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REVIEW ARTICLE

Clinical Trials and Investigations

Benefits of weight loss of 10% or more in patients with overweight or obesity: A review

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Abstract

Objective: Modest weight loss (5%-10%) is clinically meaningful in patients with overweight or obesity. However, greater weight loss may be required to achieve improvements in or remission of certain weight-related complications. Therefore, this study reviewed the effect of large weight loss (≥10%). Most studies reporting large weight loss and relevant outcomes used bariatric surgery or lifestyle modifications.

Results: Benefits of large weight loss were observed in patients with various overweight- or obesity-related complications, including improvements in comorbidities such as type 2 diabetes and hypertension. Improvements in glucose metabolism and cardiovascular risk factors were observed in patients who achieved large weight loss through lifestyle interventions or pharmacotherapy (phentermine/topiramate 15/92 mg once daily or subcutaneous semaglutide 2.4 mg once weekly). Other benefits associated with large weight loss included reduced cancer risk and improvements in knee osteoarthritis, sleep apnea, fertility-related end points, and health-related quality of life. While costly, bariatric surgery is currently the most cost-effective intervention, although most weight-management programs are deemed cost-effective.

Conclusions: Overall, large weight loss has a major beneficial impact on overweight- and obesity-related complications. Large weight loss should be the main treatment target when modest weight loss has had insufficient effects on obesity-related complications and for patients with severe obesity.

INTRODUCTION

Obesity is a multifactorial chronic disease that is associated with increased risks of type 2 diabetes (T2D), cardiovascular disease, certain cancers, sleep apnea, subfertility, and mortality, among other complications (1). For adults, the World Health Organization (WHO) defines "overweight" and "obesity" as having BMI of 25 kg/m^2 or more and 30 kg/m^2 or more, respectively (2). According to WHO estimates, almost four in ten adults (39%) were overweight and more than one in ten (13%) had obesity in 2016 globally (2). As BMI does not reflect fat distribution, waist circumference provides further information about patient risks of T2D, hypertension, and cardiovascular disease, which increase with increasing BMI and waist circumference category (Table 1) (1). Risks of comorbidities and cutoff points for considering therapeutic intervention differ in Asian versus non-Asian populations, with BMI of 23 to 27.5 kg/m^2 conferring increased risk and BMI of 27.5 kg/m^2 or more conferring high risk in Asian individuals (3). Members of Black and some minority ethnic groups are also at increased risk of chronic health conditions at a lower BMI than the White population (BMI < 25 kg/m^2) (4).

The global prevalence of obesity almost tripled between 1975 and 2016 (2), and it is increasingly becoming a public health priority. Overweight and obesity are responsible for a substantial disease burden and are associated with considerable direct costs (e.g., health care expenditure) and indirect costs (e.g., loss of productivity and gross domestic product [GDP]) (5,6). In 2014, 5% of deaths worldwide were attributable to obesity (7). Health expenditure associated with overweight/obesity is estimated to account for 2% to 8% of total health expenditure, although these values may be underestimates (5). Overweight and obesity and their consequences also negatively affect

labor force productivity and participation, and the wider economic cost of overweight and obesity is estimated to range from 0.45% to 1.62% of GDP, although, again, these values may be underestimates (5).

On average, between 2020 and 2050, it is expected that health expenditure associated with overweight and obesity will account for almost 14% of total health expenditure in the United States (5). Furthermore, across 52 countries, overweight will be responsible for 70% of all treatment costs for diabetes, 23% of all treatment costs for cardiovascular diseases, and 9% of all treatment costs for cancer (5). Overweight is projected to reduce life expectancy by 2.7 years in Organisation for Economic Co-operation and Development (OECD) countries and to reduce GDP by 3.3% in both OECD countries and 23 European Union (EU) member states (5). Preventive measures and effective treatments are required to address this growing global public health challenge (5).

Weight-management interventions include lifestyle behavioral modification, pharmacotherapy, endoscopic treatments, and bariatric surgery. Modest weight loss (5%-10%) is considered to be clinically important because it reduces cardiometabolic risk factors and improves obesity-related comorbidities in patients with overweight or obesity (8-11). However, large weight loss (≥10%) may have further benefits (9,10,12), particularly among those with BMI of 35 kg/m^{2}or more (10), who are at "very high" or "extremely high" risk of complications/comorbidities compared with people of normal weight and waist circumference (Table 1) (1). Large weight loss may be required to achieve improvements in certain weight-related complications, such as sleep apnea (8), or for the majority of patients with T2D (<6 years duration) to achieve T2D remission (defined as glycated hemoglobin [HbA_{1c}] < 6.5% without anti-diabetes drugs) (13).

Therefore, in this review, we aimed to evaluate the impact of large weight loss in patients with overweight or obesity.

Study Importance

What is already known?

- Gap analysis demonstrated that no reviews have been published on the benefits of large weight loss in recent years, to our knowledge.
- Most reviews identified focused on weight loss in specific groups of patients or on specific clinical outcomes.

What does this review add?

- In people with overweight or obesity, weight loss of 10% or more has important benefits regardless of weight-loss approach; most of the available data relate to weight loss achieved through bariatric surgery or lifestyle modifications.
- Evidence has suggested greater improvements in certain outcomes with progressive and sustained weight loss.

How might these results change the direction of research or the focus of clinical practice?

- We suggest that weight loss of 10% or more should be the main treatment target when 5% to 10% weight loss has resulted in insufficient effects on obesity-related complications and for patients with severe obesity.

METHODS

Searches covering the period between January 1, 2009, and March 4, 2020, were conducted to identify literature reporting the effects of large weight loss on overweight- and obesity-related comorbidities and complications (Figure 1). For the primary literature retrieved, abstracts were screened to identify publications reporting large weight loss and relevant clinical or economic outcomes. If percentage of weight lost was not reported in the abstract, the full text was screened using the same criteria.

TABLE 1 Classification of overweight and obesity by BMI, waist circumference, and associated disease risk (1)

			Disease risk[a] relative to normal weight and waist circumference	
	BMI, kg/m^2	Obesity class	Men ≤102 cm (≤40 in) Women ≤88 cm (≤35 in)	>102 cm (>40 in) >88 cm (>35 in)
Underweight	<18.5	–	–	–
Normal[b]	18.5-24.9	–	–	–
Overweight	25.0-29.9	–	Increased	High
Obesity	30.0-34.9	I	High	Very high
	35.0-39.9	II	Very high	Very high
Extreme obesity	≥40	III	Extremely high	Extremely high

Note: Risks of comorbidities and cutoff points for considering therapeutic intervention differ in Asian versus non-Asian populations (3). Members of Black and some minority ethnic groups are also at increased risk of chronic health conditions at a lower BMI than the White population (6).

[a]Disease risk for type 2 diabetes, hypertension, and cardiovascular disease.

[b]Increased waist circumference can also be a marker for increased risk, even in people with normal weight.

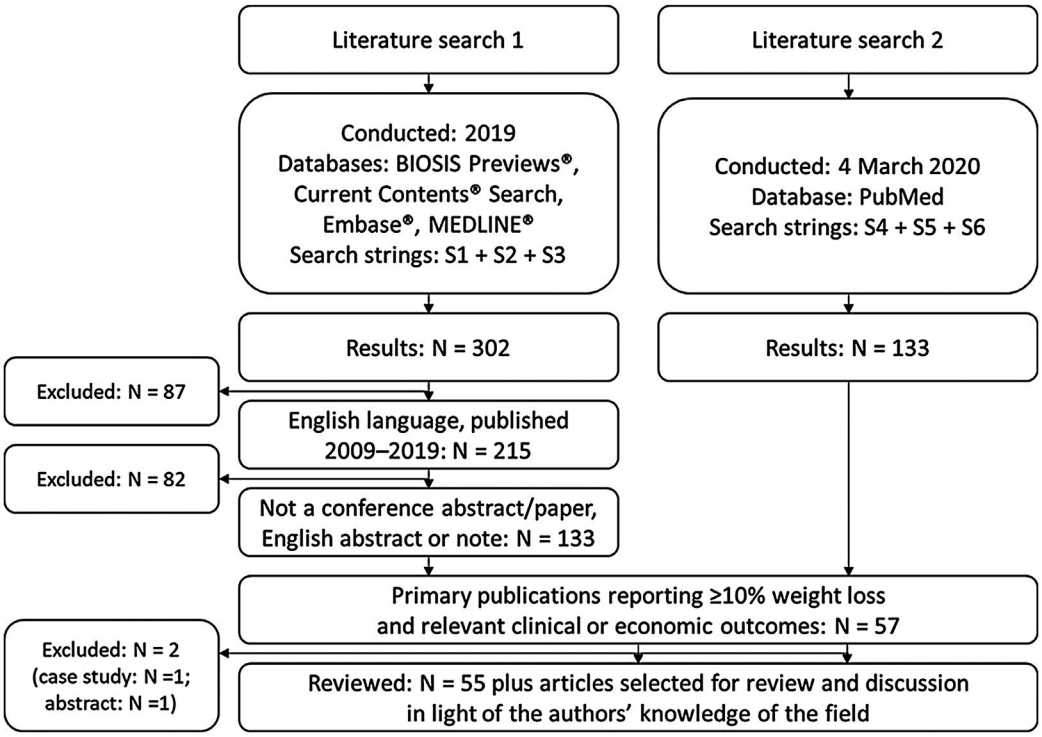

FIGURE 1 Flow diagram of literature searches and selection. N, number of publications; S1, ti,ab("Weight loss 15%" OR "Weight loss 20%" OR "progressive weight loss" or "intentional weight loss"); S2, ab,ti(overweight or obesity or "excess weight") OR MJMESH.EXACT("Obesity") OR MJEMB.EXACT("obesity"); S3, ti,ab(endpoint OR outcome OR comorbidit* OR complication* OR value OR benefit OR biomarker*); S4, (overweight[Title/Abstract] OR obesity[Title/Abstract] OR obese[Title/Abstract] OR excess weight[Title/Abstract]); S5, ("10% weight loss"[Title/Abstract] OR "15% weight loss"[Title/Abstract] OR "20% weight loss"[Title/Abstract] OR "25% weight loss"[Title/Abstract] OR "30% weight loss"[Title/Abstract] OR "35% weight loss"[Title/Abstract] OR "40% weight loss"[Title/Abstract] OR "progressive weight loss"[Title/Abstract] OR "intentional weight loss"[Title/Abstract]); S6, (endpoint[Title/Abstract] OR outcome[Title/Abstract] OR comorbidit*[Title/Abstract] OR complication*[Title/Abstract] OR value[Title/Abstract] OR benefit[Title/Abstract] OR biomarker*[Title/Abstract])

Based on these searches, 57 primary publications were identified for inclusion in this review (9,12,14-68). One case study involving a single patient (67) and one abstract (68) were subsequently excluded (Figure 1). Additional articles were selected for review and discussion in light of the authors' knowledge of the field.

Topics covered by this review include weight loss, T2D remission and metabolic control, cardiovascular risk factors and disease, cancer and associated risk markers, osteoarthritis, sleep apnea, chronic kidney disease, fertility and pregnancy, health-related quality of life (HRQoL), health care utilization and economic benefits, and adverse effects. Observations are described by type of weight-loss intervention.

RESULTS

Types of studies reporting large weight loss and relevant outcomes

Most of the evidence identified by our literature searches related to large weight loss achieved through bariatric surgery (*n* = 18/55 publications) (14,15,21,28,33,35,39,40,43,48-50,52,54,55,57-59) or lifestyle modifications (*n* = 28/55 publications) (9,12,16,19,20,22-27,30,32,36-38,41,42,44,45,51,53,56,61-65). Endoscopic techniques used included intragastric balloon (*n* = 3/55 publications) (18,29,66) and intraoperative endoscopic guidance for calibration of the gastric sleeve during laparoscopic or robotic sleeve gastrectomy (15). The latter study was classified as a bariatric surgery study. Lifestyle modifications included both group and individualized programs, dietary interventions (including caloric restriction, different types of diet, and dietary counseling), physical activity, behavioral and educational interventions, and intensive lifestyle interventions (ILIs) (9,12,16,19,20,22-27,30,32,36-38,41,42,44,45,51,53,56,61-65). Only one of the publications that was retrieved by our searches and reviewed related primarily to weight loss achieved using pharmacotherapy (31), but others were identified and are considered later in this paper (69,70). For the remaining publications identified by our searches, the weight-loss intervention was classified as "multiple" (*n* = 3) (17,47,60), "unknown" (*n* = 1 study that could not distinguish between intentional and unintentional weight loss) (34), or "none" (*n* = 1 modeling study) (46). Most of the studies identified by our literature searches were prospective: 14 were randomized controlled trials (9,12,20,25,30,31,38,41,44,4

5,51,56,61,62), and 6 were ancillary studies to randomized trials (23,24,26,37,63,64).

Clinical benefits

Table 2 summarizes the clinical effects of large weight loss in patients with overweight or obesity, describing the magnitude of weight loss and observations by topic and type of weight-loss intervention. Benefits of large weight loss were observed in patients with a range of overweight- and obesity-related complications, including T2D, prediabetes, metabolic syndrome, knee osteoarthritis, sleep apnea, chronic kidney disease, and subfertility (Table 2).

Type 2 diabetes remission and metabolic control

Surgery/intragastric-balloon therapy

Weight-management guidelines recognize that, in adults with obesity who achieve a mean weight loss of 20% to 35% after bariatric surgery, there are reductions in fasting glucose, insulin, and the incidence of T2D at 2 to 3 years (71). Among individuals with T2D at baseline, there is greater likelihood of diabetes remission, although diabetes may recur over time (71). A systematic review and meta-analysis showed that, after laparoscopic adjustable gastric banding and revisional bariatric surgery (band to Roux-en-Y gastric bypass [RYGB] or band-to-sleeve gastrectomy), almost half of patients (46.5%) experienced diabetes remission (defined as the cessation of medications, with or without additional criteria for glycemic parameters; pooled remission rate across five studies) (72). Changes in hormones regulating appetite and food intake that occur after bariatric surgery (e.g., decreased levels of ghrelin and increased levels of glucagon-like peptide-1 after RYGB) may contribute to the efficacy of these procedures (73).

Bariatric surgery patients experienced greater weight loss and better long-term outcomes, such as T2D remission, than nonsurgical groups or those receiving usual care (Table 2) (74-76). Among the bariatric surgery publications identified by our literature searches, average weight change ranged from −35% (14) to −2% (among those who did not achieve adequate weight loss after RYGB) (48) in the intervention groups and from 0% (14) to +3% (33) in the control groups (excluding change in mean excess weight). For intragastric-balloon therapy, the corresponding range was from −20.6% (at balloon removal in the downward-adjustment group) (18) to −7% (6-12 months after balloon removal among patients with BMI of 30-35 kg/m^2) (66); no data for control groups were available. The proportion of patients who experienced more than 10% weight loss was 96% to 99% with bariatric surgery (14, 54) and up to 86.5% with intragastric-balloon therapy (29) (similar proportions were not reported for any control groups). The proportion of patients with diabetes resolution ranged from 50% (48) to 76% (57) in the bariatric surgery groups at 1 year. Only one of the publications reported rates of T2D remission over time in both the intervention and control groups (14). In the prospective Utah Obesity Study of patients with severe obesity, T2D remission (defined as fasting blood glucose < 126 mg/dL and HbA_{1c} < 6.5%, without anti diabetes medication use) was experienced by 75% of patients in the RYGB group at 2 years, decreasing to 62% at 6 years (14). Corresponding rates of T2D remission in the nonsurgery control groups (patients who did not seek, or who sought but did not have, bypass surgery) were 6% to 7% at 2 years and 6% to 8% at 6 years (14). Among the bariatric surgery publications identified by our literature searches, mean changes in HbA_{1c} levels ranged from −3.0% (52) to −0.2% (14,52) in the intervention groups and from +0.1% to +0.3% in the control groups (14). Proportions of patients with diabetes remission and mean changes in HbA_{1c} levels were not reported in the intragastric-balloon therapy publications (18,29,66).

In the Swedish Obese Subjects (SOS) study, bariatric surgery was associated with mean weight loss of 23% after 2 years (compared with 0% with usual care) and lowered risk of microvascular complications (a composite of retinopathy, diabetes-related kidney disease, and neuropathy) versus usual care during a median follow-up of 19 years (76-78). The effect of bariatric surgery on microvascular complications was observed across subgroups defined by baseline glucose status (euglycemia, prediabetes, screen-detected T2D, and established T2D), although the risk reduction was most prominent in patients with prediabetes (78). These findings are consistent with results from an observational study of patients with obesity and T2D, in which bariatric surgery was associated with lower risks of incident chronic kidney disease, sight-threatening diabetic retinopathy, diabetes-related foot disease, and combined microvascular complications than nonsurgical care (79). In the SOS study, improvements in microvascular complications were observed with surgery compared with usual care, even though the proportion of patients using antidiabetes medications during follow-up was generally lower in the surgery group than in the usual-care group (78).

Lifestyle modification

Patients using lifestyle measures for weight control generally achieved lower mean weight loss than those who underwent bariatric surgery, with modest improvements in glucose metabolism (Table 2) (80). Among the lifestyle modification publications identified by our literature searches, average weight change ranged from −24.6% (38) to +1.5% (37) in the intervention groups (both values are for subgroups participating in diet and/or exercise interventions: ≥20% weight-loss group and no weight-loss group, respectively) and from −10.3% (30) to +2.5% (61) in the control groups. The proportion of patients who achieved 10% or more weight loss ranged from 3.8% (at 1 year in an exercise group) (62) to 79% (after repeated ILIs) (53) in the intervention groups (excluding a study that had ≥10% weight loss as an inclusion criterion) (32) and from 3.6% (at 1 year in a diabetes support and education [DSE] group) to 48.9% (at 1 year in a standard behavioral treatment group) (30) in the control groups. None of the publications relating to lifestyle modification reported

TABLE 2 Clinical effects of large weight loss in patients with overweight or obesity

Study	Study design	Population	Intervention	Mean weight loss	Observations
T2D remission and metabolic control					
Surgery					
Utah Obesity Study (14, 74, 82)	Prospective, controlled study	Patients with severe obesity (BMI ≥35 kg/m^2)	RYGB versus nonsurgery controls	RYGB: ~31%–35% Seeking but did not have bypass surgery (control): ~1.6% Not seeking bypass surgery (control): ~0.2% (all after 2 years)	• Among patients in the surgery group with T2D at baseline, there was significant long-term remission of T2D (defined as fasting blood glucose <126 mg/dL and HbA_{1c} <6.5%, without antidiabetes medication use for diabetes) for up to 12 years of follow-up (versus nonsurgery controls) ○ Of these patients, 62% remained in remission at 6 years and 51% at 12 years of follow-up
Changchien et al. (57)	Prospective, uncontrolled, cohort study	Patients eligible for surgery based on 1991 NIH consensus criteria	RYGB	Mean excess weight loss: 71.7% at 12 months	• The postoperative resolution rate for diabetes (as assessed by physicians at 12 months) was 75.9%
Andreas et al. (15)	Retrospective, uncontrolled, cross-sectional study	Patients with severe obesity	LSG or robotic sleeve gastrectomy with intraoperative endoscopy	NR; rate of excess weight loss was 52.1% at 6 months	• Resolution of this condition (defined as discontinuation of previous treatment) was experienced by 11/19 patients with diabetes (58%)
SOS study (76-78)	Prospective, controlled study with post hoc analysis of microvascular complications	Patients with obesity (BMI ≥34 kg/m^2 for men or ≥38 kg/m^2 for women)	Bariatric surgery versus usual care	Bariatric surgery: 23% Usual care: 0% (both after 2 years)	• Remission (defined as recovery from T2D) after 2 years of follow-up was achieved by 72% of patients with T2D in the bariatric surgery group • After 10 years, half of these patients had relapsed, but diabetes incidence was still significantly lower than in the control group (OR: 0.25; 95% CI: 0.17 to 0.38; p <0.001) • Bariatric surgery lowered the risk of microvascular complications (a composite of retinopathy, diabetes-related kidney disease, and neuropathy) versus usual care (HR: 0.56; 95% CI: 0.48 to 0.66; p <0.0001).; risk reduction was most prominent in patients with prediabetes (HR: 0.18; 95% CI: 0.11 to 0.30; p <0.0001)
Helping Evaluate Reduction in Obesity (HERO) registry study (21, 100)	Prospective, uncontrolled, cohort study	Adults with severe obesity (BMI ≥40 kg/m^2 or ≥35 kg/m^2 with severe comorbidity)	LAGB	16.9% after 1 year	• In total, (22.2%) of patients had T2D at baseline • Among those with T2D at baseline and adequate data after 1 year, 72% achieved HbA_{1c} <7.0% versus 43% at baseline • Greater mean percentage weight loss was associated with significantly increased odds of achieving target control of T2D at 1 year (each 1% of weight loss increased the likelihood of good control by 18%)

TABLE 2 (Continued)

Study	Study design	Population	Intervention	Mean weight loss	Observations
Bužga et al. (52)	Retrospective, controlled, cohort study	Patients with T2D	Laparoscopic greater curve plication, LSG, or RYGB	Laparoscopic greater curve plication: 18% LSG: 25% RYGB: 30% (all after 1 year)	• Mean fasting glycemia and HbA_{1c} levels decreased in all groups • Only the RYGB group, in which mean weight loss was greatest (30%), showed significant reductions in total cholesterol (0.85 mmol/L) and LDL cholesterol (0.82 mmol/L) levels
Michaelson et al. (39)	Prospective, uncontrolled, cohort study	Patients with obesity (BMI 30–39.9 kg/m^2)	LAGB	18.4% after 1 year	• Improvement in disease after 1 year (determined by changes in HbA_{1c} and fasting glucose levels and use of diabetes medication) was demonstrated by 6/7 patients with T2D (85.7%)
Kohli et al. (35)	Prospective, controlled, cohort study	Patients with extreme obesity	LAGB or RYGB	NR; patients studied before and after 20% weight loss	• Patients who experienced 20% weight loss after RYGB had ~2.5-fold higher levels of total fasting and postprandial bile-acid concentrations than presurgery values • This increase in bile-acid concentration was not a significant predictor of changes in glucose homeostasis or energy metabolism • Total fasting and postprandial bile-acid concentrations were either lower or did not significantly change after LAGB (fasting: 1.80-0.92 μmol/L, $p = 0.02$; postprandial: 3.71-2.82 μmol/L, $p = 0.14$).
Ikramuddin et al. (75)	Randomized controlled trial	Patients with obesity (BMI 30.0–39.9 kg/m^2) and T2D (HbA_{1c} ≥8.0%)	Intensive lifestyle–medical management intervention for 2 years ± RYGB	RYGB: 21% Lifestyle–medical management: 6% (both after 3 years)	• Full remission of diabetes at 3 years was experienced by 17% of gastric-bypass patients, compared with 0% of those receiving lifestyle–medical management (full remission: HbA_{1c} <6.0% for a full year and no glycemic medications during that time) • Mean HbA_{1c} level was significantly lower with bariatric surgery versus lifestyle–medical management at 3 years (treatment difference −1.9; 95% CI: −2.6 to −1.2; p <0.0001)
Lifestyle modification					
DiRECT (81) (Diabetes Remission Clinical Trial)	Randomized controlled trial	Patients with overweight/obesity (BMI 27–45 kg/m^2) and T2D	Primary care-led weight-management program versus best-practice care	Intervention: ~7.5% Best-practice care: ~2.3% (both after 2 years)	• After 2 years, 11% of weight-management program participants had ≥15 kg weight loss (15 kg assumed equal, on average, to ~15%) and 36% had remission of T2D (defined as HbA_{1c} <6.5% after withdrawal of antidiabetes drugs at baseline) • In a post hoc analysis of participants who maintained ≥10 kg weight loss in the weight-management program or best-practice-care control groups (45/272 with data), 29 participants (64%) achieved T2D remission after 2 years

(Continues)

TABLE 2 (Continued)

Study	Study design	Population	Intervention	Mean weight loss	Observations
Shantha et al. (42)	Retrospective, uncontrolled, cohort study	Patients with overweight/obesity and T2D	Individualized treatment consisting of a calorie-restricted diet and plans for behavior modification and increasing physical activity	~7.8% (mean follow-up: 13.2 months)	• After adjusting for antidiabetes medication use, for each 10% weight loss, the predicted reduction in HbA_{1c} level was 0.81%
Shantha et al. (65)	Retrospective, uncontrolled, cohort study	Patients with overweight/obesity and T2D	Individualized treatment typically consisting of a calorie-restricted diet and plans for behavior modification and increasing physical activity	~12.2% after 15 months	• At follow-up, there was a mean reduction in HbA_{1c} of 0.5%, and 67% of the study cohort had ≥1 dose reductions of any antidiabetes medication
Cambridge Intensive Weight Management Programme (60)	Prospective, uncontrolled, cohort study	Patients with severe obesity (BMI ≥40 kg/m^2)	24-week weight-loss program (dietary interventions, pharmacotherapy, physical activity, and behavior change counseling)	~14%–15% after 24 weeks	• Among patients with diabetes (N = 66 with T2D, N = 2 with T1D), there was a median 0.6% reduction in HbA_{1c} from baseline
Healthy Living Partnerships to Prevent Diabetes (HELP PD) study (51)	Randomized controlled trial	Adults with overweight/obesity (BMI 25–39.9 kg/m^2) and prediabetes	6-month lifestyle weight-loss intervention versus usual care	Loser/maintainer group: 8.7% Loser/regainer group: 10.2% Weight stable group: ~0.3% (all after 6 months) Loser/maintainer group: 9.9% Loser/regainer group: 3.3% Weight stable group: ~0.2% (all after 2 years)	• Weight change was significantly associated with changes in all T2D risk factors • Patients in the loser/maintainer and loser/regainer groups experienced improvements in glucose (−2.87 versus −5.47 mg/dL) and insulin (−6.69 versus −7.21 μIU/mL) levels, and HOMA-IR values (−1.81 versus −2.02 mg/dL*μIU/mL) from baseline to 6 months, compared with the group with weight that remained stable • Patients in the loser/maintainer group saw sustained improvements in all 3 risk factors from 6 to 24 months (−1.78 mg/dL, −0.98 μIU/mL, and −1.81 mg/dL*μIU/mL), while there was regression toward baseline values in the loser/regainer group
Magkos et al. (9)	Randomized controlled trial	Patients with obesity	Behavior education sessions and diet (target of 5% weight loss versus target of 5% followed by ~10% and ~15% weight loss)	Target 5% weight loss: 5% Target 10% weight loss: 11% Target 15% weight loss: 16%	• Patients who achieved increasing weight loss (target: 5%, 10%, and 15%) had magnitude-dependent improvements in insulin sensitivity and cardiometabolic outcomes

TABLE 2 (Continued)

Study	Study design	Population	Intervention	Mean weight loss	Observations
Maraki et al. (36)	Prospective, matched, controlled study	Sedentary men with obesity Age-matched, healthy, lean men	Diet and physical activity in patients with obesity	~10% after 15 weeks in patients with obesity	• A loss of 10% of body weight was associated with reductions in postprandial plasma glucose and serum insulin concentrations in patients with obesity ○ Total postprandial glucose response was 39.96 mmol/L·h before and 36.14 mmol/L·h after 10% weight loss ($p = 0.028$) ○ Total postprandial insulin response was 3,078 pmol/L·h before and 1,378 pmol/L·h after 10% weight loss ($p = 0.012$)
Rothberg et al. (41)	Randomized controlled trial	Women with obesity (BMI 35–45 kg/m^2) and anovulatory subfertility	Intensive weight-loss program (diet) versus standard-of-care nutrition counseling	Intensive program: 13% Standard of care: 4% (both after 12 weeks)	• After 12 weeks, mean weight loss was greater in the intensive weight-loss program group than in the standard-of-care nutrition counseling group ($p < 0.05$) and was only ≥10% in the former group • Patients in the intensive weight-loss program group experienced improvements in mean fasting glucose (−9 mg/dL versus +1 mg/dL with standard of care) and insulin (−10 μU/mL versus +4 μU/mL with standard of care) levels, and HOMA-IR values (−3 versus +1 with standard of care)
Nutrition and Exercise for Women (NEW) study (12, 61)	Randomized controlled trial	Postmenopausal women with overweight/obesity (BMI ≥25 kg/m^2 or ≥23 kg/m^2 if Asian American)	Diet and/or exercise versus control	Diet: 8.5% Exercise: 2.4% Diet + exercise: 10.8% Control: 0.8% (all after 1 year)	• After 1 year, diet + exercise was associated with the greatest mean weight loss (≥10%) • A significant improvement in HOMA-IR was observed in the diet (−24%) and diet + exercise (−26%) groups (both $p < 0.001$), but not in the exercise (−9%; $p = 0.22$) group versus controls (−2%) • The extent of weight loss was associated with metabolic improvements in insulin, C-peptide and glucose levels, and HOMA-IR values, with patients who lost ≥10% of weight experiencing the greatest benefits (p values for trends all < 0.001) ○ Insulin (pmol/L): <5% weight loss, −5.83; ≥5%–10% weight loss, −17.15; ≥10% weight loss, −29.66 ○ C-peptide (nmol/L): <5% weight loss, 0.007; ≥5%–10% weight loss, −0.10; ≥10% weight loss, −0.19 ○ Glucose (mmol/L): <5% weight loss, −0.01; ≥5%–10% weight loss, −0.20; ≥10% weight loss, −0.21 ○ HOMA-IR: <5% weight loss, −0.23; ≥5%–10% weight loss, −0.69; ≥10% weight loss, −1.10 • Dietary weight loss and exercise improved biomarkers of glucose metabolism independent of antidepressant use

(Continues)

Study	Study design	Population	Intervention	Mean weight loss	Observations
Chondronikola et al. (20)	Randomized controlled trial	Patients with obesity	Diet-induced weight loss (behavior education sessions, dietary counseling sessions, and low-calorie diet to achieve 5% weight loss; then meal replacements provided as needed to achieve 10% and 15% weight-loss targets) versus weight maintenance	NR; patients in the diet-induced weight loss group were studied before and after 5%, ~11% and ~16% weight loss	• Progressive (5%–16%) weight loss was associated with a progressive decrease in fasting plasma lactate concentration, which has been implicated in the pathogenesis of insulin resistance
Ebbeling et al. (25)	Randomized controlled trial	Young adults with overweight/obesity (BMI ≥27 kg/m^2)	Dietary interventions (low-fat, low-glycemic-index, very low-carbohydrate diets) after 10%–15% weight loss with a run-in diet	13.6% during run-in	• Hormones and metabolic syndrome components varied during weight maintenance by diet • Peripheral and hepatic insulin sensitivity indexes were lowest with the low-fat diet ○ Peripheral insulin sensitivity index: low-fat diet, 0.53; low-glycemic-index diet, 0.87; very low-carbohydrate diet, 0.93 ○ Hepatic insulin sensitivity index: low-fat diet, 0.93; low-glycemic-index diet, 1.04; very low-carbohydrate diet, 1.24 • The very low-carbohydrate diet produced the greatest improvements in most metabolic syndrome components; however, 24-hour urinary cortisol excretion was highest with this diet ○ Urinary cortisol excretion (μg/d): low-fat diet, 50; low-glycemic-index diet, 60; very low-carbohydrate diet, 71
Pharmacotherapy					
SEQUEL (31)	Randomized controlled trial	Patients with overweight/obesity and cardiometabolic disease	Phentermine/topiramate versus placebo	15/92 mg: 10.5% 7.5/46 mg: 9.3% Placebo: 1.8% (all after 2 years)	• Changes in fasting glucose, insulin, and HbA_{1c} levels after 2 years favored phentermine/topiramate (15/92 mg once daily) versus placebo ○ Fasting glucose: −1.2 mg/dL versus 3.7 mg/dL ($p = 0.0048$) ○ Fasting insulin: −5.2 μIU/mL versus −2.6 μIU/mL ($p = 0.0012$) ○ HbA_{1c}: 0.0% versus 0.2% ($p = 0.0003$) • Phentermine/topiramate (15/92 mg once daily) led to a 76% reduction in patients developing T2D versus placebo

TABLE 2 (Continued)

Study	Study design	Population	Intervention	Mean weight loss	Observations
STEP 1 (70)	Randomized controlled trial	Adults with overweight or obesity and without diabetes	Once-weekly subcutaneous semaglutide (2.4 mg) or placebo	Semaglutide 2.4 mg: 14.9% Placebo: 2.4% (both after 68 weeks)	• Patients who received semaglutide experienced greater reductions in fasting plasma glucose and HbA_{1c} levels from baseline than those who received placebo (between-group difference [95% CI] at week 68: −7.87 [−9.04 to −6.70] mg/dL for fasting plasma glucose and −0.29 [−0.32 to −0.26] %-points for HbA_{1c}) • Among patients with prediabetes at baseline, semaglutide was associated with improvements in HbA_{1c} levels versus placebo (between-group difference [95% CI]: −0.34 [−0.39 to −0.29] %-points), and 84.1% of those who received semaglutide had reverted to normoglycemia at week 68 (versus 47.8% of those who received placebo)
Cardiovascular risk factors and disease					
Surgery					
Duvoisin et al. (54)	Retrospective, uncontrolled, cohort study	Patients with obesity	RYGB	28.6% at 10 years after primary RYGB	• Weight loss was associated with a decrease in cardiovascular risk factors, such as levels of total cholesterol, LDL cholesterol, and triglycerides, and an increase in levels of HDL cholesterol ○ Ten years after RYGB, total cholesterol decreased from 5.34 mmol/L to 4.90 mmol/L, LDL cholesterol decreased from 3.21 mmol/L to 2.67 mmol/L, triglycerides decreased from 1.92 mmol/L to 1.28 mmol/L, and HDL cholesterol increased from 1.28 mmol/L to 1.73 mmol/L (all $p < 0.001$) • High proportions of patients experienced improvements in comorbidities, such as hypertension (>80%) and diabetes (>90%), after 10 years; many experienced complete remission of the comorbidity with no residual treatment (>65% for hypertension and >70% for diabetes)

(Continues)

TABLE 2 (Continued)

Study	Study design	Population	Intervention	Mean weight loss	Observations
Utah Obesity Study (14, 74, 82)	Prospective, controlled study	Patients with severe obesity (BMI ≥35 kg/m^2)	RYGB versus non-surgery controls	RYGB: ~31–35% Seeking but did not have bypass surgery (control): ~1.6% Not seeking bypass surgery (control): ~0.2% (all after 2 years)	• RYGB surgery led to improvements in cardiovascular risk factors (such as blood pressure and levels of LDL cholesterol, HDL cholesterol, and triglycerides) versus nonsurgery controls, which were maintained up to 12 years; adjusted mean change from baseline to 12 years: ○ Systolic blood pressure (mmHg): RYBG, 0.1; nonsurgery groups, 6.5 to 10.1 (all $p < 0.001$) ○ Diastolic blood pressure (mmHg): RYBG, 3.1; nonsurgery groups, 6.8 to 10.0 (all $p < 0.05$) ○ LDL cholesterol (mg/dL): RYBG, −11.0; nonsurgery groups: 13.8 to 19.3 (all $p < 0.001$) ○ HDL cholesterol (mg/dL): RYBG, 12.9; non-surgery groups: −3.3 to 0.8 (all $p < 0.001$). ○ Triglycerides (mg/dL): RYBG, −62.8; non-surgery groups: −7.1 to 11.7 (all $p < 0.001$) • Resolution of hypertension and dyslipidemia (defined as normalized levels of the variable without medication) was observed in 38% and 54% of RYGB patients at 2 years, respectively (versus 1% and 7%, respectively, for those who sought but did not have bypass surgery and 4% and 14%, respectively, for those not seeking bariatric surgery)
Changchien et al. (57)	Prospective, uncontrolled, cohort study	Patients eligible for surgery based on 1991 NIH consensus criteria	RYGB	Mean excess weight loss: 71.7% at 12 months	• Postoperative resolution rates for comorbidities (as assessed by physicians at 12 months) were as follows: ○ Hypertension: 62.1% ○ Hyperlipidemia: 62.4% ○ Heart failure: 66.6%
Andreas et al. (15)	Retrospective, uncontrolled, cross-sectional study	Patients with severe obesity	LSG or robotic sleeve gastrectomy with intraoperative endoscopy	NR; rate of excess weight loss was 52.1% at 6 months	• Resolution of hypertension (defined as discontinuation of previous treatment) was experienced by 43/54 patients with this condition (80%)
Helping Evaluate Reduction in Obesity (HERO) registry study (21)	Prospective, uncontrolled, cohort study	Adults with severe obesity (BMI ≥40 kg/m^2 or ≥35 kg/m^2 with severe comorbidity)	LAGB	16.9% after 1 year	• Short-term, significant improvements in hypertension were observed in patients undergoing LAGB ($p < 0.005$) • Among patients with uncontrolled blood pressure at baseline (systolic blood pressure ≥130 mmHg and diastolic blood pressure ≥80 mmHg for patients with T2D, or systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg for patients without T2D), 42% had controlled blood pressure 1 year after LAGB

TABLE 2 (Continued)

Study	Study design	Population	Intervention	Mean weight loss	Observations
Michaelson et al. (39)	Prospective, uncontrolled, cohort study	Patients with obesity (BMI 30–39.9 kg/m^2)	LAGB	18.4% after 1 year	• Improvements in hypertension and dyslipidemia were observed in 64.4% and 59.6% of patients, respectively, 1 year after LAGB
Ooi et al. (40)	Prospective, uncontrolled, cohort study	Patients with obesity and metabolic syndrome	Adjustable gastric banding	18.3% after 2 years	• There were improvements in levels of HDL cholesterol and triglycerides, and total cholesterol:HDL ratio after a threshold weight loss of 7.5% to 12.5% (OR for normalization: 1.48–2.50), with ongoing benefit after greater weight loss (OR: 18.2–30.4 with >25% weight loss) • After 2 years versus baseline (all $p < 0.001$): ○ HDL cholesterol: 1.47 mmol/L versus 1.18 mmol/L ○ Triglycerides: 1.4 mmol/L versus 2.0 mmol/L ○ Total cholesterol:HDL ratio: 3.6 versus 4.6
Bigornia et al. (17)	Prospective, uncontrolled, cohort study	Adults with overweight/obesity (BMI ≥25 kg/m^2)	Bariatric surgery or medical/dietary treatment	14% (median follow-up: 11.7 months)	• Vascular function in patients with hyperinsulinemia was improved by ≥10% weight loss (compared with <10%), as assessed by hyperemic blood flow (between-group difference >300%) and brachial artery flow-mediated vasodilation (between-group difference approximately 2%; both $p < 0.05$)
Singh et al. (83)	Retrospective, matched, controlled, cohort study	Adults with obesity (BMI ≥30 kg/m^2) Matched control patients who had not had bariatric surgery	Bariatric surgery versus routine care	Surgery: 20% Routine care: 0.8% (mean follow-up: 3.9 years)	• Patients who underwent bariatric surgery experienced significantly reduced risks of hypertension (−59%; HR [95% CI]: 0.41 [0.34 to 0.50]; $p < 0.001$) and heart failure (−43%; HR [95% CI]: 0.57 [0.34 to 0.96]; $p = 0.033$) versus routine care • A significant reduction in cardiovascular disease was observed only in the gastric-bypass group (cardiovascular disease risk −47% versus routine care; HR [95% CI]: 0.53 [0.34 to 0.81]; $p = 0.003$) during the study period
SOS study (76, 77)	Prospective, controlled study	Patients with obesity (BMI ≥34 kg/m^2 for men or ≥38 kg/m^2 for women)	Bariatric surgery versus usual care	Bariatric surgery: 23% Usual care: 0% (both after 2 years)	• During follow-up (up to 18 years), bariatric surgery was associated with significant reductions in total cardiovascular events (myocardial infarction and stroke; −33% based on the adjusted hazard ratio; HR [95% CI]: 0.67 [0.54 to 0.83]; $p < 0.001$) and fatal cardiovascular events (fatal myocardial infarction and stroke; −53%; HR [95% CI]: 0.47 [0.29 to 0.76]; $p = 0.002$) versus usual care

(Continues)

Study	Study design	Population	Intervention	Mean weight loss	Observations
Lifestyle modification					
Magkos et al. (9)	Randomized controlled trial	Patients with obesity	Behavior education sessions and diet (target of 5% weight loss versus target of 5% followed by ~10% and ~15% weight loss)	Target 5% weight loss: 5% Target 10% weight loss: 11% Target 15% weight loss: 16%	• There were progressive reductions in triglyceride concentrations from baseline up to 16% weight loss • Plasma free fatty acid concentrations decreased significantly versus baseline only after 16% weight loss (0.47 mmol/L versus 0.56 mmol/L at baseline; $p < 0.05$)
Maraki et al. (36)	Prospective, matched, controlled study	Sedentary men with obesity Age-matched, healthy, lean men	Diet and physical activity in patients with obesity	~10% after 15 weeks in patients with obesity	• There was a significant lowering of postprandial triacylglycerolemia by 27% to 46% compared with baseline in patients with obesity ($p < 0.05$)
Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy (CALERIE) study (44, 45)	Randomized controlled trial	Patients with overweight (BMI ≥25 kg/m^2 to <30 kg/m^2)	Calorie restriction or calorie restriction + exercise versus weight-maintenance diet	Calorie restriction: 10% Calorie restriction + exercise: 10% Weight-maintenance diet: 1% (all after 24 weeks)	• Mean weight loss was similar with calorie restriction and with calorie restriction + exercise (10%) • Weight loss of 10% was not associated with marked improvements in systemic inflammation or markers of inflammation (which are thought to be involved in the pathogenesis of cardiovascular disease) • Weight loss of 10% did not affect morning or diurnal salivary cortisol levels, suggesting that caloric restriction was not perceived as a stressor by the body
Cambridge Intensive Weight Management Programme (60)	Prospective, uncontrolled, cohort study	Patients with severe obesity (BMI ≥40 kg/m^2)	24-week weight-loss program (dietary interventions, pharmacotherapy, physical activity, and behavior change counseling)	~14% after 24 weeks	• There were no significant changes in blood pressure; however, there was an overall decrease in the use of antihypertensive medications (as indicated by clinicians; not consistently quantified)
Pharmacotherapy					
SEQUEL (31)	Randomized controlled trial	Patients with overweight/obesity and cardiometabolic disease	Phentermine/topiramate versus placebo	15/92 mg: 10.5% 7.5/46 mg: 9.3% Placebo: 1.8% (all after 2 years)	• Phentermine/topiramate (15/92 mg once daily) was associated with a reduction in triglycerides and an increase in HDL cholesterol versus placebo ○ Change from baseline in triglycerides: −13.7% versus 0.4% ($p < 0.0001$) ○ Change from baseline in HDL cholesterol: 11.9% versus 4.7% ($p < 0.0001$) • More patients receiving phentermine/topiramate (15/92 mg once daily) had a decrease in lipid-lowering therapies than those receiving placebo (5.8% versus 3.1%) • Patients treated with phentermine/topiramate (15/92 mg once daily) experienced a net decrease in concomitant antihypertensive medication use, whereas use of these medications increased in the placebo group (percentage of patients with net change in antihypertensive medication use: −9.8% versus 3.5%)

TABLE 2 (Continued)

Study	Study design	Population	Intervention	Mean weight loss	Observations
EQUIP (69)	Randomized controlled trial	Patients with obesity (BMI ≥35 kg/m^2)	Phentermine/topiramate versus placebo	15/92 mg: 10.9% 3.75/23 mg: 5.1% Placebo: 1.6% (all after 56 weeks)	• Phentermine/topiramate (15/92 mg once daily) was associated with significant reductions in levels of triglycerides and LDL cholesterol and an increase in levels of HDL cholesterol versus placebo ○ Change from baseline in triglycerides: −5.2% versus 9.1% ($p < 0.0001$) ○ Change from baseline in LDL cholesterol: −8.4% versus −5.5% ($p = 0.0157$) ○ Change from baseline in HDL cholesterol: 3.5% versus 0% ($p = 0.0005$) • Patients who received phentermine/topiramate (15/92 mg once daily) experienced small but significant reductions in systolic and diastolic blood pressure versus placebo ○ Change from baseline in systolic blood pressure: −2.9 mmHg versus 0.9 mmHg ($p < 0.0001$) ○ Change from baseline in diastolic blood pressure: −1.5 mmHg versus 0.4 mmHg ($p = 0.0002$)
STEP 1 (70)	Randomized controlled trial	Adults with overweight or obesity and without diabetes	Once-weekly subcutaneous semaglutide (2.4 mg) or placebo	Semaglutide 2.4 mg: 14.9% Placebo: 2.4% (both after 68 weeks)	• Semaglutide improved levels of total cholesterol, HDL cholesterol, LDL cholesterol, very LDL cholesterol, triglycerides, free fatty acids, systolic blood pressure, and diastolic blood pressure compared with placebo; ratio of week 68 value to baseline (95% CI) at week 68: ○ Total cholesterol: 0.97 (0.95 to 0.98) ○ HDL cholesterol: 1.04 (1.02 to 1.05) ○ LDL cholesterol: 0.96 (0.94 to 0.98) ○ Very LDL cholesterol: 0.84 (0.81 to 0.87) ○ Triglycerides: 0.84 (0.81 to 0.87) ○ Free fatty acids: 0.89 (0.83 to 0.94) • Between-group difference (95% CI) at week 68 (mm Hg): ○ Systolic blood pressure: −5.10 (−6.34 to −3.87); $p < 0.001$ ○ Diastolic blood pressure: −2.41 (−3.25 to −1.57) • Patients in the semaglutide group discontinued lipid-lowering medications more frequently than those in the placebo group (17% versus 12%); a similar pattern was observed for antihypertensive medications (20% versus 11%)

(Continues)

TABLE 2 (Continued)

Study	Study design	Population	Intervention	Mean weight loss	Observations
Cancer and associated risk markers					
Surgery SOS study (59, 76, 77, 87)	Prospective, controlled study	Patients with obesity (BMI ≥34 kg/m^2 for men or ≥38 kg/m^2 for women)	Bariatric surgery versus usual care	Bariatric surgery: 23% Usual care: 0% (both after 2 years) Women in bariatric surgery group: ~24% Women in usual-care group: ~0% (both after 2 years)	• In women in the SOS cohort, bariatric surgery was associated with lower risks of overall cancer (HR [95% CI]: 0.71 [0.59 to 0.85]; $p < 0.001$) and endometrial cancer (HR [95% CI]: 0.56 [0.35 to 0.89]; $p = 0.014$) than control • The effect of bariatric surgery on female-specific cancer was greatest in women with high baseline insulin levels (p interaction = 0.022) • Bariatric surgery was associated with a reduced risk of first-time cancers after inclusion in women (HR [95% CI]: 0.58 [0.44 to 0.77]; $p < 0.0001$), but not in men (HR [95% CI]: 0.97 [0.62 to 1.52]; $p = 0.90$), compared with those receiving usual care (median follow-up: 10.9 years)
Adams et al. (55)	Retrospective, controlled, cohort study	Patients undergoing RYGB versus control patients with severe obesity (BMI ≥35 kg/m^2)	RYGB versus non surgery controls	NR	• Bariatric surgery was associated with lower risks of overall cancer (HR [95% CI]: 0.76 [0.65 to 0.89]; $p = 0.0006$) and uterine cancer (HR [95% CI]: 0.22 [0.13 to 0.40]; $p < 0.0001$) than control
Lifestyle modification					
Re-Energize with Nutrition, Exercise and Weight Loss (RENEW) study (64)	Ancillary study to a randomized trial	Women with class II–III obesity (BMI ≥35 kg/m^2) Control patients without severe obesity	Diet + exercise in women with class II–III obesity	~11% after 1 year in women with class II to III obesity	• Changes in cancer-associated biomarker levels were observed in women with class II–III obesity • Soluble E-selectin, VEGF, IL-6, IL-7, and CA-125 levels decreased over 12 months, while growth hormone, adiponectin, and IGFBP-1 levels increased significantly; after 12 months versus baseline: ○ soluble E-selectin: 30.10 ng/mL versus 33.54 ng/mL ($p < 0.001$) ○ VEGF: 522.78 pg/mL versus 619.75 pg/mL ($p = 0.003$) ○ IL-6: 5.14 pg/mL versus 6.58 pg/mL ($p < 0.001$) ○ IL-7: 6.05 pg/mL versus 7.26 pg/mL ($p = 0.003$) ○ CA-125: 8.96 pg/mL versus 9.88 pg/mL ($p = 0.002$) ○ growth hormone: 1.07 ng/mL versus 0.43 ng/mL ($p < 0.001$) ○ adiponectin: 13.75 μg/mL versus 11.52 μg/mL ($p < 0.001$) ○ IGFBP-1: 4.11 ng/mL versus 3.26 ng/mL ($p < 0.001$)

TABLE 2 (Continued)

Study	Study design	Population	Intervention	Mean weight loss	Observations
Nutrition and Exercise for Women (NEW) study (24, 62)	Randomized controlled trial/ancillary study to a randomized controlled trial	Postmenopausal women with overweight/obesity (BMI ≥25 kg/m^2 or ≥23 kg/m^2 if Asian American)	Diet and/or exercise versus control	Diet: 8.5% Exercise: 2.4% Diet + exercise: 10.8% Control: 0.8% (all after 1 year)	• At 1 year, there were changes in angiogenic biomarker levels ○ PAI-1, PEDF, and VEGF levels decreased significantly in the diet + exercise group, but not in the exercise group, versus controls; absolute changes (%): ▪ PAI-1: diet + exercise, −1.30 (p <0.0001); exercise, 0.53 (p = 0.45); control, 0.27 ▪ PEDF: diet + exercise, −1.03 (p <0.0001); exercise, −0.27 (p = 0.12); control, 19.63 ▪ VEGF: diet + exercise, −31.0 (p <0.0001); exercise, −9.65 (p = 0.33); control, −3.92 • At 1 year, there were marked and significant decreases in inflammatory biomarkers in the diet and diet + exercise groups, but not in the exercise group, compared with control ○ For example, hs-CRP decreased by 0.92 mg/L (36.1%) in the diet group and by 0.87 mg/L (41.7%) in the diet + exercise group (both p < 0.001 compared with control), versus 0.19 mg/L (8.5%) in the exercise group (p = 0.367 compared with control)
Duggan et al. (23)	Ancillary study to a randomized controlled trial (NEW)	Postmenopausal women with overweight/obesity (BMI ≥25 kg/m^2) who completed 30-month assessment	Diet and/or exercise versus control	Mean reduction in BMI: Diet: 12.0% Exercise: 1.9% Diet + exercise: 13.7% Control: increase in BMI of 0.6% (all after 1 year) Mean reduction in BMI: Diet: 6.6% Exercise: 2.1% Diet + exercise: 7.9% Control: 2.9% (all after 30 months)	• Reductions in VEGF levels with intervention (diet and/or exercise) versus control persisted after 30 months of follow-up (diet: −14.1% [p = 0.02]; exercise: −19.7% [p = 0.003]; diet + exercise: −14.5% [p = 0.002]; control, −4.5%)
Fabian et al. (27)	Prospective, uncontrolled, cohort study	Postmenopausal women with overweight/obesity (BMI >25 kg/m^2)	Behavioral weight-loss intervention	NR; median: 11% after 6 months	• Favorable changes in several anthropomorphic, breast tissue and serum risk and mechanistic markers (including serum levels of SHBG, bioavailable estradiol and testosterone, insulin, adiponectin, leptin, and CRP) • Most of the tissue and serum biomarkers were modulated significantly only for women with >10% weight loss ○ For example, the relative change in estradiol was 0% (p = 0.27) with <10% weight loss and −30% (p = 0.004) with >10% weight loss (p = 0.022 for between-group comparison)

(Continues)

TABLE 2 (Continued)

Study	Study design	Population	Intervention	Mean weight loss	Observations
Befort et al. (16)	Prospective, uncontrolled, cohort study	Postmenopausal breast-cancer survivors with overweight/obesity (BMI 27–45 kg/m^2)	Group phone-based weight-loss intervention	13.9% after 6 months	• There were significant improvements from baseline in several HRQoL domains and significant reductions from baseline in insulin and leptin, but not adiponectin, levels at 6 months • HRQoL domains: significant improvements from baseline were seen for joint pain (1.10 versus 1.95 on Trial Symptom Checklist; $p = 0.001$), depressive symptoms (2.82 versus 4.50 on PHQ-9; $p = 0.001$), and body image subscales ($p = 0.02$ to < 0.001 on Body Image & Relationships Questionnaire) • At 6 months versus baseline: ○ Insulin: 6.0 μIU/mL versus 10.5 μIU/mL ($p = 0.006$) ○ Leptin: 32.3 ng/mL versus 56.2 ng/mL ($p < 0.001$) ○ Adiponectin: 9.8 μg/mL versus 9.6 μg/mL ($p = 0.58$) • Weight management could, therefore, represent an opportunity to reduce breast-cancer recurrence and have important benefits for breast-cancer survivors
Osteoarthritis					
Lifestyle modification					
Arthritis, Diet, and Activity Promotion Trial (ADAPT) (37)	Ancillary study to a randomized controlled trial	Sedentary older adults with overweight/obesity (BMI ≥28 kg/m^2) and knee osteoarthritis	Diet and/or exercise versus control	High-weight-loss group: 10.2% Low-weight-loss group: 2.7% No-weight-loss group: weight gain of 1.5% (all after 18 months)	• Mean weight loss of 10% or more led to lower knee-joint compressive loads during walking than the groups with low and no weight loss; change in compressive force after 18 months ($p = 0.05$): ○ High-weight-loss group: −2.6% ○ Low-weight-loss group: 4.5% ○ No-weight-loss group: 13.2%
Intensive Diet and Exercise for Arthritis (IDEA) trial (38)	Randomized controlled trial	Sedentary older adults with overweight/obesity (BMI 27–41 kg/m^2) and knee osteoarthritis	Diet versus diet + exercise	≥20% weight-loss group: 24.6% 10%–20% weight-loss group: 14.5% 5%–10% weight-loss group: 7.4% <5% weight-loss group: 0.2% (all after 18 months)	• A relationship between weight loss and bone-on-bone knee-joint compressive forces was demonstrated ($p < 0.0001$) ○ The ≥10% group demonstrated lower compressive forces than the <5% group (between-group difference: 306 N; $p = 0.0006$) • A significant, magnitude-dependent improvement in systemic inflammation (assessed by plasma IL-6 levels) was observed with increasing weight loss (<5% to ≥20%; $p = 0.017$) • Physical and mental subscales of SF-36 improved ($p = 0.001$ and $p = 0.02$, respectively) and WOMAC pain scores decreased ($p = 0.006$) with greater amounts of weight loss

TABLE 2 (Continued)

Study	Study design	Population	Intervention	Mean weight loss	Observations
Gudbergsen et al. (89)	Randomized controlled trial	Patients with overweight/obesity and knee osteoarthritis	8-week, low-calorie diet intervention followed by liraglutide 3.0 mg/d or placebo among those who had lost ≥5% of their initial body weight	~12% after the dietary intervention	• Participants experienced reduced knee pain (~19% improvement in Knee injury and Osteoarthritis Outcome Score) after the dietary intervention and before randomization to liraglutide 3.0 mg/d or placebo • Among those who had lost ≥5% of their initial body weight through dietary intervention, subsequent addition of liraglutide 3.0 mg/d provided further weight loss over 1 year, but did not reduce knee pain further compared with placebo treatment
Sleep apnea					
Surgery					
Utah Obesity Study (74, 82)	Prospective, controlled study	Patients with severe obesity (BMI ≥35 kg/m^2)	RYGB versus nonsurgery controls	RYGB: ~31%–35% Seeking but did not have bypass surgery (control): ~1.6% Not seeking bypass surgery (control): ~0.2% (all after 2 years)	• Patients who underwent RYGB demonstrated significant improvements in sleep apnea versus each comparative group ($p < 0.0001$)
Andreas et al. (15)	Retrospective, uncontrolled, cross-sectional study	Patients with severe obesity	LSG or robotic sleeve gastrectomy with intraoperative endoscopy	NR; rate of excess weight loss was 52.1% at 6 months	• Almost 90% of patients with sleep apnea who underwent surgery experienced resolution of this condition (defined as discontinuation of previous treatment)
Lifestyle modification					
Johansson et al. (90)	Randomized controlled trial	Men with obesity (BMI 30–40 kg/m^2) and obstructive sleep apnea	Liquid VLED for 7 weeks followed by 2 weeks of gradual introduction of normal food versus usual diet	VLED: ~16.5% Usual diet: gain of ~1.0% (both after 9 weeks)	• After 9 weeks, mean weight loss was greater in the VLED group than in the usual-diet group ($p < 0.001$) and was only ≥10% in the former group • Patients in the VLED group experienced improvements in the severity of their sleep apnea, as assessed by AHI, compared with those who continued their usual diet (mean AHI was 23 events/hour lower with intervention than control at week 9; $p < 0.001$)
Sleep AHEAD study (91)	Randomized controlled trial	Patients with overweight/obesity and T2D	ILI versus DSE	ILI: ~10.5% DSE: ~0.6% (both after 1 year)	• After 1 year, mean weight loss was greater in the ILI group than in the DSE group ($p < 0.0001$), and was only ≥10% in the former group • Weight loss achieved through ILI improved obstructive sleep apnea significantly versus DSE (adjusted decrease in AHI of 9.7 events/hour; $p < 0.001$) • Patients who lost ≥10 kg experienced the greatest improvements in AHI (reduction of 11.3 events/hour; $p < 0.01$ versus all lower weight-loss categories)

(Continues)

TABLE 2 (Continued)

Study	Study design	Population	Intervention	Mean weight loss	Observations
Chronic kidney disease					
Surgery					
SOS study (76, 77, 92)	Prospective, controlled study	Patients with obesity (BMI ≥34 kg/m^2 for men or ≥38 kg/m^2 for women)	Bariatric surgery versus usual care	Bariatric surgery: 23% Usual care: 0% (both after 2 years)	• Patients in the bariatric surgery group had lower risks of ESRD (HR [95% CI]: 0.27 [0.12 to 0.60; $p = 0.001$) and chronic kidney disease stage 4/ESRD combined (HR [95% CI]: 0.33 [0.18 to 0.62; $p < 0.001$) during follow-up than those receiving usual care (median follow-up: 18 years)
MacLaughlin et al. (93)	Randomized controlled trial	Patients with obesity and stage 3–4 chronic kidney disease	LSG versus best medical care	LSG: 29.8% Best medical care: 3.1% (both after 1 year)	• Beneficial changes in adiponectin levels, insulin resistance, insulin use, and HRQoL were observed with LSG versus best medical care, with no change in body surface area-unadjusted eGFR; between-group differences (95% CI) at 1 year: ○ Adiponectin: 6.1 (1.0 to 19.8) mg/L; $p < 0.05$ ○ Insulin resistance by HOMA-IR: −7.7 (−28.8 to −0.5); $p < 0.05$ ○ Daily mean insulin dose: −36 (−69 to −3) units ○ HADS Anxiety score: −4 (−8 to −1); $p < 0.05$ ○ HADS Depression score: −5 (−8 to −3); $p < 0.05$ ○ SF-36 Physical Domain: 22 (8 to 36); $p < 0.05$
Fertility and pregnancy					
Surgery					
Utah Obesity Study (95)	Prospective, controlled study	Men with severe obesity	RYGB versus nonsurgery controls (seeking but did not have bypass surgery or not seeking bypass surgery)	NR; decrease in BMI 16.6 kg/m^2 with RYGB and 0.46 kg/m^2 with control after 2 years	• Men who lost weight after RYGB experienced a reduction in estradiol levels, an increase in total and free testosterone levels, and improved sexual quality of life after 2 years versus baseline and versus nonsurgery controls; mean 2-year change: ○ Estradiol (pg/mL): RYBG, −8.1; control, 1.6 ($p = 0.006$) ○ Total testosterone (ng/dL): RYBG, 310.8; control, 14.2 ($p < 0.001$) ○ Free testosterone (pg/mL): RYBG, 45.2; control, −0.4 ($p = 0.047$) ○ Sexual quality of life (total score of dissatisfaction): RYBG, −7.5; control, −0.1 ($p < 0.001$)

TABLE 2 (Continued)

Study	Study design	Population	Intervention	Mean weight loss	Observations
Legro et al. (94)	Prospective, uncontrolled, cohort study	Reproductive-aged women with obesity (BMI ≥40 kg/m^2 or 35–39.9 kg/m^2 with comorbidity)	RYGB	~22% at 3 months after RYGB	• Ovulatory frequency was not modified by RYGB • Modest improvement in biochemical hyperandrogenemia was observed ○ An increase in SHBG occurred within 1 month of surgery (from approximately 35 nmol/L to >60 nmol/L; $p < 0.001$) ○ Testosterone decreased in the 3-month postoperative period (from approximately 42 ng/dL to approximately 30 ng/dL; $p = 0.002$) • There was a significant improvement in female sexual function 12 months after surgery (Female Sexual Function Index: 27.1 versus 21.2 at baseline; $p = 0.02$).
Lifestyle modification					
Rothberg et al. (41)	Randomized controlled trial	Women with obesity (BMI 35–45 kg/m^2) and anovulatory subfertility	Intensive weight-loss program (diet) versus standard-of-care nutrition counseling	Intensive program: 13% Standard of care: 4% (both after 12 weeks)	• There were improvements in metabolic and ovulatory outcomes in women who participated in the intensive weight-loss program • Three out of the six women in the intensive-program group ovulated and conceived, whereas there were no pregnancies in the standard-of-care group (0/5 women) • There were 3 live births in the intensive program group, all of which were at term
Health-related quality of life					
Surgery					
Duvoisin et al. (54)	Retrospective, uncontrolled, cohort study	Patients with obesity	RYGB	28.6% at 10 years after primary RYGB	• At 10 years of follow-up, the mean HRQoL score (assessed by the Moorehead-Ardelt questionnaire) was 1.64, a significant improvement from baseline (p <0.0001; baseline value NR)
Michaelson et al. (39)	Prospective, uncontrolled, cohort study	Patients with obesity (BMI 30–39.9 kg/m^2)	LAGB	18.4% after 1 year	• Improvements in HRQoL values were observed 1 year after surgery and correlated to weight loss ○ On a scale of 0 to 100, mean IWQOL-Lite total score increased from 62.76 at baseline to 90.56 at 1 year after surgery ($p < 0.0001$) ○ Pearson correlation coefficient for weight loss and IWQOL-Lite total score: year 1, 0.39; year 2, 0.37 • Regression analysis indicated that for each additional 10% weight loss at year 2, there was an increase in IWQOL-Lite of 7.1 points

(Continues)

TABLE 2 (Continued)

Study	Study design	Population	Intervention	Mean weight loss	Observations
Adolescent Morbid Obesity Surgery (AMOS) study (33)	Matched, controlled study	Adolescents with severe obesity (BMI ≥40 kg/m^2 or ≥35 kg/m^2 with comorbidity) Matched adults undergoing gastric-bypass surgery	RYGB versus conventional care in matched adolescents	Surgically treated adolescents: 32% Surgically treated adults: 31% Conservatively treated adolescents: weight gain of 3% (all after 2 years)	• At 2 years, adolescents in the RYGB group had significant improvements in all 4 SF-36 physical health domains, in the physical component summary score, and in 2 of the 4 SF-36 mental health domains, compared with baseline
Alberta Population-based Prospective Evaluation of Quality of Life Outcomes and Economic Impact of Bariatric Surgery (APPLES) study (10)	Prospective, controlled, cohort study	Patients with severe obesity (BMI ≥35 kg/m^2)	Bariatric surgery versus medical treatment	Bariatric surgery: 16.3% Medical treatment: 2.8% (both after 2 years)	• There were consistent, clinically important improvements in HRQoL with bariatric surgery, but not with medical treatment, over 2 years ○ In surgically treated patients, HRQoL MCIDs were reached for all instruments except the SF-12 mental component score ○ In medically managed patients, MCIDs were reached in the EQ-5D index but not the other instruments ○ HRQoL measures: SF-12 physical (MCID = 5) and mental (MCID = 5) component summary scores, EQ-5D index (MCID = 0.03) and Visual Analog Scale (MCID = 10), IWQOL-Lite total score (MCID = 12)
Lifestyle modification					
Linkov et al. (63)	Ancillary study to 2 randomized controlled trials	Patients with overweight/obesity	Diet or self-monitoring of diet and exercise	~14.5% after 6 months (data for interventions pooled)	• There was a significant decrease in the leptin level after weight-loss intervention (mean pre to post change: 20.88 ng/mL; $p < 0.0001$) • Changes in BMI (estimated effect, −1.2588; $p = 0.0033$) and leptin level (estimated effect, −0.17532; $p = 0.0063$) were significantly related to change in the physical summary score of the SF-36 • None of the biomarkers or metabolic factors was found to be a significant predictor of mental summary score
Rothberg et al. (41)	Randomized controlled trial	Women with obesity (BMI 35–45 kg/m^2) and anovulatory subfertility	Intensive weight-loss program (diet) versus standard-of-care nutrition counseling	Intensive program: 13% Standard of care: 4% (both after 12 weeks)	• HRQoL measures improved only in the intensive weight-loss program group (mean EQ-5D index increased from 0.87 to 0.92 [by 0.05, with a change of 0.03 considered to be clinically significant]) • In the standard-of-care group, there was a worsening or no change in HRQoL

TABLE 2 (Continued)

Study	Study design	Population	Intervention	Mean weight loss	Observations
Burghardt et al. (19)	Prospective, matched, controlled study	Men with obesity Matched lean men	VLED to achieve 15% weight loss in men with obesity	Men with obesity: ~16% (after 1 year)	• μ-Opioid receptor-mediated neurotransmission has a role in regulating emotional and feeding responses • In men with obesity, weight loss enhanced μ-opioid-receptor activation to a standard meal in several brain regions (ventral striatum, thalamus, and right temporal pole/amygdala) • Men with obesity showed minimal change in negative affect after a standard meal both before and after weight loss (self-reported fed-fasted change in negative affect [by Negative Affect Schedule]: 0.1 at baseline and −0.2 after weight loss versus −1.6 in lean men)
Pharmacotherapy					
STEP 1 (70)	Randomized controlled trial	Adults with overweight or obesity and without diabetes	Once-weekly subcutaneous semaglutide (2.4 mg) or placebo	Semaglutide 2.4 mg: 14.9% Placebo: 2.4% (both after 68 weeks)	• Patients in the semaglutide group reported a significantly greater increase in physical functioning from baseline to week 68 than those who received placebo (as assessed by SF-36 and IWQOL-Lite-CT physical function scores) ○ For example, IWQOL-Lite-CT physical function scores increased by 14.67 in the semaglutide group and by 5.25 in the placebo group ($p < 0.001$) • Patients were also more likely to experience clinically meaningful improvements in physical functioning with semaglutide than with placebo. OR (95% CI) for achieving a clinically meaningful within-person improvement in score: ○ SF-36 physical functioning (≥3.7 points): 2.08 (1.60 to 2.70) ○ IWQOL-Lite-CT physical function (≥14.6 points): 2.72 (2.14 to 3.47)

Abbreviations: AHEAD, action for health in diabetes; AHI, apnea–hypopnea index; CA-125, carbonic anhydrase 125 enzyme; CI, confidence interval; CRP, C-reactive protein; DSE, diabetes support and education; eGFR, estimated glomerular filtration rate; EQ-5D, EuroQol-5 dimension; ESRD, end-stage renal disease; HADS, Hospital Anxiety and Depression Scale; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; HR, hazard ratio; HRQoL, health-related quality of life; hs-CRP, high-sensitivity C-reactive protein; IGFBP, insulin-like growth factor binding protein; IL, interleukin; ILI, intensive lifestyle intervention; IWQOL-Lite, Impact of Weight on Quality of Life-Lite; IWQOL-Lite-CT, Impact of Weight on Quality of Life-Lite Clinical Trials Version; LAGB, laparoscopic adjustable gastric banding; LDL, low-density lipoprotein; LSG, laparoscopic sleeve gastrectomy; MCID, minimal clinically important difference; NR, not reported; OR, odds ratio; PAI, plasminogen activator inhibitor; PEDF, pigment epithelium-derived factor; PHQ-9, patient health questionnaire; RYGB, Roux-en-Y gastric bypass; SF-12, Short Form-12 Health Survey; SF-36, Short Form-36 Health Survey; SHBG, sex hormone-binding globulin; SOS, Swedish Obese Subjects; STEP, Semaglutide Treatment Effect in People with obesity; T1D, type 1 diabetes; T2D, type 2 diabetes; VEGF, vascular endothelial growth factor; VLED, very low-energy diet; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

the proportion of patients experiencing resolution of diabetes. Only one of these studies reported mean changes in HbA_{1c} levels, which ranged from −0.7% to −0.2% in patients with overweight or obesity and T2D who received individualized treatment (typically consisting of a calorie-restricted diet and plans for behavior modification and increasing physical activity) (65). There was evidence of greater improvements in metabolic control with progressive and sustained weight loss (9,12,20,51,81).

The Diabetes Remission Clinical Trial (DiRECT) trial evaluated a primary-care-led weight-management intervention in patients with a diagnosis of T2D in the preceding 6 years (81). The intervention consisted of withdrawal of antidiabetes and antihypertensive medications, total diet replacement (825-853-kcal/d formula diet for 12-20 weeks), and stepped food reintroduction (2-8 weeks), with subsequent support for weight-loss maintenance (81). T2D remission was defined as $HbA_{1c} < 6.5\%$ after withdrawal of antidiabetes drugs at baseline (81). Among DiRECT study participants who maintained 10 kg or more of weight loss (approximately 10%) in the weight-management program (intervention) or best-practice-care control groups, 64% achieved T2D remission at 2 years (Table 2) (81). A recent analysis showed that, in the intervention group, weight loss was the main predictor of T2D remission at 2 years, with 78.9% and 82.4% of patients achieving remission with weight losses from 10 kg up to 15 kg and 15 kg or more, respectively (compared with 10.4% and 42.2% of patients who achieved weight losses of <5 kg and 5 to <10 kg, respectively) (13). In the intervention group, overall rates of T2D remission decreased over time (46% at 1 year and 36% at 2 years) (13). However, improvements in HbA_{1c} levels were observed in the intervention group compared with control at 2 years, despite lower proportions of the intervention group receiving antidiabetes medication (40% vs. 84% in the best-practice-care control group at 2 years) (81).

Pharmacotherapy

In the SEQUEL trial of patients with overweight or obesity and weight-related comorbidities, phentermine/topiramate 15/92 mg once daily was associated with a mean weight loss of 10.5% after 2 years (compared with 1.8% with placebo; both in combination with lifestyle intervention) (31). The proportion of patients who experienced 10% or more weight loss at 2 years was 54% with phentermine/topiramate 15/92 mg once daily and 12% with placebo (31). Of the 675 patients who received a study product in SEQUEL, 145 (21.5%) had T2D at baseline (31). Changes in fasting glucose, insulin, and HbA_{1c} levels after 2 years favored treatment with phentermine/topiramate 15/92 mg once daily over placebo (e.g., HbA_{1c} change of 0% with phentermine/topiramate vs. +0.2% with placebo [$p = 0.0003$]; or HbA_{1c} change of −0.2% vs. 0%, respectively, among patients with T2D; Table 2) (31). Among patients without diabetes at baseline, phentermine/topiramate 15/92 mg once daily led to a 76% reduction in patients developing T2D compared with placebo (31).

The efficacy and safety of once-weekly subcutaneous semaglutide (2.4 mg) are under investigation among patients with overweight or obesity, with or without diabetes, in the Semaglutide Treatment Effect in People with obesity (STEP)-1 to -8 trials. In the STEP-1 trial of patients with overweight or obesity without T2D, once-weekly subcutaneous semaglutide (2.4 mg) was associated with a mean weight loss of 14.9% after 68 weeks (compared with 2.4% with placebo; both in combination with lifestyle intervention) (70). The proportion of patients with 10% or more weight loss at 68 weeks was 69% with semaglutide 2.4 mg once weekly and 12% with placebo (70). Patients who received semaglutide 2.4 mg once weekly experienced greater improvements in fasting glucose and HbA_{1c} levels from baseline than those who received placebo (e.g., HbA_{1c} change of −0.45% with semaglutide vs. −0.15% with placebo; estimated difference [95% CI]: −0.29% [−0.32% to −0.26%]; or, among patients with prediabetes at baseline, HbA_{1c} change of −0.52% vs. −0.17%, respectively; estimated difference [95% CI]: −0.34% [−0.39% to −0.29%]; Table 2) (70). Among patients with prediabetes at baseline, 84.1% of those who received semaglutide had reverted to normoglycemia at week 68 (compared with 47.8% of those who received placebo) (70).

Cardiovascular risk factors and disease

Surgery/intragastric-balloon therapy

Significant weight loss achieved through surgery was associated with long-term improvements in blood pressure and lipid profiles (Table 2) (14,40,54,74). For example, in the Utah Obesity Study, mean changes from baseline in systolic blood pressure and diastolic blood pressure and in levels of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides remained significantly better in the RYGB group compared with nonsurgery controls for up to 12 years (Table 2) (74). Improvement and, in some cases, resolution of comorbidities such as hypertension and dyslipidemia were reported after bariatric surgery (Table 2) (15,21,39,54,74,82). Among the bariatric surgery publications identified by our literature searches, the proportion of patients with resolution of hypertension ranged from 18% (21) to 80% (15) in the intervention groups and from 6% to 18% in the control groups (14). The proportion of patients with resolution of dyslipidemia ("resolution" was undefined) ranged from 0% (1 year after secondary laparoscopic adjustable gastric banding, based on a single patient with dyslipidemia before laparoscopic adjustable gastric banding) (48) to 72% (for remission of high triglycerides [≥200 mg/dL] 6 years after RYGB) (14). Only one of these publications reported rates of dyslipidemia remission over time in both the intervention and control groups (53%-71% and 6%-34% in the RYGB and nonsurgery control groups of the Utah Obesity Study, respectively, for remission of low levels of HDL cholesterol [<40 mg/dL], high levels of LDL cholesterol [≥160 mg/dL], or high levels of triglycerides [≥200 mg/dL; as separate categories] over up to 6 years) (14). The intragastric-balloon therapy publications did not report proportions of patients with resolution of hypertension or dyslipidemia (18,29,66).

In a retrospective cohort study with a median follow-up of 3.9 years, patients who underwent bariatric surgery experienced 20% weight loss (vs. 0.8% with routine care) and significantly reduced risks of hypertension (−59%) and heart failure (−43%) compared with routine care (83). A significant reduction in incident cardiovascular disease risk was observed only in the gastric-bypass group (−47% vs. routine care) (83).

During follow-up of up to 18 years in the SOS study, bariatric surgery was associated with significant reductions in total (−33%) and fatal (−53%) cardiovascular events compared with usual care (76).

Lifestyle modification

Based on between-study comparisons, weight loss achieved through lifestyle changes appeared to have less effect on cardiovascular risk factors and disease than surgery overall (Table 2). None of the lifestyle modification publications identified by our literature searches reported the proportions of patients experiencing resolution of hypertension or dyslipidemia. Among patients with obesity, benefits of large weight loss following lifestyle modification (namely individual behavior education sessions and dietary counseling) included significant lowering of triglyceride and free fatty acid concentrations from baseline (9).

The Action for Health in Diabetes (Look AHEAD) trial was designed to evaluate effects of ILI versus DSE on the development of cardiovascular disease (11). However, mean weight loss of 10% or more was not achieved in either group, and no between-group differences in cardiovascular outcomes were observed after a median follow-up of 9.6 years (11). Nonetheless, a post hoc analysis that combined patients from both treatment groups showed that achieving large weight loss (>10% of body weight) in the first year of the trial was associated with a 21% lower risk of major adverse cardiovascular events (MACE; a composite of death from cardiovascular causes, nonfatal acute myocardial infarction, nonfatal stroke, or admission to hospital for angina) and a 24% lower risk of an expanded cardiovascular end point (MACE plus coronary artery bypass grafting, carotid endarterectomy, percutaneous coronary intervention, hospitalization for congestive heart failure, peripheral vascular disease, or total mortality) over a median of 10.2 years than a stable weight or weight gain (84).

Pharmacotherapy

Phentermine/topiramate 15/92 mg once daily improved cholesterol and triglyceride levels compared with placebo in patients with overweight or obesity (Table 2) (31,69). Interestingly, in the SEQUEL trial, more patients receiving phentermine/topiramate 15/92 mg once daily also had a decrease in lipid-lowering therapies than those receiving placebo (5.8% vs. 3.1%, respectively) (31). Similarly, patients treated with phentermine/topiramate 15/92 mg once daily experienced a net decrease in concomitant antihypertensive medication use, whereas use of these medications increased in the placebo group (31). In the EQUIP trial, patients with obesity who received phentermine/topiramate 15/92 mg once daily experienced a mean body weight loss of 10.9% (vs. 1.6% with placebo) and small but significant reductions in blood pressure compared with placebo (69).

A retrospective cohort study indicated no increased risk of MACE (a composite of hospitalization for acute myocardial infarction and stroke,and in-hospital cardiovascular death) among current phentermine/topiramate users, with broad 95% CI (85).

Semaglutide 2.4 mg once weekly improved cholesterol, triglyceride, free fatty acid, and blood pressure levels compared with placebo in patients with overweight or obesity (Table 2) (70). Patients in the semaglutide group discontinued lipid-lowering medications more frequently than those in the placebo group (17% vs. 12%, respectively); a similar pattern was observed for antihypertensive medications (20% vs. 11%, respectively) (70).

The effect of once-weekly subcutaneous semaglutide 2.4 mg on MACE (a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) is currently being investigated in the SELECT trial of people with overweight or obesity (ClinicalTrials.gov identifier: NCT03574597). In patients with T2D and high cardiovascular risk, once-weekly subcutaneous semaglutide 0.5 mg or 1.0 mg significantly reduced the risk of a similar MACE outcome by 26% compared with placebo (86).

Cancer and associated risk markers

Intentional weight loss may lower the risk of cancer, particularly breast and female-specific cancers (Table 2) (87,88).

Surgery

Bariatric surgery was associated with lower risks of any cancer, endometrial cancer, and uterine cancer compared with control patients (Table 2) (55,87). Among women in the SOS cohort, bariatric surgery was associated with a 29% lower risk of cancer than conventional obesity treatment, and the number needed to treat to prevent one cancer event over 10 years was 31 (87). Approximately half of the observed cancers were female-specific, most commonly breast or endometrial cancers (87). Except for cervical cancer, the incidence rates of female-specific cancers were lower in the surgery group than in the usual-care group, but the difference was significant only for endometrial cancer (44% reduction, $p = 0.014$) (87). Although the number of first-time cancers after inclusion was lower with bariatric surgery than with conventional treatment in women, this effect was not observed in men over a median follow-up of 10.9 years (59). Similarly, in a retrospective cohort study with a mean follow-up of 12.5 years, cancer incidence was 24% lower in the gastric-bypass group than in the nonsurgical control group with severe obesity, but the decreased incidence was observed only in women (27% reduction vs. 2% change in men) (55). There was a significantly lower

uterine-cancer incidence but a significantly higher rate of vulval cancer with gastric bypass compared with nonsurgical control (55).

Lifestyle modification

Changes in cancer-associated, angiogenic, and inflammatory biomarkers were observed after mean weight loss of 10% or more achieved through lifestyle modification (diet, exercise, and/or behavioral weight-loss intervention) in women with overweight or obesity (Table 2) (23,24,27,62,64). Among postmenopausal women with overweight or obesity, only those who maintained large weight loss from baseline had significant reductions in levels of vascular endothelial growth factor (a proangiogenic factor) after 30 months compared with those who lost no weight or gained weight (23). In another study of behavioral weight-loss intervention (diet containing 1,000-1,200 calories/d, exercise, and weekly in-person group lifestyle-modification meetings), large weight loss (>10% of body weight) over 6 months was associated with favorable changes in breast tissue and serum risk biomarkers in postmenopausal women with overweight or obesity (27). Additionally, breast-cancer survivors with overweight or obesity who completed a 6-month phone-based group weight-control intervention (reduced-calorie diet, exercise, and weekly group phone sessions) lost an average of 13.9% of their baseline weight and experienced significant reductions from baseline in levels of insulin and leptin, which have been implicated in the link between obesity and breast cancer (16). It has been suggested that large weight loss should be the goal for breast cancer risk-reduction studies in women with obesity (27), and weight management could represent an opportunity to reduce breast-cancer recurrence (Table 2) (16).

Osteoarthritis

In patients with overweight or obesity and knee osteoarthritis, mean weight loss of 10% or more achieved through diet and/or exercise led to lower knee-joint loads, less systemic inflammation, and reduced knee pain (Table 2) (37,38,89). In the Intensive Diet and Exercise for Arthritis (IDEA) trial of sedentary older adults with overweight or obesity and knee osteoarthritis, these effects were magnitude dependent, with the greatest benefits observed among patients experiencing weight loss of 10% to 19.9% or weight loss of 20% or more (38). Authors of the IDEA publication proposed that large weight loss should be part of the standard of care for older adults with overweight or obesity and knee osteoarthritis (38).

Sleep apnea

Surgery

Patients who underwent bariatric surgery and achieved substantial weight loss (>50% excess weight loss in one study and approximately 31% mean weight loss in another) also experienced improvements in sleep apnea (Table 2) (15,82). For example, in a retrospective study of patients with severe obesity, 20 out of 23 patients (almost 90%) with sleep apnea who underwent laparoscopic or robotic sleeve gastrectomy experienced resolution of this condition (defined as discontinuation of previous treatment) (15). Consistent with this, in a systematic review and meta-analysis of revisional bariatric surgery after failed laparoscopic adjustable gastric banding, 80.8% of patients experienced improvement or remission of obstructive sleep apnea (pooled rate from two studies: one of the studies considered improvement to be apnea-hypopnea index [AHI] < 30 and remission to be AHI < 15; the other study defined remission as cessation of the use of continuous positive airway pressure) (72).

Lifestyle modification

Men with obesity and moderate-to-severe obstructive sleep apnea (AHI ≥ 15 events/h) who lost approximately 16.5% of their weight through diet experienced improvements in sleep apnea severity compared with control patients who adhered to their usual diet (Table 2) (90). After an energy-restricted diet, 50% of the intervention group had milder disease (AHI 5-14.9 events/h), and 17% of this group were considered free of sleep apnea (AHI < 5 events/h) (90). In the control group, who were instructed to continue with their usual diet, all patients except one had an AHI remaining at ≥15 events/h (90). These observations are consistent with results from the Sleep AHEAD study, in which weight loss achieved through ILI significantly improved obstructive sleep apnea in patients with overweight or obesity and T2D relative to DSE (adjusted decrease in AHI of 9.7 events/h, $p < 0.001$; Table 2) (91).

Chronic kidney disease

In the SOS study, bariatric surgery patients had a lower risk of advanced chronic kidney disease during a median follow-up of 18 years than control patients who received usual obesity care (Table 2) (92). Specifically, the long-term risk of end-stage renal disease was over 70% lower and the risk of stage 4 chronic kidney disease and end-stage renal disease combined was approximately 65% lower in the surgery group than in the control group (92). Therefore, weight loss could form part of the strategy for the prevention of advanced chronic kidney disease among patients with obesity (92).

Sleeve gastrectomy was associated with several benefits compared with best medical care in patients with obesity and comorbid chronic kidney disease (Table 2) (93). In a small randomized controlled study of patients with obesity and stage 3 to 4 chronic kidney disease, those who underwent sleeve gastrectomy experienced mean weight loss of 29.8% (compared with 3.1% in

those with best medical care) after 1 year (93). Favorable changes in serum adiponectin, insulin resistance, insulin use, and HRQoL were observed with sleeve gastrectomy compared with best medical care, with no change in body surface area-unadjusted estimated glomerular filtration rate (93). Further study is required to establish the renal effects of weight loss in patients with obesity and chronic kidney disease and to investigate the relevant mechanisms.

Fertility and pregnancy

Surgery

Improvements in sex hormones and sexual function have been reported with large weight loss after RYGB (Table 2) (94). In men with severe obesity, increased BMI was associated with lower testosterone levels and reduced sexual quality of life scores, both of which improved among those who lost weight through RYGB (Table 2) (95). In women, obesity has been associated with longer menstrual cycles, mainly due to lengthening of the follicular phase (94). Among reproductive-aged women with severe obesity, the effects of weight loss on reproductive function were modest, with bariatric surgery having little effect on the ovulatory cycle except to shorten the follicular phase (94). There was a significant decrease in overall menstrual cycle length at 6 months after surgery but not after 12 months (94). However, biochemical hyperandrogenism improved, with an increase in serum sex hormone-binding globulin levels and decrease in testosterone levels, and sexual function improved by 28% from baseline to 12 months (94). Other studies have reported improvements in menstrual cycle length and regularity, conception rates, and pregnancy rates among women who have undergone bariatric surgery (96).

Bariatric surgery may improve pregnancy outcomes in women with obesity by reducing gestational diabetes, gestational hypertension, and macrosomia rates (97). However, this intervention is associated with an increased risk of small-for-gestational-age fetus and prematurity (97).

Lifestyle modification

In women with severe obesity and anovulatory subfertility, intensive weight-loss intervention based on a very low-energy diet was associated with weight loss of 13% and improvements in metabolic and ovulatory outcomes (Table 2) (41). Within 6 months of completing the intensive weight-loss intervention, three out of six of the patients in the intensive-weight-loss group became pregnant (41). Of these patients, two conceived after receiving one cycle of clomiphene, and one conceived without ovulation induction (41). Despite an average of three cycles of ovulation induction medication, none of the five patients in the standard-of-care nutrition counseling group (who lost an average of 4% of their initial weight) became pregnant (41). However, between-group differences in ovulation and conception did not reach statistical significance (41).

HRQoL

Surgery

Bariatric surgery improved long-term HRQoL outcomes from baseline and compared with medical treatment in patients with obesity (Table 2) (10,33,39,54). For example, in patients with obesity who underwent primary RYGB, there was an increase in HRQoL from baseline to 1 year that slightly declined with further time, but was significantly improved compared with baseline at 10 years (as assessed by the Moorehead-Ardelt questionnaire) (54). Weight regain between nadir weight at approximately 3 years and 10 years was 26%, but whether the decline in HRQoL over time was related to weight regain after surgery was not reported (54). Patients with obesity also experienced improvements in HRQoL after laparoscopic adjustable gastric banding (39). Specifically, on a scale of 0 to 100, mean Impact of Weight on Quality of Life-Lite (IWQOL-Lite) total score increased from 62.76 at baseline to 90.56 at 1 year after surgery ($p < 0.0001$) (39). In a regression analysis, there was an increase in IWQOL-Lite total score of 7.1 points for each additional 10% weight loss at year 2 (39).

Lifestyle modification

Lifestyle changes resulting in large weight loss had positive impacts on HRQoL (Table 2) (41,63). For example, in women with severe obesity and anovulatory subfertility who participated in an intensive weight-loss intervention associated with mean weight loss of 10% or more, there was an increase in mean EuroQol-5-dimension (EQ-5D) index of 0.05, with an increase of 0.03 being considered a clinically significant improvement (41). In the standard-of-care nutrition counseling group, who lost an average of 4% of their initial weight, there was a worsening or no change in HRQoL (41). The study was small, and patients were followed for 6 months after the intervention to 1 year or more (41).

Pharmacotherapy

In the STEP-1 trial, patients with overweight or obesity in the semaglutide 2.4 mg once-weekly group (who lost an average of approximately 15% of their baseline weight) reported a significantly greater increase in physical functioning from baseline to week 68 than those who received placebo (as assessed by Short Form-36 Health Survey and IWQOL-Lite Clinical Trials Version [IWQOL-Lite-CT] questionnaire physical function scores; Table 2) (70). Patients were also more likely to experience

clinically meaningful improvements in physical functioning with semaglutide than with placebo. For example, 51.2% of patients in the semaglutide group experienced an increase in IWQOL-Lite-CT physical function score of 14.6 or more compared with 32.9% in the placebo group (odds ratio [95% CI]: 2.72 [2.14-3.47]) (70).

Health care utilization and economic benefits

Surgery

Bariatric surgery reduced postoperative pharmacy use and costs compared with a propensity-matched, nonsurgical control group during a 4-year follow-up period (98).

The Review of Behaviour and Lifestyle Interventions for Severe Obesity: an Evidence Synthesis (REBALANCE) systematic review and economic evaluation compared the cost-effectiveness of bariatric surgery, weight-management programs, and orlistat pharmacotherapy for adults with severe obesity (99). RYGB was identified as the most cost-effective intervention (99).

Lifestyle modification

According to the REBALANCE systematic review, most weight-management programs are cost-effective compared with current population obesity trends (99).

Pharmacotherapy

Modeling suggests that Medicare could make significant cost savings through medications associated with 10% to 15% weight loss in older adults with overweight or obesity (46).

Magnitude-dependent effects of weight loss on outcomes

Based largely on between-study comparisons, bariatric surgical procedures promote different levels of weight loss, which can have varying effects on outcomes (Table 2) (15,29,39,52,66,82). Individuals may experience inadequate weight loss or weight regain after bariatric surgery, with risk of comorbidities returning (47). Adjuvant pharmacotherapy may be helpful in these situations (47).

Magnitude-dependent effects of weight loss achieved using lifestyle modification were observed (Table 2) (9,12,20,38). The efficacy of behavioral treatments for overweight or obesity may be improved by integrating self-regulation skills that are part of acceptance-based behavioral treatment (30). Repeated ILIs could be considered for those at risk of regaining weight (53).

Adverse effects

There is a risk of complications and adverse effects with weight-loss interventions (Table 3).

Hypoalbuminemia was associated with increased odds of death, serious morbidity, and 30-day readmissions following bariatric surgery (28). In patients with hypoalbuminemia, preoperative weight loss of 10% or more increased the odds of death and serious morbidity following surgery compared with patients without preoperative weight loss (28).

ILI did not change cognitive function significantly compared with DSE in patients with obesity and T2D (26).

Patients who experienced large weight loss before deceased-donor kidney transplantation were at increased risk of adverse outcomes compared with recipients who had less than 5% weight change (34).

Limitations and areas of uncertainty

A few limitations and areas of uncertainty should be noted. First, most studies on large weight loss assessed surgical or lifestyle interventions. More research is needed to understand how large weight loss achieved using pharmacotherapy affects clinical outcomes, health care utilization, and costs. Second, between-study comparisons of the benefits of large weight loss should be made with caution, owing to differences in populations, design, and the extent of weight loss achieved. Third, additional analyses by baseline BMI would be instructive. Fourth, there is a need for tools to identify potential responders to weight-loss treatment and to evaluate who will benefit from this treatment in terms of cardiometabolic risk at the level of the individual. Scores combining epidemiological and interventional data may be helpful in this respect (34). Finally, we need to understand how to maximize the effects of weight-loss approaches to achieve large weight loss and develop appropriate cost-effectiveness models.

CONCLUSION

There are differences in weight loss according to the type of intervention used, with surgery rather than lifestyle intervention generally having the largest effect based on between-study comparisons and randomized controlled trial data. Weight loss has important benefits in people with overweight or obesity regardless of approach, although evidence has suggested greater improvements in certain outcomes with progressive and sustained weight loss. Given that large weight loss has a major beneficial effect on overweight- and obesity-related complications, we suggest that weight loss of 10% or more should be the main treatment target when modest weight loss has insufficient effects on obesity-related complications and for patients with severe obesity. However, more research is needed to understand how large weight loss achieved using pharmacotherapy affects clinical outcomes, health care utilization, and costs.O

TABLE 3 Selected complications and adverse effects reported with weight-loss interventions in patients with overweight or obesity

Complication/adverse effect (intervention of interest)	Timing and frequency
Surgery/endoscopy	
Death or serious morbidity; increased likelihood in patients with hypoalbuminemia and preoperative weight loss >10% (surgery/RYGB) (14, 28, 43, 48, 54, 59)	• Death or serious morbidity within 30 days of surgery: 3.5% (28) ○ Among patients with severe hypoalbuminemia: 9.6% (28) ○ Among patients with severe hypoalbuminemia and preoperative weight loss >10%: 37.5% (28) • Death over up to 10 years: 0%–5% (14, 28, 43, 48, 54, 59) ○ Death by the end of the 6-year follow-up: RYGB, 3%; seeking but did not have bypass surgery (control), 3%; not seeking bypass surgery (control), 1% (14) ○ Death within 30 days of surgery: 0.1% (28) ○ Procedure-related death ≥2 months after surgery: RYGB, 0.95%; LAGB: 0% (43) ○ Death during the first postoperative month: 0.15%; death during 10-year follow-up from causes unrelated to surgery: 5% (54) ○ Death within 90 days from the start of the study: surgery group, 0.25%; conventional treatment group (control), 0.1% (59) ○ Death after failed RYGB and secondary LAGB (mean follow-up: 14.0 months): 2.3% (48)
Endoscopic dilation resulting in perforation and death due to uncontrolled sepsis (RYGB) (43)	• Procedure-related death ≥2 months after surgery: RYGB, 0.95%; LAGB: 0% (43)
Band erosion and septic shock leading to death (LAGB) (48)	• After failed RYGB and secondary LAGB (mean follow-up: 14.0 months): 2.3% (48)
Sepsis, septic shock (surgery) (28)	• Among 106,577 patients within 30 days of surgery: 150 sepsis and 89 septic-shock complications (28)
Suicide/poisoning of undetermined intention (RYGB) (14)	• Suicides by the end of the 6-year follow-up: RYGB, 0.96%; control, 0.00% (14) • Poisonings of undetermined intention by the end of the 6-year follow-up: RYGB, 0.48%; control, 0.14% (14)
Depression (LAGB) (39)	• Through 2 years after LAGB: 7.5% (39)
Conversion to open procedure due to technical difficulties (RYGB, LAGB) (43)	• RYGB: 2.9% (43) • LAGB: 1.6% (43)
Failed insertion (gastric-balloon therapy) (18)	• At time of scheduled insertion: 4.1% (18)
Inability to tolerate oral fluids/food (gastric-balloon therapy) (29, 66)	• Unable to tolerate oral fluids (timing unclear): 18% (29) • Food intolerance: 5 cases in a study of 51 patients (timing NR) (66)
Acute renal failure due to dehydration requiring short-term dialysis (LAGB) (43)	• Within 30 days: 0.8% (43)
Prolonged hospital stay (further 24 hours of fluid and medication support) (gastric-balloon therapy) (29)	• In the first days after the procedure: 9% (29)
Intubation/ventilator required (surgery) (28)	• Among 106,577 patients within 30 days of surgery: 204 intubation and 126 ventilator complications (28)
Perioperative complications (RYGB) (14)	• RYGB surgery perioperative complications (30 day): 3% (14)
Hospitalization (increased likelihood in patients with hypoalbuminemia); bariatric surgery-related hospitalization (surgery/RYGB) (14, 28, 33)	• Readmission 3 days after discharge following RYGB: 1.2% (33) • Readmission within 30 days of surgery: 4.4% (28) ○ Among patients with severe hypoalbuminemia: 8.5% (28) • Bariatric surgery-related hospitalizations by the end of the 6-year follow-up: RYGB, 7.9%; seeking but did not have bypass surgery (control), 3.9%; not seeking bypass surgery (control), 2.0% (14)
Catheter-induced hematuria requiring readmission (LAGB) (48)	• After failed RYGB and secondary LAGB (mean follow-up: 14.0 months): 2.3% (48)
Postprocedural/postoperative pain (LAGB, vagal-nerve blockade [vBloc device]) (39, 49)	• Postprocedural pain through 2 years after LAGB: 19.7% (39) • Postoperative pain within 30 days of vBloc-device removal: 3.3% (49)
Implant-/port-site pain (LAGB) (39)	• Implant-site pain through 2 years after LAGB: 6.8% (39) • Access-port revisions because of a flipped port and port-site pain through 2 years after LAGB: 1.3% (39)

(Continues)

TABLE 3 (Continued)

Complication/adverse effect (intervention of interest)	Timing and frequency
Shoulder pain, back pain (LAGB) (39)	• Shoulder pain through 2 years after LAGB: 10.2% (39) • Back pain through 2 years after LAGB: 8.8% (39)
Headache (LAGB) (39)	• Through 2 years after LAGB: 9.5% (39)
Pyrexia (LAGB) (39)	• Through 2 years after LAGB: 6.1% (39)
Contact dermatitis due to surgical glue (vagal-nerve blockade [vBloc device]) (49)	• Within 30 days of vBloc-device removal: 3.3% (49)
Wound disruption, complications (surgery) (28, 59); wound separation, wound seroma (LAGB) (50)	• Wound complications after surgery (timing NR): 1.8% (59) • Wound disruption complications among 106,577 patients within 30 days of surgery: 47 (28) • Wound separation and wound seroma among 115 adolescents who underwent LAGB (postoperative; timing NR): 1 (50)
Seroma formation at the neuroregulator site (vagal-nerve blockade [vBloc device]) (49)	• Within 30 days of vBloc-device removal: 23.3% (49)
Superficial/deep surgical-site infection; organ-space surgical-site infection (surgery) (28); band infection (restrictive procedures) (58); wound infection (RYGB) (43); trocar-/port-site wound infection (LAGB) (43); device-related infection (LAGB) (21); port-site infection (vagal-nerve blockade [vBloc device]) (49)	• Among 106,577 patients within 30 days of surgery: 507 superficial, 87 deep, and 307 organ-space surgical site infections (28) • Deep infections after surgery (timing NR): 2.1% (59) • Causes of failed restrictive procedures included band infection (3%; timing NR) (58) • Wound infections within 30 days among 105 patients in the RYGB group: 2 (43) ○ Timing and frequency of trocar-/port-site wound infections in the LAGB group unclear • Device-related infection up to 18 months after LAGB: 0.5% (21) • Port-site infection within 30 days of vBloc-device removal: 3.3% (49)
Plantar fasciitis (LAGB) (50)	• One case among 115 adolescents who underwent LAGB (postoperative; timing NR) (50)
Urinary tract infection (surgery) (28)	• Among 106,577 patients within 30 days of surgery: 380 urinary tract infections (28)
Sinusitis (LAGB) (39)	• Through 2 years after LAGB: 8.8% (39)
Bronchitis (LAGB) (39)	• Through 2 years after LAGB: 5.4% (39)
Pulmonary complications, pneumonia (surgery) (28, 59); pneumonia requiring prolonged hospital stays and intravenous antibiotics ± subphrenic abscess (RYGB) (43); aspiration pneumonia (LAGB) (43)	• Pulmonary complications after surgery (timing NR): 6.1% (59) • Among 106,577 patients within 30 days of surgery: 258 pneumonia cases (28) • Pneumonia within 30 days in the RYGB group: 2.9% (43) • One case of aspiration pneumonia among 127 patients in the LAGB group over 10 years (43)
Deep-vein thrombosis, pulmonary embolism, thrombosis/embolism (surgery) (28, 59); pulmonary embolism (LAGB) (43)	• Among 106,577 patients within 30 days of surgery: 200 deep-vein thrombosis cases and 120 pulmonary embolism cases (28) • Thrombosis/embolism after surgery (timing NR): 0.8% (59) • Pulmonary embolism within 30 days in the LAGB group: 0.8% (43)
Cardiac arrest, myocardial infarction, cerebrovascular event (surgery) (28)	• Among 106,577 patients within 30 days of surgery: 54 cardiac arrests, 42 myocardial infarctions, and 15 cerebrovascular events (28)
Hypertension (LAGB) (39)	• Through 2 years after LAGB: 6.1% (39)
Postoperative bleeding (surgery) (59); intra-abdominal bleeding requiring hematoma evacuation, oversuturing of staple-bleeding site and/or blood transfusion (RYGB) (43); trocar-site bleeding (LAGB) (43)	• Bleeding after surgery (timing NR): 0.5% (59) • Intra-abdominal bleeding within 30 days in the RYGB group: 3.8% (43) • Trocar-site bleeding within 30 days in the LAGB group: 0.8% (43)
Transfusion (surgery/RYGB) (28, 33, 43)	• Intra-abdominal bleeding within 30 days in the RYGB group requiring blood transfusion: 1.9% (43) • Blood transfusion required due to bleeding after RYGB (timing unclear): 2.5% (33) • Among 106,577 patients within 30 days of surgery: 784 transfusions (28)

TABLE 3 (Continued)

Complication/adverse effect (intervention of interest)	Timing and frequency
Reoperation (surgery/RYGB/LAGB) (28, 48, 50, 54, 59), need for revisional procedures/device removal (surgery/restrictive procedures/RYGB/LAGB/vagal-nerve blockade [vBloc device]) (21, 43, 48, 49, 58)	• Among 106,577 patients within 30 days of surgery: 1599 reoperations (28) • Reoperation required (timing NR): 2.2% (59) • Required long-term reoperation after RYGB (10-year data): 14.6% (54) • Reoperation after failed RYGB and secondary LAGB (mean follow-up: 14.0 months): 21% (48) • Reoperations (owing to port displacement, leak associated with the port, band, or tubing, or bleeding at the port site, malpositioned/slipped bands, or bowel obstruction; timing NR): adolescents: 7.8%; adults: 8.7% (50) • Study of patients with failed restrictive procedures converted to LSG (58) • Study of patients undergoing LAGB after failed RYGB; band removal: 16% (mean follow-up: 14.0 months) (48) • Surgical revisions related to the LAP-BAND AP System after up to 18 months: 2.7% (21) • Access-port revisions because of a flipped port and port-site pain through 2 years after LAGB: 1.3% (39) • Revision of access ports due to breakages/leaks in the LAGB group from 30 days to 10 years: 16.5% (43) • Band removal or revision to a different bariatric procedure due to complications/failure to lose sufficient weight in the LAGB group: 15% after 7 years and 23% after 10 years (43) • Study of patients requiring vBloc-device removal (49)
Early removal (including deflation) (gastric-balloon therapy) (18, 66)	• Early removal (by 12 months): 28.8% (18) • Balloon removed through vomiting after spontaneous deflation: 1 case in a study of 51 patients (timing NR) (66) • Extraction at 3.7 months due to unexpected pregnancy: 1 case in a study of 51 patients (66)
Early removal/adjustment due to intolerance (gastric-balloon therapy) (18, 29, 66)	• Early removal due to intolerance and refusal of adjustment: 5.5% (18) • Downward adjustment (~1.5 months): 13.7% (18) • Adverse reactions and balloon extraction after 6 days: 2% (29) • Removal associated with complications: 7 cases in a study of 51 patients (timing NR) (66)
Catheter migration/impaction in the duodenum requiring surgical extraction (gastric-balloon therapy) (18)	• At or beyond 12 months: 2.7% (18)
Port displacement, flipped port, port leak (LAGB) (21, 39); access-port breakage or leakage requiring operative repair (LAGB) (43); port-related complications (LAGB after failed RYGB) (48)	• Port displacement up to 18 months after LAGB: 1.8% (21) • Port leak up to 18 months after LAGB: 0.1% (21) • Flipped port through 2 years after LAGB: 0.7% (39) • Access-port breakage or leakage requiring operative repair: 21 cases among 127 patients in the LAGB group over 10 years (43) • Port-related complications after failed RYGB and secondary LAGB (mean follow-up: 14.0 months): 5% (48)
Failure due to inadequate weight loss; increase in weight after surgery (restrictive procedures/RYGB) (33, 58); gastrogastric fistula with VBG and weight gain (restrictive procedures) (58)	• Increase in weight among adolescents during the second year after RYGB: 43% (33) • Causes of failed restrictive procedures included inadequate weight loss (47%), weight gain (19%), and gastrogastric fistula with VBG and weight gain (3%; timing NR) (58)
Failure to lose sufficient weight (RYGB, LAGB, gastric-balloon therapy) (43, 66); further procedure/revision secondary to inadequate weight loss (restrictive procedures; LSG or robotic sleeve gastrectomy with intraoperative endoscopy after failed restrictive procedures) (58)	• Excess weight loss <25% after 1 year: RYGB, 3.4%; LAGB, 27.8% (43) • Excess weight loss <25% after 10 years: RYGB, 0%; LAGB, 28.2% (43) • Excess weight loss <20% immediately after intragastric-balloon removal at 6 months: 22.9% (66) • Excess weight loss <20% 6–12 months after intragastric-balloon removal: 79.3% (66) • Further procedure/revision secondary to inadequate weight loss after restrictive procedure and LSG: ≤6.3% (mean follow-up: 26 months) (58)
Scheduled for adjustment due to weight plateau ± subsequent failure/non-response (gastric-balloon therapy) (18)	• Scheduled for adjustment due to weight plateau: 69.9% (1-year data) (18) ○ Adjustments failed: 8.2% (18) • Non-response: 9.6% (18)

(Continues)

TABLE 3 (Continued)

Complication/adverse effect (intervention of interest)	Timing and frequency
Device removal (for reasons including device malfunction, pain at the neuroregulator site, retrosternal/epigastric pain, severe nausea, dissatisfaction with weight loss, or weight regain) (vagal-nerve blockade [vBloc device]) (49)	• Study of patients requiring vBloc-device removal (49) • Median time from implantation to removal: 41 months (49) • Removal reason (49): ○ Device malfunction: 23.3% ○ Pain at the neuroregulator site: 16.7% ○ Retrosternal/epigastric pain: 36.7% ○ Severe nausea: 6.7% • Dissatisfaction with weight loss or weight regain: 50%
Concurrent procedures during device removal, including conversion to other bariatric surgical procedures (vagal-nerve blockade [vBloc device]) (49)	• Concurrent procedures during device removal: 23% (49) • Conversion to other bariatric surgical procedures: 13% (49)
Weight (re)gain after surgery/balloon extraction (RYGB, gastric-balloon therapy) (29, 43, 54, 66)	• Ten years after primary RYGB, 0.6% of patients were heavier than before surgery (54) • NR; percentage excess weight loss in the RYGB group was significantly lower after 7 years (58.6%) than after 3 years (79.9%) or 4 years (81.1%) (43) • Six months after intragastric-balloon extraction, 20% of patients returned to their index BMI from the beginning of treatment, 8% exceeded the index BMI and 23% underwent a gastric-sleeve procedure (47% maintained their weight/BMI after balloon extraction) (29) • Among 35 patients who entered a study, 19 achieved weight loss ≥10% at intragastric-balloon removal; although 12 patients maintained their weight below this threshold during the 6–12 following months, 7 regained weight above this threshold (66)
Dissatisfaction with device (restrictive procedures) (58)	• Causes of failed restrictive procedures included dissatisfaction with device (3%) (timing NR) (58)
Band slippage (restrictive procedures) (58); band slippage ± pouch dilation, gastric prolapse (LAGB) (21, 39, 43); band slippage/migration (LAGB after failed RYGB) (48)	• Causes of failed restrictive procedures included band slippage (16%) (timing NR) (58) • Band slippage up to 18 months after LAGB: 0.6% (21) ○ Band slippage and pouch dilation: 0.3% (21) • Band slippage through 2 years after LAGB: 5.4% (8 patients) (39) ○ Two patients had serious band slips (prolapse of the stomach through the band) (39) • Gastric prolapse or band slippage in the LAGB group over 10 years: 5.5% (43) • Band migration after failed RYGB and secondary LAGB: 5% (mean follow-up: 14.0 months) (48)
Band too tight (LAGB) (39, 43)	• Band too tight through 2 years after LAGB: 1.3% (39) • Band too tight within 30 days (causing immediate pouch obstruction requiring laparoscopic exploration and band repositioning): 0.8% (43)
Band erosion ± abdominal cavity abscess (LAGB) (21, 39, 43)	• Band erosion up to 18 months after LAGB: 0.5% (21) • Serious device-related adverse event of band erosion with abdominal cavity abscess (through 2 years after LAGB): 0.7% (39) • Band erosion (chronic, through 10 years after LAGB): 0.8% (43)
Inflamed stomach around band (LAGB) (39)	• Inflamed stomach around band through 2 years after LAGB: 0.7% (39)
Band leakage (LAGB after failed RYGB) (48)	• After failed RYGB and secondary LAGB (mean follow-up: 14.0 months): 2% (48)
Band removal due to intolerance/other reasons (LAGB, LAGB after failed RYGB) (21, 39, 40, 43, 48)	• LAP-BAND AP System explanted after up to 18 months: 1.6% (21) • Band removed through 2 years after LAGB: 3.4% (39) • Withdrew by 2 years due to LAGB explant: 6.9% (40) • Band removed through 10 years after LAGB: 22.8% (43) • Band removal after failed RYGB and secondary LAGB (mean follow-up: 14.0 months): 16% (48)
Lead erosion requiring repair of the gastrotomy (vagal-nerve blockade [vBloc device]) (49)	• Within 30 days of vBloc-device removal: 3.3% (49)

TABLE 3 (Continued)

Complication/adverse effect (intervention of interest)	Timing and frequency
Intra-abdominal abscess (vagal-nerve blockade [vBloc device]) (49)	• Within 30 days of vBloc-device removal: 3.3% (49)
Tear of silastic ring (restrictive procedures) (58)	• Causes of failed restrictive procedures included tear of silastic ring (3%; timing NR) (58)
Esophageal dilation (restrictive procedures/LAGB) (50, 58); gastric-pouch dilations requiring band deflation ± esophageal dilation, with or without band removal (43) (LAGB), pouch dilation (LAGB) (21); stoma obstruction, dilation (LAGB) (43)	• Causes of failed restrictive procedures included esophageal dilatation (3%; timing NR) (58) • Esophageal dilation (timing NR): 0.9% (50) • Among 127 patients in the LAGB group from 30 days to 10 years: 57 gastric-pouch dilations that required band deflation (43) ○ Four (3.1%) of the patients with gastric-pouch dilations also had esophageal dilations; two of these patients required band removal (43) • Pouch dilation up to 18 months after LAGB: 1.1% (21) • Four cases of 'stoma obstruction, dilation' requiring revision and five further cases requiring band removal among 127 patients in the LAGB group over 10 years (43)
Esophagitis (gastric-balloon therapy) (66)	• Observed at balloon extraction (6 months): 2.9% of patients with gastroscopy (66)
Stenosis of the gastric sleeve at the incisura (LSG or robotic sleeve gastrectomy with intraoperative endoscopy) (15)	• Two cases among 100 patients; fixed with endoscopic dilation at 2 and 3 months postoperatively (15)
Dysphagia (LAGB) (21, 39), persistent dysphagia (LAGB after failed RYGB) (48)	• Dysphagia through 2 years after LAGB: 34.0% (39) • LAP-BAND AP System (LAGB) removal due to dysphagia up to 18 months post implantation: 0.2%; corresponding value for revision due to dysphagia: 0.1% (21) • Persistent dysphagia after failed RYGB and secondary LAGB (mean follow-up: 14.0 months): 7% (48)
Gastric-outlet obstruction (LAGB) (39)	• Serious device-related adverse event of gastric-outlet obstruction and dysphagia (through 2 years after LAGB): 0.7% (39)
Gastric dilatation (LAGB) (39)	• Through 2 years after LAGB: 6.1% (39)
Dyspepsia, gastroesophageal reflux (LAGB) (39, 43); reflux-like symptoms (vagal-nerve blockade [vBloc device]) (49)	• Dyspepsia through 2 years after LAGB: 12.2% (39) • Gastroesophageal reflux disease through 2 years after LAGB: 36.7% (39) • Stomal obstruction with severe gastroesophageal reflux and complete dysphagia with solid food (through 10 years after LAGB): 9.4% (43) • Reflux-like symptoms within 30 days of vBloc-device removal: 3.3% (49)
Intractable nausea and vomiting (restrictive procedures) (58); prolonged nausea, dysphagia, ileus (RYGB, LAGB) (43); nausea, vomiting, regurgitation of food (LAGB) (39); nausea, vomiting, abdominal pain/discomfort (gastric-balloon therapy) (29, 66); persistent nausea (vagal-nerve blockade [vBloc device]) (49); persistent vomiting (LAGB after failed RYGB) (48)	• Causes of failed restrictive procedures included intractable nausea and vomiting (3%; timing NR) (58) • Prolonged nausea, dysphagia, ileus within 30 days: 8 cases among 105 patients in the RYGB group; 5 cases among 127 patients in the LAGB group (43) • Nausea through 2 years after LAGB: 22.4% (39) • Vomiting through 2 years after LAGB: 64.6% (39) • Regurgitation of food through 2 years after LAGB: 8.2% (39) • Nausea, vomiting, abdominal discomfort (mostly minor): usually occurred within the first day after gastric-balloon implantation; frequency NR (overall minor complications, 18%) (29) • Nausea, vomiting, abdominal pain (food intolerance): frequency unclear; timing NR but 'high incidence' of nausea and vomiting within the first 3 days of gastric-balloon implantation noted (66) • Nausea leading to vBloc-device removal: 6.7% (timing NR) (49) • Persistent nausea within 30 days of vBloc-device removal: 3.3% (49) • Persistent vomiting following secondary LAGB after failed RYGB: 5% (timing NR) (48)

(Continues)

TABLE 3 (Continued)

Complication/adverse effect (intervention of interest)	Timing and frequency
Required buscopan to alleviate abdominal cramps (gastric-balloon therapy)	• Required buscopan to alleviate abdominal cramps: 15% (1-year data) (18)
Abdominal pain (RYGB, LAGB) (21, 33, 39, 54); band/adhesions with repeated episodes of abdominal pain (RYGB) (54); chronic abdominal pain (LAGB after failed RYGB) (48); abdominal pain and contained leak (LSG or robotic sleeve gastrectomy with intraoperative endoscopy after failed restrictive procedures) (58)	• Abdominal pain 9–21 months after RYGB: <5% (33) • Band/adhesions with repeated episodes of abdominal pain up to 10 years after RYGB: 2.4% (54) • Reversal to normal anatomy after RYGB due to chronic, unexplained abdominal pain (up to 10 years): 0.15% (54) • Abdominal pain through 2 years after LAGB: 12.2% (39) • Upper abdominal pain through 2 years after LAGB: 10.9% (39) • LAP-BAND AP System (LAGB) removal due to abdominal pain up to 18 months after implantation: 0.3% (21) • Chronic abdominal pain after failed RYGB and secondary LAGB (mean follow-up: 14.0 months): 2% (48) • Abdominal pain and contained leak after failed restrictive procedures and secondary LSG or robotic sleeve gastrectomy with intraoperative endoscopy: 3.1% (mean follow-up after LSG: 26 months) (58)
Entry of the catheter tip into the duodenum causing abdominal pain and nausea ± vomiting (gastric-balloon therapy) (18)	• Through 12 months: 2.7% (18)
Diarrhea (LAGB) (39)	• Through 2 years after LAGB: 9.5% (39)
Flatulence (LAGB) (39)	• Through 2 years after LAGB: 6.1% (39)
Constipation (LAGB) (39)	• Through 2 years after LAGB: 17.7% (39)
Serious device-related adverse event with abdominal pain and bowel obstruction with ileus (LAGB) (39)	• Through 2 years: 0.7% (39)
Ileus (RYGB, LAGB) (33, 50); operated for ileus (RYGB) (33)	• Ileus among adolescents who underwent LAGB: 0.9% (postoperative; timing NR) (50) • Operated for ileus up to 5 years after RYGB: 4.9% (33)
Anastomotic stricture, stricture at gastrojejunostomy (RYGB) (43, 54)	• Anastomotic stricture up to 10 years after RYGB: 0.95% (43) • Stricture at gastrojejunostomy up to 10 years after RYGB: 5.8% (54)
Anastomotic leakage/malfunction (stenosis, ulcer) (RYGB) (43)	• Two cases of anastomotic leakage within 30 days among 105 patients in the RYGB group (43) • Three cases of anastomotic malfunction (stenosis, ulcer) over 10 years among 105 patients in the RYGB group (43)
Marginal ulcer (43, 54)	• Two marginal ulcers over 10 years among 105 patients in the RYGB group (43)
Anastomotic ulcer perforation (43)	• Two cases of anastomotic ulcer perforation over 10 years among 105 patients in the RYGB group (43)
Peptic ulcer (gastric-balloon therapy) (18, 66)	• Asymptomatic gastric ulcers observed at balloon extraction at 12 months: 2.7% (18) • New peptic ulcers observed at balloon extraction (6 months): 5.7% of patients with gastroscopy (66)
Required doubling of the drug dose of PPIs owing to peptic complaints (gastric-balloon therapy)	• 26% (1-year data) (18)
Intussusception (RYGB) (54)	• Intussusception up to 10 years after RYGB: 0.5% (54)
Candy cane syndrome (RYGB) (54)	• Candy cane syndrome up to 10 years after RYGB: 0.3% (54)
Adhesions (RYGB) (33); dense adhesions (vagal-nerve blockade [vBloc device]) (49)	• Laparoscopically operated with finding of adhesions during 2-year follow-up: 1.2% (33) • Dense adhesions noted at the time of vBloc-device removal: 43.3% (49)
Internal hernia ± acute abdomen and sepsis, incisional hernia, bowel obstruction (RYGB) (43, 54); bowel occlusion due to band/adhesions/internal hernia (RYGB) (54); additional surgery, for reasons including internal hernia (33) (RYGB); catheter impaction in an unrecognized hiatal hernia, requiring surgical extraction (gastric-balloon therapy) (18)	• Internal hernia, bowel obstruction in the RYGB group over 10 years: 15.2% (43) ○ Internal hernia with acute abdomen and sepsis requiring bowel resection: 0.95% (43) • Internal hernia in the RYGB group over 10 years: 8.2% (54) • Incisional hernia in the RYGB group over 10 years: 1.5% (54) • Bowel occlusion due to internal hernia in the RYGB group over 10 years: 2.6% (54) • Bowel occlusion due to band/adhesions in the RYGB group over 10 years: 2.1% (54) • Additional surgical interventions over 2 years in the group of adolescents who underwent RYGB: 15% (33) ○ Operation for internal hernia: 6.2% (33) • Catheter impaction in an unrecognized hiatal hernia, requiring surgical extraction within 1 year of gastric-balloon implantation: 1.4% (18)

TABLE 3 (Continued)

Complication/adverse effect (intervention of interest)	Timing and frequency
Tubing palpated in umbilical hernia (LAGB) (39)	• Through 2 years after LAGB: 0.7% (39)
Gallstone cholecystitis, cholecystectomy (RYGB) (33, 54)	• Cholecystectomy due to symptomatic gallstone over 2 years in the group of adolescents who underwent RYGB: 7.4% (33) • Gallstone cholecystitis in the RYGB group over 10 years: 0.1% (54)
Nutrient deficiency (RYGB) (43, 54); anemia (RYGB, LAGB) (39, 43, 54)	• Nutrient deficiency over 10 years: 3 cases among 105 patients in the RYGB group (43) ○ Iron-deficiency anemia requiring repeated iron transfusions: 1.9% (43) • All patients who underwent RYGB required ≥1 specific supplement, despite routine daily multivitamins/minerals; 32.5% developed temporary anemia (10-year data) (54) • Anemia through 2 years after LAGB: 5.4% (39)
Excess skin (RYGB) (33)	• Affected most adolescents who lost weight following RYGB (not quantified; timing NR) (33)
Cancer of the vulva (RYGB) (55)	• With surgery, 0.11/1,000 patient-years, versus 0.02/1,000 patient-years with control ($p = 0.02$; mean follow-up 12.5 years)
Lifestyle intervention	
Discontinuation due to relapse in HbA_{1c} levels (typically as a consequence of weight regain) (42)	• Discontinued: 78% (patients exited the study cohort if they had an increase in HbA_{1c} levels at any time during their follow-up; mean follow-up: 13.2 months) (42)
Weight regain after program completion (27)	• Among women with >10% weight loss after a 6-month behavioral intervention, only 38.5% had maintained >10% loss at 12 months after study completion (23.1% at 24 months after study completion) (27)
Diet	
Loss of thigh-muscle volume, total hip-bone mineral density, and bone mineral density at the femoral neck; increase in markers of bone turnover; increase in an inhibitor of bone formation (serum sclerostin) (56)	• Loss of thigh-muscle volume: NR; −6.2% decrease during the 1-year intervention (56) • Loss of total hip-bone mineral density: NR; −2.6% decrease during the 1-year intervention (56) • Loss of bone mineral density at the femoral neck: NR; −2.3% (timing NR) (56) • Increase in markers of bone turnover (56) • Increase in an inhibitor of bone formation (serum sclerostin) (56)
Weight regain after completion of diet (23)	• NR; weight loss was 12.0% at 12 months and 6.64% at 30 months (23)
Suicidal ideation/worsening suicidal ideation (31)	• Responded 'yes' to C-SSRS questionnaire categories of suicidal ideation and suicidality: 15/92 mg, 0.7%; 7.5/46 mg, 0.65%; placebo, 1.3% (31) • Worsening suicidal ideation: 15/92 mg, 0.7%; 7.5/46 mg, 0.65%; placebo, 0.9% (31) • No increase in serious suicidal ideation or suicidal behavior based on the C-SSRS questionnaire was observed over 108 weeks in patients treated with phentermine/topiramate (31)
Anxiety- and depression-related adverse events (31)	• Anxiety-related adverse events over 2 years: 15/92 mg, 9.5%; 7.5/46 mg, 6.5%; placebo, 3.1% (31) • Depression-related TEAEs over 2 years: 15/92 mg, 8.1%; 7.5/46 mg, 3.9%; placebo, 7.9% (31)
Influenza (31)	• TEAEs, weeks 0–56: 15/92 mg, 4.4%; 7.5/46 mg, 7.2%; placebo, 4.9% (31) • TEAEs, weeks 56–108: 15/92 mg, 6.4%; 7.5/46 mg, 6.5%; placebo, 3.5% (31)
Nasopharyngitis (31)	• TEAEs, weeks 0–56: 15/92 mg, 13.2%; 7.5/46 mg, 13.1%; placebo, 15.4% (31) • TEAEs, weeks 56–108: 15/92 mg, 8.8%; 7.5/46 mg, 8.5%; placebo, 11.5% (31)
Sinusitis (31)	• TEAEs, weeks 0–56: 15/92 mg, 13.2%; 7.5/46 mg, 11.1%; placebo, 8.4% (31) • TEAEs, weeks 56–108: 15/92 mg, 9.5%; 7.5/46 mg, 7.8%; placebo, 7.9% (31)
Upper respiratory tract infection (31)	• TEAEs, weeks 0–56: 15/92 mg, 18.6%; 7.5/46 mg, 15.0%; placebo, 20.7% (31) • TEAEs, weeks 56–108: 15/92 mg, 15.3%; 7.5/46 mg, 17.0%; placebo, 18.5% (31)
Bronchitis (31)	• TEAEs, weeks 0–56: 15/92 mg, 5.8%; 7.5/46 mg, 5.9%; placebo, 3.5% (31) • TEAEs, weeks 56–108: 15/92 mg, 3.4%; 7.5/46 mg, 5.2%; placebo, 3.1% (31)
Urinary tract infection (31)	• TEAEs, weeks 0–56: 15/92 mg, 4.4%; 7.5/46 mg, 5.2%; placebo, 4.9% (31) • TEAEs, weeks 56–108: 15/92 mg, 6.1%; 7.5/46 mg, 9.2%; placebo, 5.7% (31)
Gastroenteritis (31)	• TEAEs, weeks 0–56: 15/92 mg, 4.1%; 7.5/46 mg, 2.0%; placebo, 5.3% (31) • TEAEs, weeks 56–108: 15/92 mg, 3.1%; 7.5/46 mg, 1.3%; placebo, 2.6% (31)

(Continues)

TABLE 3 (Continued)

Complication/adverse effect (intervention of interest)	Timing and frequency
Dry mouth (31)	• TEAEs, weeks 0–56: 15/92 mg, 20.0%; 7.5/46 mg, 13.7%; placebo, 2.2% (31) • TEAEs, weeks 56–108: 15/92 mg, 1.4%; 7.5/46 mg, 0.7%; placebo, 0.4% (31)
Dysgeusia (31)	• TEAEs, weeks 0–56: 15/92 mg, 13.2%; 7.5/46 mg, 11.8%; placebo, 1.8% (31) • TEAEs, weeks 56–108: 15/92 mg, 1.0%; 7.5/46 mg, 0.7%; placebo, 0.0% (31)
Nausea (31)	• TEAEs, weeks 0–56: 15/92 mg, 6.4%; 7.5/46 mg, 3.3%; placebo, 5.7% (31) • TEAEs, weeks 56–108: 15/92 mg, 1.4%; 7.5/46 mg, 6.5%; placebo, 1.8% (31)
Diarrhea (31)	• TEAEs, weeks 0–56: 15/92 mg, 7.1%; 7.5/46 mg, 9.2%; placebo, 5.3% (31) • TEAEs, weeks 56–108: 15/92 mg, 3.7%; 7.5/46 mg, 2.0%; placebo, 1.3% (31)
Constipation (31)	• TEAEs, weeks 0–56: 15/92 mg, 21.0%; 7.5/46 mg, 16.3%; placebo, 7.1% (31) • TEAEs, weeks 56–108: 15/92 mg, 4.1%; 7.5/46 mg, 7.2%; placebo, 3.1% (31)
Headache (31)	• TEAEs, weeks 0–56: 15/92 mg, 9.5%; 7.5/46 mg, 5.2%; placebo, 9.3% (31) • TEAEs, weeks 56–108: 15/92 mg, 4.1%; 7.5/46 mg, 2.6%; placebo, 2.6% (31)
Back pain (31)	• TEAEs, weeks 0–56: 15/92 mg, 7.1%; 7.5/46 mg, 7.2%; placebo, 8.4% (31) • TEAEs, weeks 56–108: 15/92 mg, 5.1%; 7.5/46 mg, 5.9%; placebo, 3.1% (31)
Procedural pain (31)	• TEAEs, weeks 0–56: 15/92 mg, 5.8%; 7.5/46 mg, 4.6%; placebo, 2.6% (31) • TEAEs, weeks 56–108: 15/92 mg, 4.7%; 7.5/46 mg, 5.2%; placebo, 1.8% (31)
Arthralgia (31)	• TEAEs, weeks 0–56: 15/92 mg, 4.4%; 7.5/46 mg, 8.5%; placebo, 8.8% (31) • TEAEs, weeks 56–108: 15/92 mg, 5.4%; 7.5/46 mg, 4.6%; placebo, 6.2% (31)
Paresthesia (31)	• TEAEs, weeks 0–56: 15/92 mg, 21.0%; 7.5/46 mg, 13.7%; placebo, 2.6% (31) • TEAEs, weeks 56–108: 15/92 mg, 3.4%; 7.5/46 mg, 0.7%; placebo, 0.0% (31)
Insomnia (31)	• TEAEs, weeks 0–56: 15/92 mg, 8.1%; 7.5/46 mg, 7.8%; placebo, 6.6% (31) • TEAEs, weeks 56–108: 15/92 mg, 3.7%; 7.5/46 mg, 5.9%; placebo, 3.5% (31)
Fatigue (31)	• TEAEs, weeks 0–56: 15/92 mg, 5.8%; 7.5/46 mg, 4.6%; placebo, 4.9% (31) • TEAEs, weeks 56–108: 15/92 mg, 1.4%; 7.5/46 mg, 1.3%; placebo, 0.9% (31)
Dizziness (31)	• TEAEs, weeks 0–56: 15/92 mg, 6.8%; 7.5/46 mg, 5.9%; placebo, 2.6% (31) • TEAEs, weeks 56–108: 15/92 mg, 0.3%; 7.5/46 mg, 1.3%; placebo, 0.9% (31)
Discontinuation owing to an adverse event (31)	• By week 108: 15/92 mg, 4.4%; 7.5/46 mg, 4.5%; placebo, 3.1% (31)
Pharmacotherapy: once-weekly subcutaneous semaglutide 2.4 mg	
Death (70)	• Fatal event (timing NR): semaglutide, 0.1%; placebo, 0.2% (70) ○ One death was reported in each group; neither was considered to be related to study drug (70)
Psychiatric disorders (70)	• Semaglutide, 9.5%; placebo, 12.7% (timing NR) (70)
Nasopharyngitis (70)	• Semaglutide, 21.5%; placebo, 20.3% (timing NR) (70)
Upper respiratory tract infection (70)	• Semaglutide, 8.7%; placebo, 12.2% (timing NR) (70)
Serious gastrointestinal disorders (70)	• Semaglutide, 1.4%; placebo, 0.0% (timing NR) (70)
Gastrointestinal disorders (70)	• Semaglutide, 74.2%; placebo, 47.9% (timing NR; most gastrointestinal events were transient) (70)
Nausea (70)	• Semaglutide, 44.2%; placebo, 17.4% (timing NR) (70)
Diarrhea (70)	• Semaglutide, 31.5%; placebo, 15.9% (timing NR) (70)
Vomiting (70)	• Semaglutide, 24.8%; placebo, 6.6% (timing NR) (70)
Constipation (70)	• Semaglutide, 23.4%; placebo, 9.5% (timing NR) (70)
Dyspepsia (70)	• Semaglutide, 10.3%; placebo, 3.5% (timing NR) (70)
Abdominal pain (70)	• Semaglutide, 10.0%; placebo, 5.5% (timing NR) (70)
Gallbladder-related disorders (70)	• Semaglutide, 2.6%; placebo, 1.2% (timing NR) (70)
Serious hepatobiliary disorders (70)	• Semaglutide, 1.3%; placebo, 0.2% (timing NR) (70)
Hepatobiliary disorders (70)	• Semaglutide, 2.5%; placebo, 0.8% (timing NR) (70)
Cholelithiasis (70)	• Semaglutide, 1.8%; placebo, 0.6% (timing NR) (70)
Hepatic disorders (70)	• Semaglutide, 2.4%; placebo, 3.1% (timing NR) (70)
Acute pancreatitis (70)	• Semaglutide, 0.2%; placebo, 0.0% (timing NR) (70)
Change in amylase levels (70)	• Frequency NR; ratio to baseline at week 68: semaglutide, 1.14; placebo, 1.03 (70)

TABLE 3 (Continued)

Complication/adverse effect (intervention of interest)	Timing and frequency
Change in lipase levels (70)	• Frequency NR; ratio to baseline at week 68: semaglutide, 1.41; placebo, 0.97 (70)
Cardiovascular disorders (70)	• Semaglutide, 8.2%; placebo, 11.5% (timing NR) (70)
Change in pulse (70)	• Frequency NR; change from baseline to week 68: semaglutide, 3.52 bpm; placebo, −0.74 bpm (70)
Headache (70)	• Semaglutide, 15.2%; placebo, 12.2% (timing NR) (70)
Allergic reactions (70)	• Semaglutide, 7.4%; placebo, 8.2% (timing NR) (70)
Injection-site reactions (70)	• Semaglutide, 5.0%; placebo, 6.7% (timing NR) (70)
Malignant neoplasms (70)	• Semaglutide, 1.1%; placebo, 1.1% (timing NR) (70)
Acute renal failure (70)	• Semaglutide, 0.2%; placebo, 0.3% (timing NR) (70)
Hypoglycemia (70)	• Semaglutide, 0.6%; placebo, 0.8% (timing NR) (70)
Decrease in total lean body mass (70)	• Frequency NR; decrease in total lean body mass, week 68: semaglutide, −5.26 kg; placebo, −1.83 kg (70)
Discontinuation of study drug owing to an adverse event (70)	• Semaglutide, 7.0%; placebo, 3.1% (timing NR) (70)
Discontinuation of study drug owing to a gastrointestinal disorder adverse event (70)	• Semaglutide, 4.5%; placebo, 0.8% (timing NR; most gastrointestinal events were transient) (70)
Rescue interventions required (70)	• Rescue intervention required (timing NR): semaglutide, 0.5%; placebo, 2.0% (70) • Bariatric surgery required (timing NR): semaglutide, 0.15%; placebo, 0.46% (70) • Other anti-obesity medication required (timing NR): semaglutide, 0.38%; placebo, 1.53% (70)

Note: Data are from the 55 primary references reporting large weight loss (≥10%) and relevant outcomes that were identified by literature searches and selected for review (see Figure 1) and (70).

Abbreviations: bpm, beats per minute; C-SSRS, Columbia Suicide Severity Rating Scale; HbA_{1c}, glycated hemoglobin; LAGB, laparoscopic adjustable gastric banding; LSG, laparoscopic sleeve gastrectomy; NR, not reported; RYGB, Roux-en-Y gastric bypass; TEAEs, treatment-emergent adverse events; VBG, vertical banded gastroplasty.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Both authors selected articles for review and discussion in light of their knowledge of the field, critically revised the manuscript for important intellectual content, and approved the final version. The authors agree to be accountable for all aspects of the work.

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