 24-h post-glucose loading. This extended timeframe will contribute to a more comprehensive assessment of the risk of developing hypoglycemic episodes, including the exploration of nocturnal HG (Lupoli et al. 2020). There is also a pressing need for further research to evaluate the influence of DM2 on the comparative effectiveness of RYGB versus LSG in terms of overall weight loss and BMI reduction. Understanding how diabetes affects these outcomes is pivotal for customizing surgical approaches to different patient populations. Moreover, future studies should emphasize assessing the relative risk of PBSH specifically in DM2 patients undergoing RYGB. Our study has indicated a trend that identifies them as a particularly vulnerable patient group. Further exploration of this trend will shed light on specific considerations for diabetic individuals undergoing these BS procedures.

Conclusions

The primary aim of the present study was to scrutinize the comparative impacts of RYGB and LSG concerning PBSH. Additionally, we conducted an extensive exploration of a broad spectrum of outcomes related to glycemia and hormonal responses following oral glucose loading. This comprehensive approach sought to unveil potential pathophysiological mechanisms that underlie the observed long-term distinctions between these two BS approaches in terms of hypoglycemic risk. Our findings unveiled a 50% higher relative risk of developing PBSH with RYGB compared to LSG when utilizing OGTT data. This risk doubled when considering data derived from questionnaires. Moreover, we observed lower plasma glucose levels two hours after the commencement of OGTT in the RYGB group, which was considered a precursor to the development of hypoglycemic episodes. Patients who had undergone RYGB also displayed higher peak glucose levels and lower nadir levels. Additionally, plasma glucose variability was significantly greater in these patients,

suggesting that glycemic instability may present an even greater risk for diabetic individuals. These insights contribute to our comprehension of the implications of different BS techniques on glucose metabolism and PBSH risk, underscoring the need for personalized surgical approaches based on patient characteristics and diabetes status. Further research is warranted to validate and expand upon these findings.

Abbreviations

BMI	Body mass index
BPD	Biliopancreatic diversion
BS	Bariatric surgery
cc	Cubic centimeters
CENTRAL	Cochrane Central Register of Controlled Trials
CGM	Continuous glucose monitoring
$CI_{95\%}$	95% Confidence interval
cm	Centimeters
df	Degrees of freedom
dl	Deciliters
DM2	Type 2 diabetes mellitus
DS	Duodenal switch
EBW	Excess body weight
EBWL	Excess body weight loss
EHSS	Edinburgh hypoglycemia symptom scale
Fr	French (catheter scale)
g	Grams
GIP	Gastric inhibitory polypeptide (glucose-dependent insulinotropic polypeptide)
GLP-1	Glucagon-like peptide-1
GV	Glycemic variability
HbA1c	Glycosylated hemoglobin
HG	Hypoglycemia/hypoglycemic
HK	Hartung–Knapp
HOMA-IR	Homeostatic model assessment for insulin resistance
hr	Hour
IG	Interstitial glucose
IQR	Interquartile range
Kcal	Kilocalories
Kg	Kilograms
l	Liters
LSG	Laparoscopic sleeve gastrectomy
m	Meters
MA	Meta-analysis
MD	Mean difference
mg	Milligrams
MH	Mantel–Haenszel
min	Minutes
MMTT	Mixed-meal tolerance test
MRA	Meta-regression analysis
ng	Nanograms
NIPHS	Non-insulinoma pancreatogenous hypoglycemia syndrome
NOS	Newcastle–Ottawa scale
OGTT	Oral glucose tolerance test
OLGB	Omega-loop gastric bypass
OR	Odds ratio
PB	Publication bias
PBSH	Post-bariatric surgery hypoglycemia
PHH	Postprandial hyperinsulinemic hypoglycemia
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
Q	Questionnaires
RCT	Randomized controlled trial
REML	Restricted maximum likelihood (statistical method)
ROB	Risk of bias
ROBINS-I	Risk of bias in non-randomized studies-of interventions
RR	Relative risk
RYGB	Roux-en-Y gastric bypass
SA	Sensitivity analysis
SADI-S	Single anastomosis duodeno-ileal bypass
SD	Standard deviation
SGA	Subgroup analysis
SS	Search strategy
URL	Uniform resource locator
VSG	Vertical sleeve gastrectomy
WL	Weight loss
WR	Weight regain
ΔBMI	BMI change (from baseline)
ΔWC	Change in waist circumference (from baseline)

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s42269-023-01145-3.

Additional file 1: Supplementary figures containing graphs that complement the study demographics, as well as the analysis of primary and secondary outcomes.

Additional file 2: Qualitative assessment forms of the studies included, for each domain of the ROBINS-I tool. Abbreviations: ROBINS-I: Risk of Bias in Non-randomized Studies of Interventions.

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Author contributions
SA has given substantial contributions to the conceptualization, data curation, formal analysis, data investigation, methodology implementation, project administration, acquisition of resources, software utilization, procedure validation, visualization of results, original draft formulation, as well as the final review & editing of the present study. DA has given substantial contributions in data curation, formal analysis, data investigation, project administration, acquisition of resources, as well as procedure validation. SS has given substantial contributions in conceptualization, methodology implementation, software utilization, procedure validation, as well as critical review of the final manuscript. DT has given substantial contributions in supervision, data validation, as well as critical review of the final manuscript. GZ held the position of general supervisor during the elaboration of the present study. All authors have read and approved the final manuscript.

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Availability of data and material
All the data utilized and statistical code developed are available at the following link: https://github.com/sotbike/SILENUS.git.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
Sotirios Artsitas (SA) [1], Dimitrios Artsitas (DA) [2], Spyridon Smparounis (SS) [3], Dimitrios Theodorou (DT) [4], George C. Zografos (GZ) [5] declare that they have no conflict of interest.

Author details
[1]Geniko Nosokomeio Athenon Ippokrateio, Vasilisis Sofias Str. 114, 11527 Athens, Greece. [2]1st Propaedeutic Department of Surgery, School of Medicine, National and Kapodistrian University of Athens (NKUA), Mikras Asias Str. 75, 11527 Athens, Greece. [3]2nd Department of Orthopaedics, KAT Hospital, Nikis

Str. 2, 14561 Kifissia, Athens, Greece. [4]Professor at National and Kapodistrian University of Athens (NKUA), Geniko Nosokomeio Athenon Ippokrateio, Vasilisis Sofias Str. 114, Athens, Greece.

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