Association of metabolic–bariatric surgery with long-term survival in adults with and without diabetes: a one-stage meta-analysis of matched cohort and prospective controlled studies with 174 772 participants

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Summary

Background Metabolic–bariatric surgery delivers substantial weight loss and can induce remission or improvement of obesity-related risks and complications. However, more robust estimates of its effect on long-term mortality and life expectancy—especially stratified by pre-existing diabetes status—are needed to guide policy and facilitate patient counselling. We compared long-term survival outcomes of severely obese patients who received metabolic–bariatric surgery versus usual care.

Methods We did a prespecified one-stage meta-analysis using patient-level survival data reconstructed from prospective controlled trials and high-quality matched cohort studies. We searched PubMed, Scopus, and MEDLINE (via Ovid) for randomised trials, prospective controlled studies, and matched cohort studies comparing all-cause mortality after metabolic–bariatric surgery versus non-surgical management of obesity published between inception and Feb 3, 2021. We also searched grey literature by reviewing bibliographies of included studies as well as review articles. Shared-frailty (ie, random-effects) and stratified Cox models were fitted to compare all-cause mortality of adults with obesity who underwent metabolic–bariatric surgery compared with matched controls who received usual care, taking into account clustering of participants at the study level. We also computed numbers needed to treat, and extrapolated life expectancy using Gompertz proportional-hazards modelling. The study protocol is prospectively registered on PROSPERO, number CRD42020218472.

Findings Among 1470 articles identified, 16 matched cohort studies and one prospective controlled trial were included in the analysis. 7712 deaths occurred during 1·2 million patient-years. In the overall population consisting 174 772 participants, metabolic–bariatric surgery was associated with a reduction in hazard rate of death of 49·2% (95% CI 46·3–51·9, p<0·0001) and median life expectancy was 6·1 years (95% CI 5·2–6·9) longer than usual care. In subgroup analyses, both individuals with (hazard ratio 0·409, 95% CI 0·370–0·453, p<0·0001) or without (0·704, 0·588–0·843, p<0·0001) baseline diabetes who underwent metabolic–bariatric surgery had lower rates of all-cause mortality, but the treatment effect was considerably greater for those with diabetes (between-subgroup I^2 95·7%, p<0·0001). Median life expectancy was 9·3 years (95% CI 7·1–11·8) longer for patients with diabetes in the surgery group than the non-surgical group, whereas the life expectancy gain was 5·1 years (2·0–9·3) for patients without diabetes. The numbers needed to treat to prevent one additional death over a 10-year time frame were 8·4 (95% CI 7·8–9·1) for adults with diabetes and 29·8 (21·2–56·8) for those without diabetes. Treatment effects did not appear to differ between gastric bypass, banding, and sleeve gastrectomy (I^2 3·4%, p=0·36). By leveraging the results of this meta-analysis and other published data, we estimated that every 1·0% increase in metabolic–bariatric surgery utilisation rates among the global pool of metabolic–bariatric candidates with and without diabetes could yield 5·1 million and 6·6 million potential life-years, respectively.

Interpretation Among adults with obesity, metabolic–bariatric surgery is associated with substantially lower all-cause mortality rates and longer life expectancy than usual obesity management. Survival benefits are much more pronounced for people with pre-existing diabetes than those without.

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Introduction

The rising prevalence of obesity and overweight exerts a major public-health toll worldwide, contributing to 5 million deaths and 160 million disability-adjusted life-years in 2019.[1,2] High body-mass index—or more precisely, visceral adiposity—is a component of the constellation of cardiovascular risk factors that comprise the metabolic syndrome,[3] and has strong epidemiological

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Research in context

Evidence before this study

We searched PubMed, Scopus, and MEDLINE (via Ovid) without language restrictions for randomised trials, prospective controlled studies, and matched cohort studies comparing all-cause mortality after metabolic–bariatric surgery versus non-surgical management of obesity published between inception and Feb 3, 2021. We also searched grey literature by reviewing bibliographies of included studies as well as review articles. The search terms are available in the appendix. We excluded studies that exclusively enrolled individuals with specific comorbidities other than type 2 diabetes or adolescents, non-comparative studies, and case reports. WHO estimates that in 2016, 13% of the world's population was obese. Metabolic–bariatric surgery is an approved treatment for severe obesity in many countries; however, fewer than 1% of patients who qualify are actually treated each year. Most studies on metabolic–bariatric operations have focused on weight-related outcomes. A growing body of evidence has also found remission or improvement of obesity-related cardiometabolic risks and complications including diabetes, hypertension, obstructive sleep apnoea, osteoarthritis, gout flares, and non-alcoholic steatohepatitis following metabolic–bariatric surgery. These metabolic benefits appear to be durable in the long term, as shown in a 10-year follow-up of a randomised trial comparing metabolic surgery with conventional medical therapy on type 2 diabetes remission and complications. However, the long-term survival outcomes of metabolic–bariatric surgery have only been reported much more recently, with 15 of the 17 studies we elected to include in this meta-analysis published after 2015. For this pooled analysis, we included 16 high-quality matched cohort studies and one prospective controlled trial that compared all-cause mortality or long-term survival in a group of patients who received metabolic–bariatric surgery versus a control group of baseline-matched participants who received conventional care.

Added value of this study

This pooled analysis was done to obtain more robust and precise estimates of long-term survivorship after metabolic–bariatric surgery in adults with obesity. It combines several features that should be useful for the development of clinical guidelines and international public health policies, and for the facilitation of patient counselling. First, with just under 8000 events recorded during approximately 1·2 million patient-years of follow-up, the present analysis using reconstructed survival data of about 175 000 patients should have adequate power to accurately estimate the long-term survival outcomes of patients with metabolic–bariatric surgery for up to 3 decades. Second, we presented results using various summary statistics to enhance interpretation and facilitate communication, including hazard ratio estimates, numbers needed to treat, and median life expectancy. Third, we did subgroup analyses to discern treatment effects by one of the most important effect modifiers: type 2 diabetes.

Implications of all the available evidence

Our meta-analysis adds to a growing evidence base supporting a role for metabolic–bariatric surgery in the management of obesity, especially in patients with type 2 diabetes. These findings should be of interest to policy makers developing coordinated strategies to tackle the increasing prevalence of obesity and diabetes—and all their public health and economic consequences—as well as general practitioners, endocrinologists, and cardiologists who play a vital part in managing patients who are overweight and have cardiometabolic comorbidities.

associations with diabetes, coronary heart disease,[4] hypertension, certain cancers,[5,6] and premature death.[7,8] Consequently, clinical practice guidelines in endocrinology and cardiology emphasise weight control and weight loss interventions—through behavioural and lifestyle modification, pharmacotherapy, and metabolic–bariatric surgery—as a cornerstone of lowering macrovascular disease risk.[9–13] Several medium-term to long-term observational studies and randomised controlled trials have reported that in addition to inducing substantial and durable weight loss, metabolic–bariatric surgery commonly facilitates improvement or remission of metabolic complications including type 2 diabetes, dyslipidaemia, and obstructive sleep apnoea in individuals with obesity,[14–23] which is the basis for recent and ongoing expansion in the eligibility criteria for weight-loss surgery and the reason why such procedures have been termed metabolic–bariatric surgery. [9–11]

Hitherto, data concerning the long-term health effects of metabolic–bariatric surgery are largely limited to evidence from observational cohort studies rather than randomised controlled trials with long-term follow-up.[24–33] It is important, however, to recognise that despite having large denominators, the actual number of deaths recorded in individual studies is very low (eg, event rates of 5·2–10·7 deaths per 1000 person-years in the recent Swedish Obese Subjects [SOS] study),[24] since the median baseline age of participants is only 40–50 years in many studies. The exceedingly low incidence of mortality severely hampers precision, reduces power, and might give rise to sparse-data bias in individual studies quantifying the treatment effect of metabolic–bariatric surgery. Furthermore, only a few studies exploited rigorous study designs to minimise confounding and selection biases.

In light of these considerations, we did a pooled analysis using reconstructed individual participant data[34,35] from high-quality matched cohort studies and prospective controlled trials, to obtain more robust and accurate estimates regarding the long-term effect of metabolic–bariatric surgery on all-cause mortality and

life expectancy, which are vital to guide policy and facilitate patient counselling.

Methods

Search strategy and selection criteria

This meta-analysis was done in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[36] and Meta-Analysis of Observational Studies in Epidemiology (MOOSE)[37] guidelines. We searched PubMed, Scopus, and MEDLINE (via Ovid) without language restrictions for randomised trials, prospective controlled studies, and matched cohort studies comparing all-cause mortality after metabolic–bariatric surgery versus non-surgical management of obesity published from inception to Feb 3, 2021. The search terms are available in the appendix (p 37). We searched grey literature by reviewing the bibliographies of included studies as well as review articles. To ensure our findings are based on rigorous evidence, we only included investigations with low risk of bias. Excluded from the meta-analysis were studies that exclusively enrolled patients with specific comorbidities other than type 2 diabetes (eg, end-stage renal failure[38] and type 1 diabetes[39]) or adolescents, non-comparative studies, and case reports. For publications that constitute re-analyses of similar or overlapping patient populations,[40–45] we chose the publication that we deemed to provide the most pertinent or recent information, and also took into considerations such as the image quality of published Kaplan-Meier curves, which are important to ensure accurate reconstruction of individual participant time-to-event data. Studies had to provide cumulative incidence function or Kaplan-Meier survivor curves for matched cohorts to be considered for inclusion. Studies that used other methods of confounder control (including covariance adjustment, stratification, and inverse probability of treatment weighting) were excluded because although these techniques can be effective at mitigating bias, the balancing effect is lost when applied to meta-analysis using reconstructed individual patient data, since the patient-level covariates or propensity-scores used for controlling bias are unbeknownst to meta-analysts.

Risk of bias assessment

Two reviewers (ZJK and CAC) assessed the quality of included studies using the Newcastle-Ottawa Scale for cohort studies,[46] and disagreements were resolved by consensus or appeal to a third author (AS). Studies that scored 7–9 points, 4–6 points, and 3 or fewer points were considered to be at low, moderate, and high risk of biases, respectively.

Data extraction and reconstruction of individual patient data

Four review authors (LZW, NLS, DJL, and YEL) extracted study characteristics, including patients' demographics and clinical characteristics, details of interventions in the metabolic–bariatric surgery and usual care groups, and the procedure and covariates used for matching. Validated algorithms by Guyot and colleagues[47] were used to recover participant-level survival data from published Kaplan-Meier curves.[48–52] Briefly, we downloaded, pre-processed, and digitised vector and raster images of survivor or failure curves to obtain their step function values and timings of the steps.[47] Additional information including number-at-risk tables and total number of events were used, if reported, to further improve the calibration of time-to-events.[47] Survival information on individual patients was then recuperated by solving the inverted Kaplan-Meier product-limit equations.[47] Side-by-side comparisons of reconstructed and original curves are provided in the appendix (pp 15–36), showing that the algorithms[47] robustly recovered individual participant data from published studies.

See Online for appendix

Data synthesis

The Kaplan-Meier method was used to calculate overall survival. One-stage meta-analyses were carried out using Cox proportional hazards models that address between-study heterogeneity using a variety of approaches.[53–56] The primary analysis was based on the shared frailty model, because it most explicitly accounts for between-study heterogeneity by incorporating a random-effects term that models patients within each study as being similarly failure-prone as other individuals belonging to the same study.[53,54,56] Across studies, frailties are gamma-distributed and affect the hazard function in a latent, multiplicative

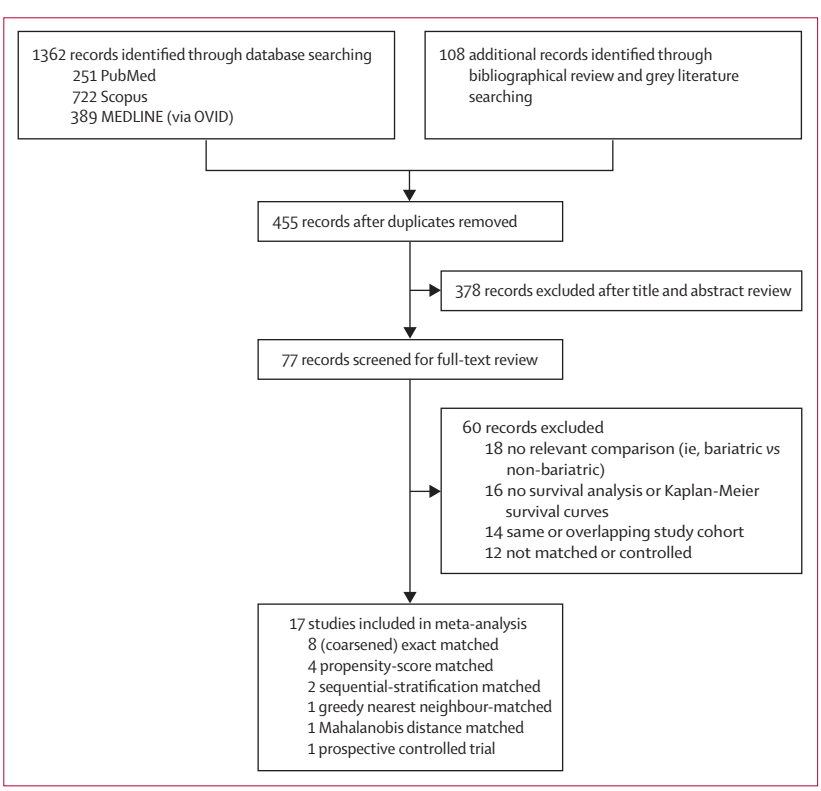

Figure 1: **Study selection**

manner. As sensitivity analysis, we also used stratified Cox models, which adjust for inter-study heterogeneity by allowing patients from a particular study to share a baseline hazard unique only to that study, while constraining partial likelihood estimates of the Cox coefficients to be equal across strata.[53–56] Marginal Cox models—which assume that no heterogeneity exists among studies—were also fitted. As a final sensitivity analysis, we also computed two-stage hazard ratios (HRs) using inverse variance-weighted random-effects meta-analysis and corrected for publication bias and small-study effects using the random-effects trim-and-fill (R_0 estimator) procedure. Median follow-up was calculated using the reverse Kaplan-Meier method,[57] and the proportional hazards assumption was evaluated by testing for the presence of a non-zero slope in a generalised linear regression of scaled Schoenfeld residuals on time.[58]

To ensure relevance to stakeholders, such as patients and health-care decision makers,[59] we also computed the numbers needed to treat (NNT) using the formulae by Altman and Andersen[60] based on the shared-frailty HR estimates and survival rates at discrete timepoints of

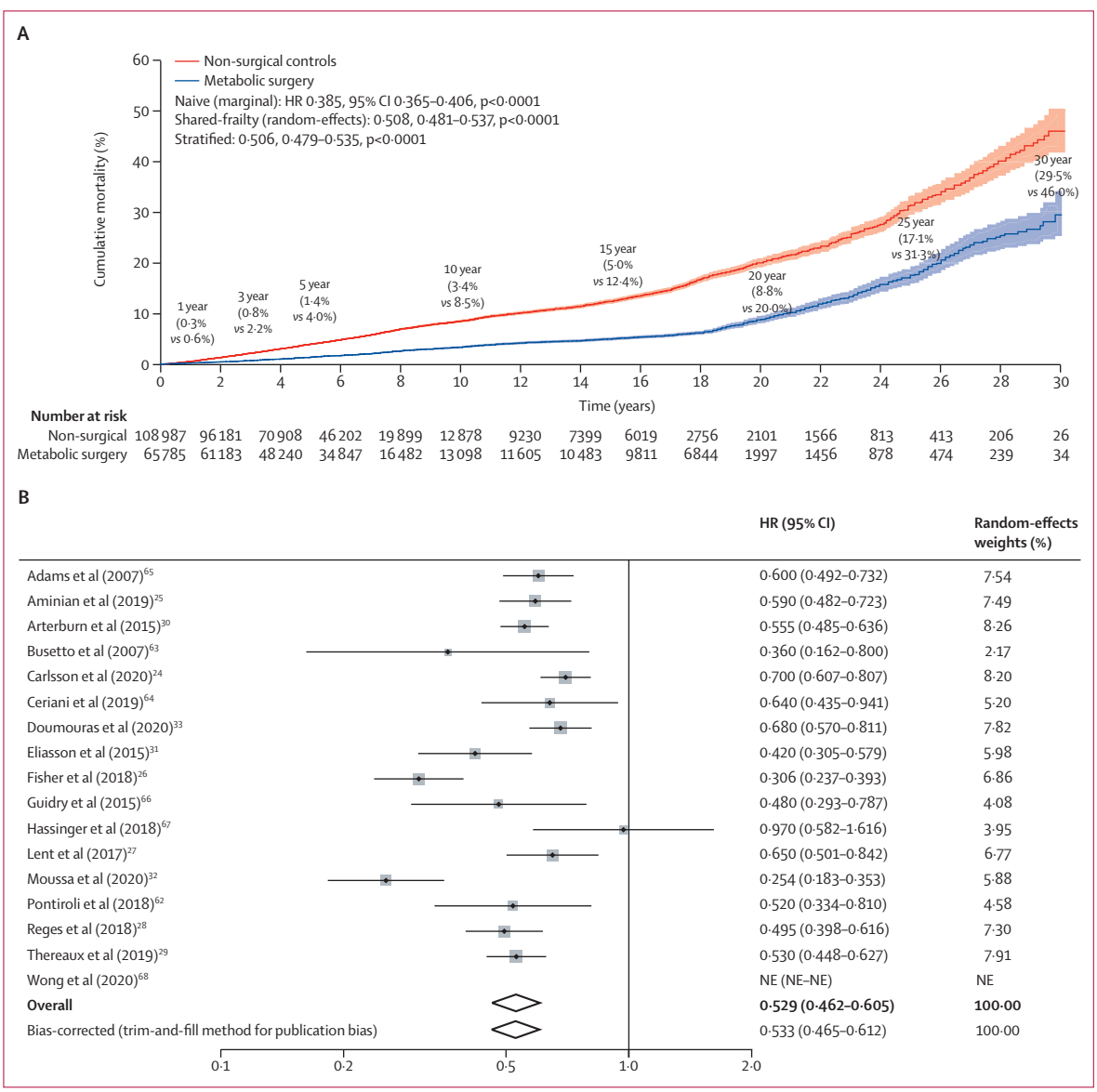

Figure 2: **Cumulative mortality and numbers-at-risk table for all participants who underwent metabolic–bariatric surgery *vs* usual non-surgical management of obesity**

(A) One-stage meta-analyses. (B) Two-stage aggregate data meta-analysis. Hazard ratio estimates were NE for the Wong et al (2020)[68] study, and did not contribute any computational weights to either the one-stage or two-stage random-effects meta-analyses, since no events occurred in their surgical group. Note that the relative hazard reduction is computed as (1–HR) × 100% (eg, a HR of 0·508 translates to a reduction in the hazard rate of death of 49·2%). HR=hazard ratio. NE=not evaluable.

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interest in the non-surgical group. Since more than 50% of patients remained alive in both the treatment and control groups at the end of follow-up, the actual median survival was not attained in either group. To report median life expectancy, we used the same modelling strategies featured in the recently published SOS study,[24] which parametrically extrapolated survival curves using out-of-sample predictions until half the populations have died in each group. Like the SOS study, we evaluated an array of parametisations including the Gompertz, Weibull, generalised gamma, log-logistic, and exponential models, and similarly observed that the (shared-frailty) Gompertz regression provided the best fit based on visual inspection and Akaike information criteria.[24] Bias-corrected confidence intervals for the median life expectancy difference were obtained from 10 000 bootstrap replications. We calculated the global potential life-years that could be gained as the product of the worldwide number of adults with severe obesity, utilisation rates stratified by diabetes status, and the difference in median expected lifespan of surgical patients and non-surgical controls. All analyses were done in Stata (version 16.1) and nominal p values of less than 0·05 were regarded to indicate statistical significance. The study protocol is prospectively registered on PROSPERO, number CRD42020218472 (appendix pp 5–14).

Role of the funding source

There was no funding source for this study.

Results

The search strategy retrieved 1362 potentially relevant articles, and 108 additional records were identified through searching grey literature. After titles were de-duplicated and abstracts screened, 77 full-text articles were reviewed, of which a further 60 articles were excluded for various reasons (figure 1). Notably, we excluded the study by Christou and colleagues,[61] even though it met all prespecified inclusion criteria, because we deemed it to be at risk of considerable residual confounding because the only variables controlled for were age and gender, but no weight-related covariates or comorbidities were used in their matching process. We also elected to exclude the study by Sheetz and colleagues[38] because it focused exclusively on patients with pre-existing end-stage renal failure; we considered the characteristics of this extremely high-risk patient population and the interventions they received (such as a much higher rate of kidney transplant procedures) to be vastly different from all other studies, and decided that its inclusion would only render the pooled treatment effects difficult to interpret and generalise.

In total, 17 articles were included, of which eight (coarsened exact) matched with user-specified bins,[27,29,31,62–65] four used propensity-score matching,[25,32,66–68] two employed sequential stratification matching,[28,30] one matched on the Mahalanobis distance metric,[26] one had greedy nearest neighbour matching,[33] and one study was a prospective controlled trial[24] that used sequential treatment assignment to create a contemporaneously-matched control group. Patient characteristics and intervention details are summarised in the appendix (pp 42–46). All studies were judged by two reviewers completing the Newcastle-Ottawa checklist to be high quality (ie, ≥7 of a maximum of 9 points; appendix pp 40–41).

In the overall cohort of 174 772 patients, the median follow-up was 69·4 months (IQR 42·2–84·9), and 7712 deaths occurred over 1 156 376 patient-years (figure 2). Among 65 785 patients who underwent metabolic–bariatric surgery, 1813 deaths occurred over a period of 496 771 patient-years. Among 108 987 matched non-surgical controls, 5899 deaths occurred over 659 605 patient-years at-risk. After accounting for random-effects, metabolic–bariatric surgery was associated with a reduction in the

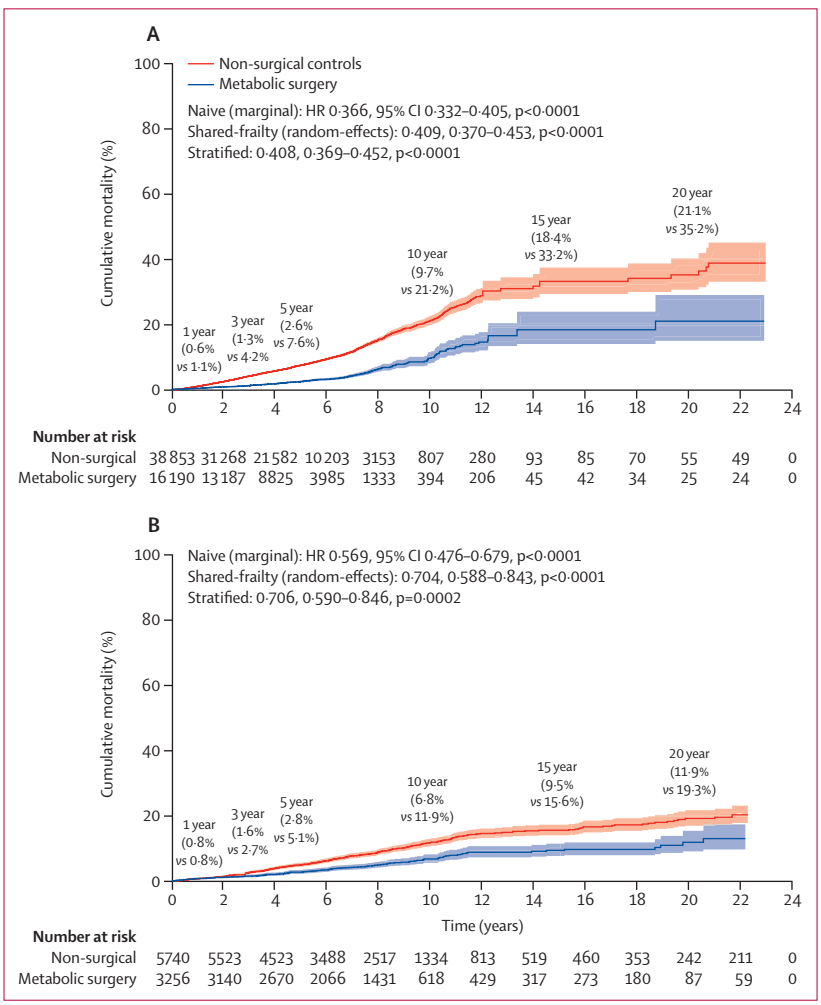

Figure 3: **Cumulative mortality and numbers-at-risk table for all participants who underwent metabolic–bariatric surgery *vs* usual non-surgical management of obesity, stratified by diabetes status**

(A) Subgroup analysis of patients with type 2 diabetes. (B) Subgroup analysis of patients without type 2 diabetes. Note that the relative hazard reduction is computed as (1−HR) × 100% (eg, a HR of 0·409 translates to a reduction in the hazard rate of death of 59·1%). HR=hazard ratio.

hazard rate of death of 49·2% (95% CI 46·3–51·9, p<0·0001; p=0·35 for test of proportional hazards). HR estimates changed modestly in sensitivity analyses using one-stage stratified Cox regression or two-stage meta-analyses (with or without correction for publication bias; figure 2), indicating that the results are robust to model specification and publication bias. On the basis of the shared-frailty HR estimate and applying the formulae of Altman and Andersen[60] to the survival probabilities in figure 2, the NNT to prevent one additional death was 24·4 (95% CI 23·1–26·0) at the 10-year follow-up and 10·8 (10·2–11·5) at the 20-year follow-up. By using the same modelling strategy as in the SOS study[24], this meta-analysis estimated a median life expectancy 6·1 years (95% CI 5·2–6·9) longer in the surgery group than in the control group.

Next, we did subgroup analyses to distil treatment effects according to type 2 diabetes status, which previous research had suggested to be an important effect modifier.[27] For patients with diabetes at baseline, metabolic–bariatric surgery was associated with a HR for all-cause mortality of 0·409 (95% CI 0·370–0·453, p<0·0001; p=0·20 for test of proportional hazards; figure 3). Among 16 190 surgically-treated patients, 456 deaths occurred over a follow-up of 70 984 patient-years, whereas 2939 of 38 853 non-surgical matched controls died during a period of 170 933 patient-years (figure 3). The NNT was 8·4 (95% CI 7·8–9·1) at the 10-year follow-up and 5·3 (4·9–5·8) at the 20-year follow-up, indicating that one death over a 10 and 20 year horizon could be averted for every eight or five patients with diabetes who undergo metabolic–bariatric surgery. Median life expectancy was approximately 9·3 years (95% CI 7·1–11·8) longer for patients with diabetes in the surgery group than in the control group.

A smaller treatment effect was observed for patients without diabetes (HR 0·704, 95% CI 0·588–0·843, p<0·0001; p=0·40 for test of proportional hazards), corresponding to a median life expectancy gain of 5·1 years (95% CI 2·0–9·3; figure 3). Among 8996 patients without diabetes at the beginning of follow-up, 165 deaths were recorded during 25 054 years at-risk among 3 256 surgically-treated patients, whereas 510 of 5740 non-surgical patients died over 44 756 patient-years. The NNT for people without diabetes was higher than for those who had diabetes, with NNTs to prevent one death of 29·8 (95% CI 21·2–56·8) at the 10-year follow-up and 19·0 (13·4–36·3) at the 20-year follow-up. There was substantial between-subgroup heterogeneity (I^2 95·7%, p<0·0001 from a two-stage meta-analysis) when comparing subgroups based on diabetes status, which can be interpreted to indicate that the magnitude of the survival benefit conferred by metabolic–bariatric surgery is significantly greater for patients with diabetes than for those without diabetes.

About 184 million people worldwide have severe obesity, but uptake of metabolic–bariatric surgery remains less than 1% among eligible adults who qualify based on weight-centric eligibility criteria.[18,69–72] To glean further insights into the potential policy effect of improving uptake of metabolic–bariatric surgery we calculated the number of potential years of life that could be gained among the global pool of eligible candidates if uptake rates were hypothetically increased. We assumed that 30% of the eligible cohort (ie, 55·2 million adults) have preoperative diabetes, in keeping with published estimates on the co-prevalence of severe obesity and diabetes. On this basis, every 1·0% absolute increase in metabolic–bariatric surgery use among candidates with diabetes yields 5 133 600 future life-years and without diabetes yields 6 568 800 future life-years. This would imply that if metabolic–bariatric surgery uptake in 2014 were 1·0% among candidates with and without diabetes, then increasing utilisation rates to 2·5% and 1·5% respectively would generate 10 984 800 additional potential life-years (figure 4). If uptake rates increased to 3·5% and 2·0%, among candidates with or without diabetes respectively, this would generate a potential future gain of 19 402 800 life-years globally would be seen (figure 4).

Finally, we honed in on studies that focused on specific metabolic–bariatric operations (figure 5). Of 23 450 patients undergoing Roux-en-Y gastric bypass, 546 patients died during a follow-up of 216 413 patient-years; whereas the matched control population of 26 554 individuals recorded 1070 deaths over a period of 185 593 patient-years (HR 0·430, 95% CI 0·387–0·478, p<0·0001; p=0·0008 for test of proportional hazards).

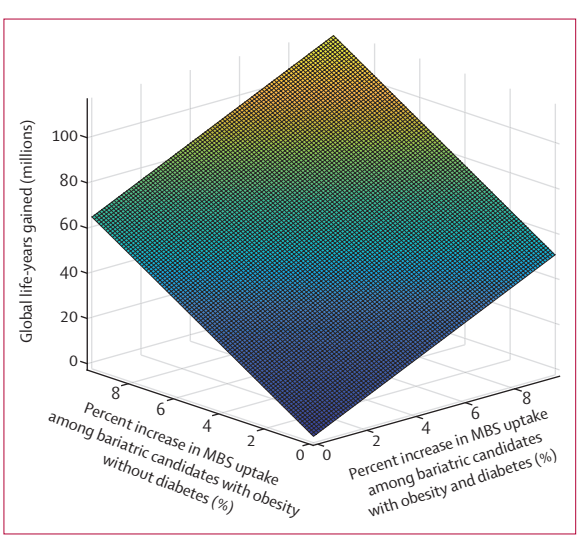

Figure 4: **Relationship between potential life-years gained on a global level for every percentage increment in MBS utilisation rates among the global pool of eligible candidates with or without diabetes**
Assuming 258 million individuals worldwide have severe obesity, every 1·0% absolute increase in MBS use among candidates with and without diabetes would yield 5 133 600 and 6 568 800 potential life-years, respectively. For example, if MBS uptake is currently 1·0% among candidates with and without diabetes, then hypothetically increasing utilisation rates to 2·5% and 1·5%, respectively, would generate 10 984 800 additional potential life-years. MBS=metabolic–bariatric surgery.

59 of 7373 patients who underwent sleeve gastrectomy died over a follow-up of 38 531 patient-years; whereas those who received routine care recorded 209 deaths of 14 097 patients over 58 559 patient-years of follow-up (HR 0·475, 95% CI 0·354–0·639, p<0·0001; p=0·21 for test of proportional hazards). There were 96 deaths among 4815 patients who underwent adjustable gastric banding compared with 454 deaths among 12 407 matched controls, with overall follow-up durations of 34 369 and 82 038 patient-years in both groups, respectively (HR 0·500, 95% CI 0·401–0·624, p<0·0001; p=0·062 for test of proportional hazards). The magnitude of treatment effects was not dissimilar between these three bariatric procedures (between-subgroup heterogeneity I^2 3·4%, p=0·36 from a two-stage meta-analysis).

Discussion

In this meta-analysis of 174 772 individuals with 1·2 million person-years of follow-up, metabolic–bariatric surgery was associated with approximately half the rate of death from any cause compared to usual care in the overall population, with more marked benefits among patients with pre-existing diabetes compared to individuals who did not have diabetes at baseline. These pooled associations, which are predicated on reconstructed patient-level time-to-event data from high-quality matched cohort and prospective controlled studies, have strong biological plausibility and—in the absence of randomised trials with long-term follow-up—represent an important contribution regarding the potential public health and long-term effect of this underused weight-loss modality.

In subgroup analyses, gastric bypass, banding, and sleeve gastrectomy were associated with 50–57% lower rates of all-cause mortality compared with matched adults with obesity in the non-surgical group. Proponents of the notion that survival benefit is correlated with the extent of weight loss and remission of cardiometabolic comorbidities might observe that intervention effect sizes were greatest for Roux-en-Y gastric bypass, followed by sleeve gastrectomy, and then banding procedures, and argue that this ranking of treatment effects appears to mirror the gradation of weight-loss outcomes and rates of comorbidity resolution for each type of operation.[14–23] However, our results do not support such a notion since we did not detect any statistically significant heterogeneity in the quantum of survival benefit conferred by these three types of operations; although conversely, it must be emphasised that this result does not, therefore, necessarily validate the null hypothesis (of homogeneity of treatment effects across the three procedures). The comparison of intervention effects across bariatric operations is weakened by several limitations. First, the Cochran Q test, which underpins this result, has inherently low power to detect differences in the magnitude of treatment effects across subgroups. Second, the low power of this test is further diminished by the small sample size of each subgroup, and the fact that few participants in the sleeve gastrectomy group and their matched controls died over the course of their short follow-up (which was only up to 7 years). Third, the HR estimate in the gastric bypass group was not constant over time because there was evidence of departure from proportional hazards, which is probably related to an accelerated (steeper) failure rate in the non-surgical group beginning from the 14-year mark. For these

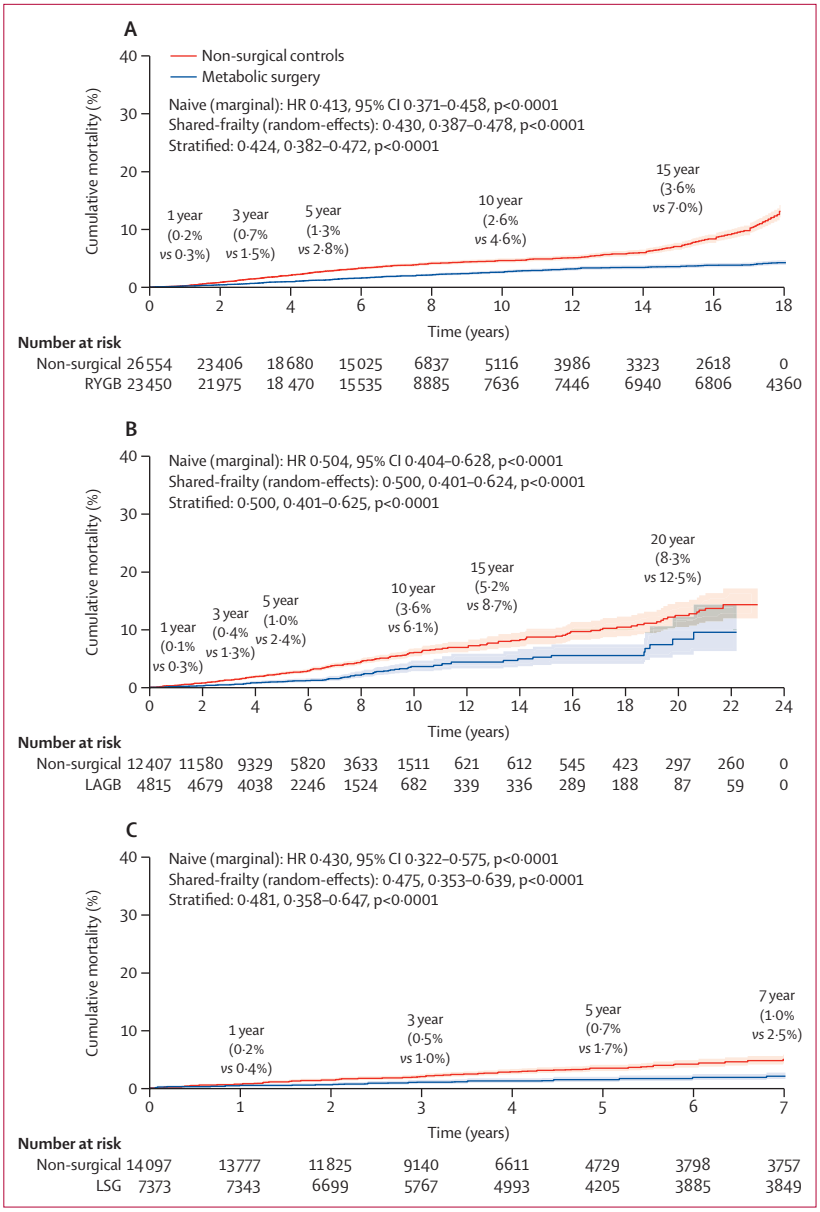

Figure 5: **Cumulative mortality and numbers-at-risk table for all participants who underwent metabolic–bariatric surgery versus usual nonsurgical management of obesity, stratified by type of operation**
(A) Subgroup analysis of RYGB patients and their matched controls. (B) Subgroup analysis of LAGB patients and their matched controls. (C) Subgroup analysis of LSG patients and their matched controls. Note that the relative hazard reduction is computed as (1–HR) × 100% (eg, a HR of 0·475 translates to a reduction in the hazard rate of death of 52·5%). HR=hazard ratio. LAGB=laparoscopic adjustable gastric banding. LSG=laparoscopic sleeve gastrectomy. RYGB=Roux-en-Y gastric bypass.

reasons, it is our view that the comparative effects of different bariatric procedures on long-term survival remains unresolved.

Our results are largely consistent with recent studies but should provide more accurate and precise estimates of long-term survival and intervention effects to guide policy and facilitate patient counselling. With approximately 8000 events recorded over a follow-up period up to 3 decades, the present analysis has adequate power to paint an accurate picture of the long-term survival outcomes of patients with metabolic–bariatric surgery. There were some differences between our conclusions and those of individual studies. For example, the studies by Lent and colleagues[27] and Pontiroli and colleagues[62] found no significant reduction in all-cause mortality for patients without diabetes, whereas our study delineated a clinically and statistically significant survival advantage in this subgroup. This result is probably explained by the lack of statistical power in individual studies, considering that their point estimates indicated large numerical reductions in the hazard rate of death in the metabolic–bariatric surgery group but did not meet criteria for statistical significance because of their wide confidence intervals. The observation that patients with diabetes benefit more from metabolic–bariatric surgery correlates with findings from the SOS study, which has previously shown that raised baseline glucose and insulin concentrations were predictive of favourable treatment effects.[73] This finding is important, with implications for future planning, development of clinical algorithms, and prioritisation of patients for metabolic–bariatric surgery.

Furthermore, median life expectancy projected in our study was 6·1 years longer for the metabolic–bariatric surgery group than for the control group, which is larger than the 3·0-year difference forecasted by SOS investigators, although we used identical modelling techniques (Gompertz proportional-hazards model) as the SOS study.[24] The longer life expectancy difference estimated in our pooled patient-level analysis compared with the recently published SOS study warrants discussion. A plausible explanation relates to residual confounding in the SOS trial, which could have biased their results against the surgery group.[24] As detailed in the appendix (pp 42–46), only 12·9% and 63·8% of participants in the SOS control group had diabetes and hypertension at baseline compared with 17·2% and 78·4% respectively in the surgery group. Additionally, more participants in the SOS control group (21·1%) had a university degree, which is a known predictor of lifespan, compared with 12·8% in the surgery group. Such imbalances—where participants in the control group are ostensibly healthier and more educated at baseline than surgical patients—could bias results in favour of conventional obesity management. A further contributing reason could be the fact that in the SOS study,[24] close to 90% of patients underwent vertical banded gastroplasty (69%) or gastric banding (18%)—which could engender fewer metabolic benefits in terms of diabetes resolution and weight loss—whereas our meta-analysis had a higher proportion of patients undergoing Roux-en-Y gastric bypass or sleeve gastrectomy. Taken together, these factors could cause life expectancy differences between the surgical and control groups to be slightly underestimated in the SOS trial, and potentially account for the discrepancy between our estimates (gain in life expectancy of 6·1 years in our pooled analysis of 174 772 individuals *vs* 3·0 years in the SOS study[24]).

Aside from large sample numbers, there are other strengths notable in the present work. To improve generalisability of treatment effects, our primary analyses and conclusions are driven by random-effects (shared-frailty) models.[53–56] These not only make the assumption that individual studies' effect sizes deviate from the true common effect size due to sampling error, but also account for an additional source of variance that stems from heterogeneity in participant characteristics and interventions across studies. Moreover, our results changed very modestly in sensitivity analyses using conventional aggregate data meta-analysis or stratified Cox models, which are alternative methods that have been advocated for addressing between-study heterogeneity arising due to the clustering of participants at the study-level,[53–56] indicating that the pooled effect sizes are robust. This study is, to our knowledge, the first meta-analysis in this field to make use of reconstructed individual participant data meta-analysis, which is heralded as the gold standard for evidence synthesis.[35] Furthermore, the inclusion of 16 high-quality matched cohort studies and one controlled prospective trial in this meta-analysis should alleviate some of the criticisms of previous studies, such as reverse causality, confounding by baseline covariate imbalances, and selection biases.

Our study has several limitations and caveats. First, pharmacological interventions for obesity as well as its associated health complications have evolved tremendously in recent years, and it is unclear whether the magnitude of the survival advantage may be attenuated by advances in pharmacotherapy.[74] Similarly, it is also important to recognise limitations in the comparisons with respect to the lack of standardisation in the non-surgical control group, in which patients might receive a more varied level of intervention. For example, this is evidenced in the SOS study, where the authors acknowledged this limitation varies from intensive medical intervention to none at all. Several newer classes of diabetes medications have since been approved after the turn of the century, including DPP-4 inhibitors, GLP-1 agonists, and SGLT-2 inhibitors. Some of these drugs have also shown significant risk reductions for cardiovascular death and hospitalisation and have recently gained approval for treatment of heart failure.[75–79] More options have also emerged for treatment of obesity itself, including orlistat, high-dose liraglutide,[80,81] semaglutide,[82–86] phentermine plus topiramate, and naltrexone plus

bupropion.[87,88] For example, semaglutide 2·4 mg once weekly has shown metabolic outcomes (eg, approximately 15% weight loss on average and HbA1c reduction of about 1·5%) that are comparable to gastric banding and, therefore, it is interesting to speculate whether semaglutide could also yield comparable long-term mortality benefits.[77,78,82–86] However, most included studies used techniques that explicitly controlled for the cohort entry year, such as sequential stratification matching,[28,30] sequential allocation,[24] matching on the index date,[25,29,31,33,65,66,68] or simply setting the recruitment window to be no more than 2 years apart (eg, 2002–03);[29,66] hence, chronological bias should be minimal in included studies. Second, it is crucial to recognise that patients in the metabolic–bariatric surgery group—even though this was not necessarily stated in included studies—most likely continued to receive lifestyle and pharmacological interventions after metabolic–bariatric surgery. Hence, a more nuanced interpretation of our findings should be that metabolic–bariatric surgery, when used in conjunction with conventional care (medical and lifestyle therapies), is associated with the effect sizes obtained in our study. Third, although the algorithm we applied allows us to closely approximate the original individual patient time-to-event within the matched studies,[47] it does not provide us with additional patient-level covariates, which could potentially afford greater insight. Fourth, we concentrated on all-cause mortality, because it was the most consistently reported primary endpoint across studies, whereas other time-to-event outcomes such as cardiovascular mortality had variable definitions that precluded meta-analysis and are also more likely to be affected by detection bias. Lastly, interpretation of our results must take into account the fact that most included studies were observational. Although their matched designs might mitigate confounding and selection biases, other sources of bias—arising from patient attrition, medication non-adherence, as well as data collection being less than rigorous (missing data and misclassified International Classification of Disease-9 codes)—cannot be eliminated.

Randomised clinical trials with sufficient power to assess a rare outcome such as mortality are unlikely to ever be done because such studies require large sample numbers, long-term follow-up spanning decades, and are prohibitively expensive. As such, our study—using one-stage meta-analysis to synthesise evidence from the few high-quality longitudinal studies published to date—is likely to have important clinical, public-health policy, and research implications. One of the outstanding questions not adequately clarified by this review is whether the magnitude of survival benefits conferred by different types of metabolic–bariatric procedures are truly comparable or actually differ slightly.

An intricately-related area of research is whether there is a disparity in the number of quality-adjusted life-years after different procedures. If survival benefits are truly equal for all three procedures, then Roux-en-Y gastric bypass could be associated with the fewest quality-adjusted life-years, given that it is associated with a higher rate of long-term complications such as micronutrient and endocrine derangements.[89] However, this cursory cost-utility analysis becomes more convoluted if the long-term survival of Roux-en-y gastric bypass is shown to be superior to other procedures, owing to the countervailing considerations of longer survival versus potentially worse quality-of-life utilities. The large UK By-Band-Sleeve study (NCT02841527) is currently ongoing to assess health-related quality of life and health economics of these procedures. Future research should also attempt to better address the extent to which survival benefit is mediated by weight loss, and to characterise such a relationship in detail. Numerous studies have suggested that gastrointestinal operations can exert weight-independent effects on diabetes[18,90] and, therefore, it might be interesting to speculate whether some of the beneficial effects of metabolic–bariatric surgery on long-term survival could also be weight-independent.[91] Finally, it would be instructive to harmonise reporting of other time-to-event endpoints (eg, cardiovascular mortality) and competing risks to facilitate future attempts at individual patient data meta-analysis.

In conclusion, the results of this study show that metabolic–bariatric surgery is associated with substantially lower all-cause mortality rates and longer life expectancy among adults with severe obesity, with reasonably low numbers needed to treat to prevent one additional death within 10 years. Substantially greater survival benefits are seen among people with pre-existing diabetes than those without. As such, clinicians and policymakers should not hesitate to consider metabolic–bariatric surgery in the management of patients with obesity and type 2 diabetes.

Contributors

NLS, AS, and LZW were responsible for the concept and design of the study. NLS, DJL, JJZ, YEL, LZW, ZJK, CAC, and AS did the search strategy and selection of eligible studies. NLS, JJZ, DJL, YEL, and BCT reconstructed the individual participant data. NLS, JJZ, ML, and BCT did the statistical analyses. ZJK, CAC, AS, and NLS did the risk-of-bias assessment. NLS, ZJK, CAC, DJL, AS, BCT, ML, GK, JB-YS, LMK, DEC, and JBD interpreted the data. NLS, LZW, DEC, JD, LMK, and AS drafted the manuscript. NLS, ZJK, JJZ, CAC, DJL, AS, ML, BCT, GWK, JB-YS, YEL, LZW, ZJK, LMK, DEC, and JBD critically revised the manuscript for important intellectual content. AS, GK, JB-YS, ML, BCT, LMK, DEC, and JBD supervised the study. All authors had full access to all the data in the study, and NLS and AS had final responsibility for the decision to submit for publication.

Declaration of interests

JBD has consultancies with Bariatric Advantage, iNova, and Reshape; and is on advisory boards for Novo Nordisk and Nestlé Health Science. LMK has received funds from Boehringer Ingelheim, Ethicon, Gelesis, GI Dynamics, Johnson & Johnson, Pfizer, Novo Nordisk, and Rhythm Pharmaceuticals. DEC is on the scientific advisory boards for GI Dynamics, DyaMx, Magnamosis, Metavention, and Gila Therapeutics. All other authors declare no competing interests.

Data sharing

This manuscript makes use of publicly available data from published studies; therefore, no original data are available for sharing.

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