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Meta-analysis of randomized controlled trials for the development of the International Federation for Surgery of Obesity and Metabolic Disorders-European Chapter (IFSO-EC) guidelines on multimodal strategies for the surgical treatment of obesity

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Abstract

Background: Randomized, controlled trials (RCTs) comparing the effectiveness of metabolic bariatric surgery (MBS) in addition to one or more treatment interventions for obesity (i.e., lifestyle structured interventions—LSI, medical therapy—MT, obesity management medication—OMM or endobariatric procedures—EP) are lacking. This study aims to assess the effectiveness of multiple simultaneous (before or immediately after MBS) interventions for treating obesity.

Methods: We performed a meta-analysis including all RCTs enrolling patients undergoing different MBS procedures add-on to other anti-obesity strategies (LSI, MT, OMM or ES) versus MBS alone, with a duration of at least 6 months. The primary outcome was BMI at the end-point; secondary end-points included percentage total and excess weight loss (%TWL%, and EBWL%), total weight loss (TWL), fasting plasma glucose (FPG), HbA1c, surgical and non-surgical severe adverse events (SAE), mortality, remission of type 2 diabetes, hypertension, dyslipidemia and health-related quality of life (HR-QoL).

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Results: A total of 25 RCTs were retrieved. The addition of either OMM (i.e., liraglutide) or EP (i.e., intragastric balloon—IB, endosleeve-ES) to MBS was associated with a significantly lower BMI at the end-point ($p = 0.040$). The addition of liraglutide only to MBS was associated with a greater %EWL%, but not %TWL and TBWL ($p = 0.008$). Three trials evaluated end-point HbA1c, showing a significant reduction in favour of liraglutide as an add-on therapy to MBS ($p = 0.007$). There was no mortality.

Conclusions: MBS combined with non-surgical approaches appears more effective than MBS alone in reducing BMI. Further RCTs on combined therapies to MBS for severe obesity are needed to enhance the tailoring of treatment for severe obesity.

KEYWORDS
bariatric surgery, GLP-1 analogue, meta-analysis, obesity therapy

1 | INTRODUCTION

The global prevalence and burden of obesity and diabetes are rapidly increasing, becoming a major public health concern worldwide.[1] The dramatic impact of overweight and obesity on complications, mortality, quality of life and healthcare costs has been extensively described.[2] Obesity-related medical conditions (i.e., diabetes mellitus, hypertension, dyslipidemia, obstructive sleep apnea syndrome [OSAS], metabolic dysfunction–associated fatty liver disease [MAFLD]) can negatively impact public health and healthcare economic burden worldwide.

Lifestyle changes can play an important role in managing overweight and obesity. Patients should always be encouraged to adopt a healthy and balanced lifestyle, adding psychological support, limiting the intake of processed and high-calorie food and practising regular physical activity.[3] However, lifestyle changes alone are insufficient to achieve or maintain weight loss goals, which is why further add-on therapies must be considered.

Pharmacological and surgical (i.e., bariatric and endoscopic) therapies have been developed to address the complex nature of obesity and its related medical conditions, aiming at reducing long-term healthcare costs.[4–6]

Pharmacological treatments for obesity include a high number of approved drugs, such as orlistat, lorcaserin, phentermine/topiramate, naltrexone/bupropion, liraglutide, semaglutide and tirzepatide. These drugs mostly act by reducing food intake and increasing satiety, thereby promoting weight loss.[7–9] Moreover, an impressive number of upcoming obesity management medications (OMM) are currently under investigation, such as GLP1/glucagon dual agonists, GIP/GLP1/glucagon triagonists and leptin sensitizers, possibly revolutionizing the overall management of overweight and obesity.[10]

Metabolic and bariatric surgery (MBS), such as Adjustable Gastric Banding (AGB), Sleeve Gastrectomy (SG), Roux-en-Y Gastric Bypass (RYGB), One Anastomosis Gastric Bypass (OAGB), Bilio-Pancreatic Diversion with Duodenal Switch (BPD-DS) Single anastomosis Duodeno–Ileal Bypass with Sleeve Gastrectomy (SADI-S) have also been approved for the treatment of obesity. Patients undergoing these procedures are more likely to achieve significant and sustained weight loss versus other therapies.[11]

Endoscopic procedures, such as Intragastric Balloons (IB), Endo-Barrier System (EBS) and Endoscopic Sleeve Gastroplasty (ESG) are minimally invasive options, showing promising results in terms of weight loss, but to a lesser extent when compared to MBS.[11,12]

Notably, although the efficacy of OMM, MBS and endoscopic procedures has been widely demonstrated, patients can experience suboptimal weight responses after all three treatment modalities.[13] Thus, there is increasing evidence that these options, if used alone, may not be sufficient to effectively achieve and maintain an appropriate body weight loss and/or control obesity-related medical conditions.[14] Especially if one considers that weight loss should not be the only parameter to indicate the efficacy of any anti-obesity treatment strategy. Instead, long-term weight-loss outcomes, glycaemic control, remission of obesity-related medical conditions and quality of life must also be considered.

All the above-mentioned considerations highlight the need for a multimodal treatment of obesity. Unfortunately, very few studies have assessed the efficacy and safety of concomitant interventions (i.e., extensive lifestyle interventions, pharmacological therapy, endoscopic procedures and MBS) for obesity management.[15–17] In addition, there are many randomized controlled trials (RCT) assessing the long-term outcomes of a single surgical procedure without including the standard preoperative guidance programme—an additional structured lifestyle intervention.[12,18]

Several systematic reviews and meta-analyses evaluating adjunctive therapy options with bariatric surgery have been published in recent years. However, they included RCTs not fulfilling our inclusion criteria (i.e., (i) RCTs on multimodal therapy only in patients with either recurrent weight gain or suboptimal weight loss,[19] (ii) using non-preplanned additional strategies to MBS,[20,21] (iii) adjunctive therapies before performing MBS (i.e., not on multimodal therapy)[22] or (iv) including also RCTs comparing MBS with LSI.[23]

The International Federation for Surgery of Obesity and Metabolic Disorders-European Chapter (IFSO-EC) recognized the need to

develop rigorous guidelines aimed at further improving healthcare professionals' awareness of the importance of a 'multimodal' approach (from the early phase of preoperative assessment and surgical optimization) for the treatment of obesity and associated medical problems in patients undergoing MBS.

The aim of this systematic review and meta-analysis was therefore to assess the efficacy and safety of MBS in addition to at least one other treatment for obesity (i.e., structured lifestyle intervention, pharmacological treatment or endoscopic bariatric procedures) in patients with BMI ≥30 Kg/m^2 and indication for MBS in trials with a follow-up of at least 26 weeks.

2 | MATERIALS AND METHODS

This meta-analysis was designed following the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[24] and was developed in order to address three clinical questions, using the PICO conceptual framework (i.e., Population, Intervention, Comparison and Outcome).

The following three PICOs have been developed for assessing the efficacy and safety of MBS in addition to other strategies:

1. In patients with BMI ≥30 kg/m^2 and an indication for MBS, is a pre- and/or post-treatment with extensive structured lifestyle interventions preferable to MBS alone for the treatment of obesity?
2. In patients with BMI ≥30 kg/m^2 and an indication for MBS, is a pre- and/or post-treatment with approved OMM preferable to bariatric and metabolic surgery alone for the treatment of obesity?
3. In patients with BMI ≥30 kg/m^2 and an indication for MBS, is a pre- and/or post-treatment with endoscopic bariatric procedures preferable to MBS alone for the treatment of obesity?

2.1 | Search strategy and selection criteria

This meta-analysis is part of a wider meta-analysis of RCTs on metabolic surgery, obesity and diabetes[11,12] uploaded on PROSPERO (http://www.crd.york.ac.uk/PROSPERO, #160359) previously conducted for the development of GRADE-based methodology Italian Guidelines for the metabolic and bariatric surgical treatment of obesity (Società Italiana di Chirurgia dell'Obesità e delle malattie metaboliche -SICOB)[25] and updated up to 1 June 2024. Briefly, the present analysis includes all RCTs enrolling patients affected by obesity undergoing different MBS procedures (AGB, SG, RYGB, OAGB, SADI-S, VBG, BPD and GCP) in addition to other anti-obesity strategies (extensive lifestyle interventions—LSI, OMM or EP), with a duration of at least 6 months. RCTs excluded were on either recurrent weight gain (WR) or insufficient weight loss (IWL) after MBS unless the use of LSI or other obesity-management strategies was preplanned for all included patients (not only for those with suboptimal clinical response). RCTs not including MBS as one of the possible obesity-management strategies were also excluded. For obesity management medications, only RCTs adopting approved doses for the treatment of obesity (e.g., liraglutide [3.0 mg], semaglutide [2.4 mg] or tirzepatide [10–15 mg]) have been included.

A Medline and Embase search was performed using the following keywords: obesity AND (surgery OR AGB OR SG OR RYGB OR OAGB OR SADI-S OR VBG OR BPD OR GCP) AND (orlistat OR phentermine OR topiramate OR lorcaserin OR naltrexone OR bupropion OR liraglutide OR semaglutide OR tirzepatide OR Intragastric Balloon OR EndoBarrier System OR Endoscopic Sleeve Gastroplasty). Detailed information on the search strategy is reported in Table S1. Studies in the English language published elsewhere (i.e., conference abstracts, abstracts of dissertations for university degrees) were not included.

2.2 | Possible interventions as add-on therapy to MBS

Lifestyle intervention: Any structured intervention more than the standard guidance programme of MBS, maintained for all the study period. Programmes should include at least one of the following items: dietary intake, physical activity, healthy eating behaviour, psychological guidance or a combination to be considered structured lifestyle interventions.

Drugs: Orlistat or phentermine plus topiramate or lorcaserin or naltrexone plus bupropion or liraglutide (3.0 mg) or semaglutide (2.4 mg), or tirzepatide (10–15 mg).

Endoscopic bariatric procedures: Intragastric Balloons (IB), EndoBarrier System (EBS) and Endoscopic Sleeve Gastroplasty (ESG).

2.3 | Data extraction

Summary estimates of the variables of interest at end-point(i.e., BMI), percentage of Excess Body Weight Lost (EBWL%), Fasting Plasma Glucose (FPG), Glycated Haemoglobin (HbA1c), surgical and non-surgical Serious Adverse Events (SAE), complete and partial type 2 diabetes mellitus (T2DM) remission, hypertension and dyslipidemia remission were defined following the American Diabetes Association 'Standards of Medical Care in Diabetes',[26] Remission of OSAS, defined as continuous positive airway pressure(CPAP) discontinuation, was taken into consideration only where crearly reported in the main manuscripts retrieved. Data extraction was performed independently by two of the authors (B.R., G.B), and conflicts were resolved by a third investigator (M.M.).

The information collected for each trial is summarized in Table 2S.

The risk of bias was assessed using the Cochrane recommended tool to assess the risk of bias in RCTs.[27] The risk of bias was described and assessed in seven specific domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases. The results of these domains were graded as low, high or uncertain risk of bias.

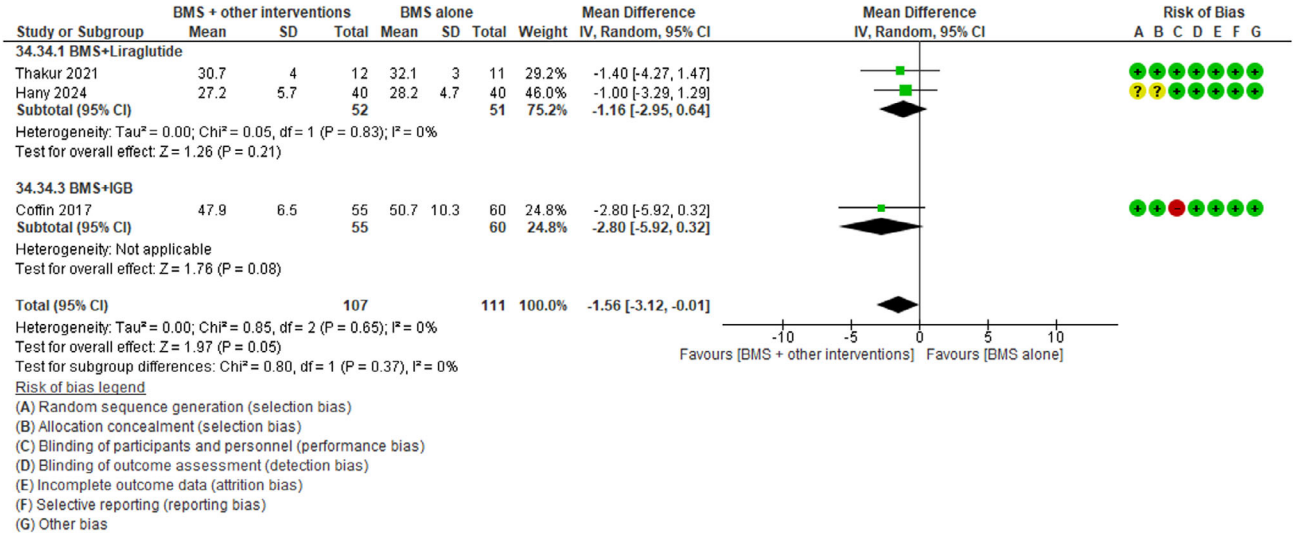

FIGURE 1 Effects of metabolic and bariatric surgery (MBS) as add-on therapy to other strategies (LSI: Life Style Interventions; OMMs: Obesity Management Medications; Endoscopic bariatric procedures) in comparison with MBS alone on end-point BMI. GRADE evidence: 'low' for BMS + liraglutide and 'very low' for BMS + IGB (see Table 3S).

2.4 | Data analysis

The primary end-point was BMI, whereas secondary end-points included TBWL, TBWL%, EBWL%, Fasting Plasma Glucose (FPG), HbA1c, surgical and non-surgical Serious Adverse Events (SAE), mortality, complete and partial T2DM remission, hypertension and dyslipidemia remission and quality of life (QoL). Mean and 95% Confidence Intervals for continuous variables were calculated as standardized mean differences; Mantel–Haenszel Odds Ratio (MH-OR) for categorical variables were calculated using random effect models.

A pre-specified analysis on trials comparing MBS add-on to either structured LSI or approved OMM, or endoscopic surgery, with trials on MBS alone, was performed. A total of 16 RCTs were analysed. To compare these two latter groups of trials, a 'case–control' design was used, by matching with a 1:1 ratio RCTs performed assessing MBS in adjuntion to other anti-obesity strategies with trials using MBS alone. Matching parameters considered were: the same type of surgical intervention, mean BMI at entry±2 Kg/m^2, mean age at entry ±5 years and duration of treatment ±6 months. Trials used as 'control study' were chosen among trials included in a previously published recent meta-analysis.[11] A study can represent, whenever needed, the control for more than one 'case study'.

Statistical heterogeneity was assessed by I^2 test, whereas Funnel plots were used to detect publication bias for principal end-points with at least 10 trials.

All analyses were performed using Review Manager (RevMan), Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

The GRADE methodology[28] was used to assess the quality of the body of retrieved evidence, using the GRADEpro GDT software (GRADEpro Guideline Development Tool. McMaster University, 201 518. Available from gradepro.org).

3 | RESULTS

3.1 | Retrieved trials

The trial flow summary is reported in Figure 1S of Supporting Information. The search of the Medline and Embase databases allowed the identification of 325 items. After excluding 292 articles by reading the titles and the abstracts, a further eight trials were excluded after reviewing the full text. The remaining 25 trials fulfilling all the inclusion criteria have been included in the main analysis.

The quality of studies was heterogeneous (Figure 2S of Supporting Information). All trials were open-label except four.[16,17,29,30] In several trials[17,31–38] the allocation, blinding of assessors and attrition rate were inadequately or not described.

3.2 | Trials specifically designed to assess the effects of multiple anti-obesity interventions

Four trials[15–17,29] used at least one further anti-obesity intervention in addition to MBS in comparison with MBS alone. Three trials were performed using liraglutide[16,17,29] and one IB.[15] No trials assessing the effects of LSI add-on to MBS versus MBS alone have been retrieved. The main characteristics of these trials are reported in Table 2S of Supporting Information.

3.3 | Effects on body weight

All the four trials included,[15–17,29] except one[29] which did not report mean end-point BMI ± SD, provided information on BMI at the end-point (primary end-point). The addition of either liraglutide or IGB was

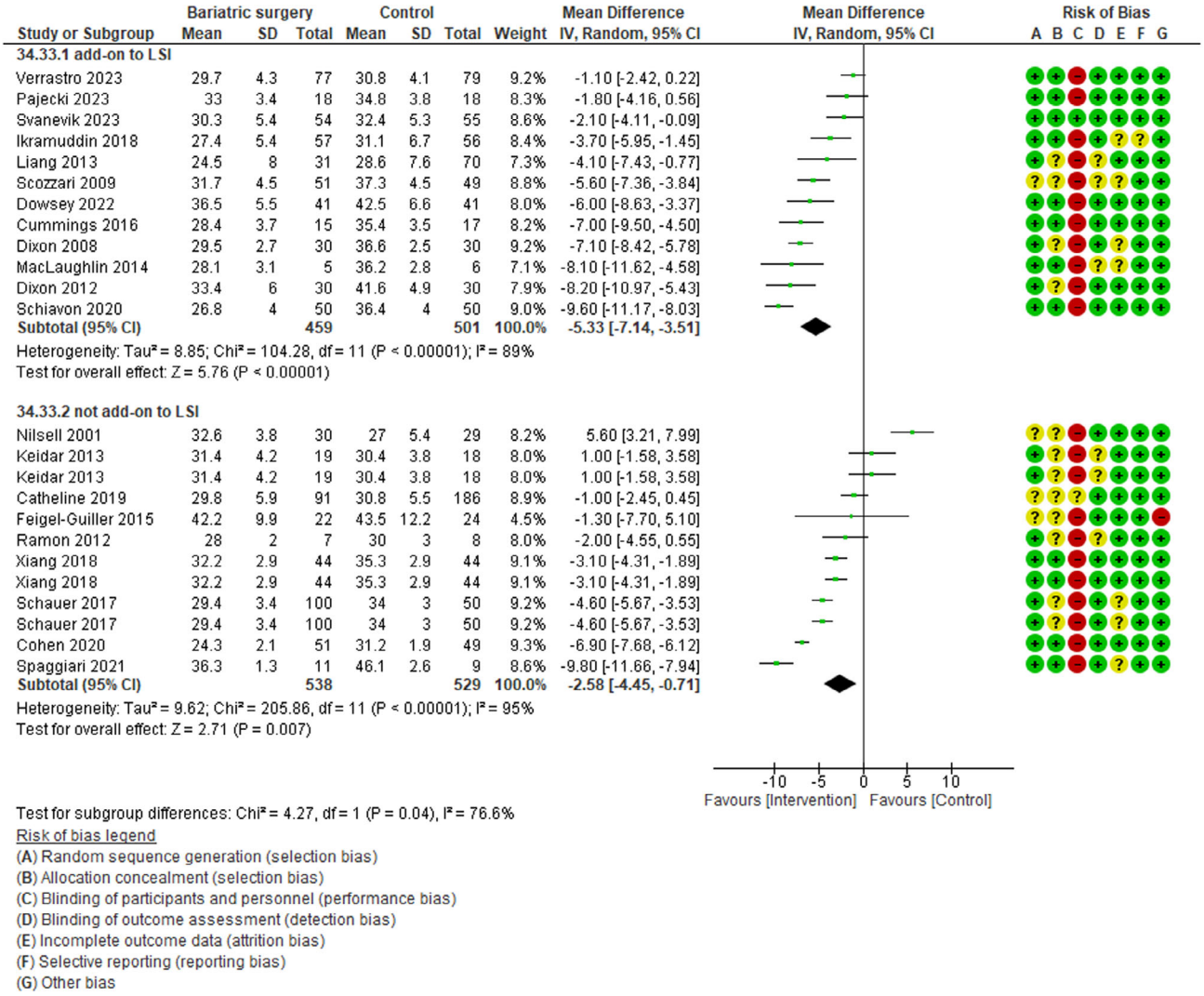

FIGURE 2 Effects of the addition of Life Style Interventions (LSI) to MBS on end-point BMI in comparison with matched trials performed with MBS alone. GRADE evidence: 'moderate' (see Table 3S).

associated with a significantly lower BMI at the end of the study (WMD: −1.59 [−3.15, −0.04] Kg/m^2, $p = 0.040$, $I^2 = 0\%$, with no significant differences across groups; Figure 1). The evaluation of the quality of retrieved evidence for PICO 2 and 3 (primary end-point) was 'low' for BMS + liraglutide and 'very low' for BMS + IGB (Table 3S).

Information on TBWL,[16,29] TBWL%[16,17] and EBWL%[16,17] was available only for two trials all performed with liraglutide. The addition of liraglutide to MBS was associated with a greater EBWL%, but not TBWL and TBWL%, with a (WMD of 9.06 [2.38, 15.74] %, $p = 0.008$, I^2: 52%; Figure 3–5S of Supplementary Materials).

3.4 | Glucometabolic control and obesity-related medical conditions

Only one trial reported information on FPG at the end-point without significant differences between groups (WMD: −1.20 [−16.57, 14.17], $p = 0.88$). Three trials evaluated end-point HbA1c, showing a significant reduction in favour of liraglutide add-on to MBS when compared to MBS alone (WMD: −0.48 [−0.83, −0.13] %, $p = 0.007$, I2: 0%; Figure 6S of Supplementary Materials). Two trials reported information on complete T2DM remission[16,17,29] with no effect of combined therapy on this end-point (MH-OR (in favour of combined therapy): 1.29 [0.11, 15.51], $p = 0.84$, I^2: 24%; Figure 7S of Supplementary Materials). One, two and three studies (all analysing liraglutide as add-on therapy) reported OSAS, hypertension and dyslipidemia remission rates, respectively. The combined therapy compared to MBS alone did not provide any significant advantages in terms of obesity-related medical conditions remission (Figures 8–10S of Supplementary Materials).

3.5 | All-cause mortality and serious adverse events

No deaths were reported among included trials.[15–17,29] Only one periprocedural SAE was reported in one trial in the interventional arm.[16] No other SAEs during follow-up were recorded.

3.6 | Quality of life

Out of the four available trials, three[15,16,29] reported measures of QoL. Different tools were used for QoL assessment: Short Form Health Survey-12 (SF-12)[15]; Impact of Weight on Quality of Life questionnaire (IWQOL)[15,29] and Bariatric Analysis and Reporting Outcome System (BAROS).[16] Heterogeneity of instruments and reporting did not allow any formal meta-analysis. However, by considering individual studies, measures of QoL did not show any significant difference between combined therapies and MBS alone.

3.7 | Case–control study on trials adopting either multiple interventions or MBS alone

A preplanned sensitivity analysis[20] was carried out to assess the effects of the addition of other anti-obesity interventions to MBS (combined therapy) in a 'case–control' modality. For the 'case study' we intended RCT comparing combined therapy either with LSI or placebo (i.e., MBS add-on to LSI vs. LSI or MBS add-on to an OMM vs. LSI/Placebo or MBS add-on to endobariatric treatments vs. LSI/Placebo) and reporting data on BMI at the end-point. Studies labelled as 'control' are RCTs matched with the case study for the type of MBS procedure employed (the same), mean age, BMI at entry and duration of follow-up (as for traditional nested case–control study) as reported in detail in the Method section.

We retrieved 12 studies performed with several types of MBS in addition to a structured LSI[30,31,35–44] versus LSI alone (no trials with other anti-obesity strategies have been retrieved); these latter trials were matched with 12 control RCTs performed without any structured LSI in addition to MBS. Three trials[45–47] have been selected as control each for two case studies, due to the lack of suitable control trials fulfilling all the matching criteria selected.

3.8 | Weight loss outcomes

Main characteristics of the 12 'cases' and the nine 'control trials' are reported in Table 2S of Supporting Information.

The addition of LSI to MBS was associated with a statistically significant greater reduction of end-point BMI (p for interaction: 0.040; Figure 2) in comparison with trials using MBS without LSI. The evaluation of the quality of retrieved evidence for PICO 1 (primary end-point) was 'moderate' (Table 3S).

Information regarding TBWL has been reported by seven case trials and five control studies. Combined therapy with LSI was associated with higher values of TBWL when compared to RCTs performed with MBS alone (Figure 11S of Supplementary Materials). Similar figures have been observed both for TBWL% (#trials: 6) and EWBL% (#trials: 6), despite not achieving any statistically significant between-group differences (Figures 12S and 13S of Supplementary Materials).

3.9 | Glucometabolic control and associated obesity-related complications

Only four trials reported information on end-point FPG, showing a statistically significant reduction in favour of the addition of LSI to MBS (p for interaction = 0.040; Figure 14S of Supplementary Materials).

Eight trials evaluated end-point HbA1c, showing a non-significant difference between the two groups of RCTs (Figure 15S of Supplementary Materials).

Only six trials reported information on complete T2DM remission. The addition of LSI to MBS, when compared to LSI alone, was associated with a significantly higher rate of T2DM remission (p for interaction: 0.008, I^2: 85%; Figure 16S of Supplementary Materials).

No formal analyses could be performed for OSAS, HTN and DL remission rates due to the scarcely reported remission rates of these obesity-related medical conditions.

3.10 | All-cause mortality and serious adverse events (SAEs)

Only a few, both periprocedural and overall (during follow-up), deaths were reported among included trials, not allowing any reliable analyses (data not shown). No differences were observed between groups for both periprocedural and overall SAE (Figures 17S and 18S of Supplementary Materials).

4 | DISCUSSION

Obesity has become a global public healthcare concern.[1] Several studies have shown that obesity is a major contributor to the risk of an expanding group of debilitating diseases, such as T2DM, heart failure, hormonal and non-hormonal cancers, end-stage liver and kidney disease and osteoarthritis.[1,2]

Available weight loss options based on LSI alone often fail to attain sustainable results and usually require adjunctive approaches, such as OMM and MBS.[8,9] The efficacy of MBS in terms of weight loss and obesity-related medical conditions has been demonstrated by several trials and meta-analyses.[48–50] However, few authors have assessed the effectiveness of combining more than one anti-obesity strategy.

As previously stated in the Introduction, in literature, there are multiple systematic reviews and meta-analyses evaluating adjunctive therapy options with bariatric surgery. However, they did not include studies assessing the effect of preplanned multimodal strategies, but only RCTs adopting additional treatment in patients failing to MBS[19] or as bridging therapy.[22]

Considering one of the most recently published meta-analyses of RCTs[11] including 65 studies, only a limited fraction reported structured lifestyle interventions as add-on therapy to MBS. In this meta-analysis,[11] many of the included trials compared different

surgical procedures with LSI, as the latter was an alternative therapy to MBS.[11] Similar considerations can also be made for the combination of MBS with either OMM or endoscopic bariatric interventions. Only a few studies explored the efficacy of 'multimodal' strategies with non-surgical approaches in obese patients with surgical indication.[15–17,29] The above assumptions can be explained by the fact that insufficient evidence is available to conclude to what extent changes in BMI are related to improving health outcomes in the context of MBS.

Very few studies were designed to assess the addition of either OMM or IB to MBS. The present meta-analysis shows that adding either liraglutide or IB to MBS versus MBS alone is associated with an overall higher reduction in BMI and EBWL%. The paucity of retrieved studies did not allow any reliable subgroup analyses for OMM and IB, which did not achieve statistical significance when analysed separately, easily explainable by underpowered analyses. Moreover, the retrieval of a scarce number of RCTs strongly limits the strength of recommending either pharmacological or endoscopic treatment in conjunction with MBS. Speculatively, for the same reason, the combined therapy did not provide any significant advantage in terms of obesity-related medical conditions remission and glucometabolic control.

More interestingly, we did not retrieve any RCT comparing LSI add-on to MBS to MBS alone, preventing any direct evidence on the effectiveness of maintaining LSI even among patients undergoing MBS. To overcome this lack of evidence, we decided to perform a 'case–control meta-analysis' by matching, with a 1:1 ratio, RCTs performed using MBS in addition to LSI with trials using MBS alone.[51] RCTs adopting LSI together with MBS were associated with a statistically significant greater reduction of endpoint BMI, higher values of TBWL and lower end-point FPG levels, with no increase of SAE in comparison with RCTs using MBS alone; this could be related to the additional improvement in impaired physical function, cardiovascular fitness and mobility impairments intrinsically associated with obesity. A main limitation of this new statistical 'artefact' that we have called 'case–control meta-analysis' is the comparison of RCTs with similar but not identical characteristics. However, the comparison between the matching parameters between the two datasets of RCTs did not highlight any statistically significant differences.

Several other limitations should be acknowledged when interpreting the results reported by our meta-analysis. The main limitation is represented by the paucity of retrieved studies (with limited follow-up period) comparing MBS in conjunction with other anti-obesity strategies to MBS alone. Despite some of the assessed end-points reaching statistical significance, the limited number of studies, their heterogeneity and the low number of included patients limited the reliability of this analysis. Moreover, only one study on endobariatric procedures was retrieved (i.e., IB), preventing any reliable conclusions; moreover, it cannot be ruled out that other EP can be more effective. Another crucial point is represented by the retrieval of few studies on OMMs in conjunction with MBS, all performed with a relatively outdated drug (i.e., liraglutide). Other newer molecules have shown greater efficacy in reducing weight and obesity-related medical conditions, such as semaglutide and tirzepatide.[7–9] It can be speculated that the use of these newer OMMs could provide better results in terms of weight-loss outcomes, but, nowadays, no sufficient patient-level data are available. Moreover, these newer drugs have been demonstrated to have a greater efficacy on glycaemic control, metabolic-associated fatty liver disease (MAFLD), and OSAS remission; therefore, they could also have favourable outcomes not observed with liraglutide.[7–9] Not to mention, since various postulated mechanisms of weight loss associated with both MBS and OMMs are complex and multifactorial, adding further evidence for clinicians in counselling a possible role of adjunctive OMM strategy to MBS to reach a higher sustained and efficient weight-lowering effect is mandatory, taking into consideration the combination of their different biological effects and impact on humoral and enteroendocrine signalling. The quality of trials is not homogeneous, possibly introducing publication bias. The open-label design, which is inevitable when comparing surgical and non-surgical strategies (see case–control analyses), could produce a bias due to a possible placebo effect of surgery. Furthermore, in some of the included trials, the number of patients lost at follow-up was significant. Despite no differences in terms of rates of patients lost at follow-up between MBS and LSI groups having been observed, this limitation could reduce the reliability of the final results. The included RCTs evaluating combined treatment to MBS alone were small, with limited follow-up time. While some studies report promising results during the initial weight-loss phase, more and larger studies with longer follow-up times are necessary to evaluate nadir weight loss and weight regain. One study reports non-inferior weight loss without using GLP-1RA during 12 months follow-up.[25] The aim of our work is not to establish whether a specific surgical treatment is superior to the same intervention combined with others, but to highlight the importance and paramount role of multimodal strategies to provide healthcare professionals with the most reliable and feasible options in the obesity armamentarium and how to combine them for the most effective tailored therapy. Finally, the reliability of a meta-analysis is often limited by heterogeneity, which suggests that the observed effect of a treatment may differ since it is affected by the design of the parental trials. Heterogeneity could represent a major limitation of any meta-analysis unless underlying mechanisms are identified. In the present meta-analysis, no attempts to explore possible sources of heterogeneity have been performed due to the paucity of retrieved studies. However, the number of studies on this area is still scarce, and most of them did not evaluate obesity management options as a part of a preplanned strategy. The publication of further large-scale trials on MBS added to other anti-obesity strategies would, therefore, be mandatory for better clarifying the role of multimodal treatments of overweight and obesity in surgical patients. Further research should focus on examining the long-term effect of novel incretin-based obesity medications agonists (i.e., tirzepatide, GLP-1/GIP receptor agonists) compared with MBS to enhance appropriate patient counselling and perioperative planning, taking into consideration the newly published definition of Clinical Obesity by the Lancet Commission and possible adipocyte subtype-specific responses involved in the complex pathophysiology and classification

of obesity.[52] Nevertheless, future large RCTs should represent the stepping stone for science-based health counselling guiding tailored combination protocols for patients affected by obesity.

5 | CONCLUSIONS

The results obtained in the present analysis highlight the potential of adding specific lifestyle interventions to MBS. Of all available add-on therapies, OMM appears to represent the most promising approach in cases of a suboptimal clinical response after MBS. Moreover, particularly for those patients who do not achieve sustained T2DM control after MBS or experience weight recurrence, optimization with newer, more efficacious pharmacological treatment options (i.e., tirzepatide, semaglutide) might be required. Therefore, further RCTs exploring the impact on long-term weight loss with a combined use of bariatric surgery and newer GLP-1 receptor agonists are necessary. Nevertheless, the use of GLP-1 receptor agonists among patients experiencing weight recurrence following MBS is another area requiring further research.

AUTHOR CONTRIBUTIONS

MM, AB and MDL were involved in each of the following points: Design; Data collection; Analysis; Writing the manuscript. All the other authors were involved in each of the following points: Manuscript revision; Writing manuscript.

The panel for the IFSO-EC on the surgical treatment of obesity using multimodal strategies is composed of: Maurizio De Luca, Amanda Belluzzi, Paulina Salminen, Marco Bueter, Juan Pujol-Rafols, Nasser Sakran, Christine Stier, Halit Eren Taskin, Sonja Chiappetta, Francesco Maria Carrano, Nicola Di Lorenzo, Simon Nienhuijs, Ramón Vilallonga Puy, Erik Stenberg, Marloes Emous, Gerhard Prager, Jacques Himpens, Daniel Moritz Felsenreich, Antonio Iannelli, Chetan Parmar, Catalin Copaescu, Martin Fried, Elena Ruiz-Úcar, and Matteo Monami.

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CONFLICT OF INTEREST STATEMENT

Authors have no relevant COI to declare. All the authors approved the final version of this manuscript. Dr. M.M. is the person who takes full responsibility for the work as a whole, including the study design, access to data and the decision to submit and publish the manuscript.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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