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REVIEW

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Potent incretin-based therapy for obesity: A systematic review and meta-analysis of the efficacy of semaglutide and tirzepatide on body weight and waist circumference, and safety

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Summary

Potent incretin-based therapy shows promise for the treatment of obesity along with reduced incidence of cardiovascular events in patients with preexisting cardiovascular disease and obesity. This study assessed the efficacy and safety of the incretin-based obesity treatments, once-weekly subcutaneous semaglutide 2.4 mg and tirzepatide 10 or 15 mg, in people with obesity without diabetes. Of the 744 records identified, seven randomized controlled trials ($n = 5140$) were included. Five studies ($n = 3288$) investigated semaglutide and two studies ($n = 1852$) investigated tirzepatide. The treatment effect, shown as placebo-subtracted difference, on body weight was −15.0% (95% CI, −17.8 to −12.2) with −12.9% (95% CI, −14.7 to −11.1) for semaglutide and −19.2% (95% CI, −22.2 to −16.2) for tirzepatide. The treatment effect on waist circumference was −11.4 cm (95% CI, −13.7 to −9.2) with −9.7 cm (95% CI, −10.8 to −8.5) for semaglutide and −14.6 cm (95% CI, −15.8 to −13.4) for tirzepatide. The adverse events related to semaglutide and tirzepatide were primarily of mild-to-moderate severity and mostly gastrointestinal, which was more frequent during the dose-titration period and leveled off during the treatment period. This emphasizes that once-weekly subcutaneous semaglutide 2.4 mg and tirzepatide 10 or 15 mg induce large reductions in body weight and waist circumference and are generally well-tolerated.

KEYWORDS
GLP-1, glucagon-like peptide-1 receptor agonist, weight loss

Abbreviations: BMI, Body mass index; CI, Confidence interval; GLP-1, Glucagon-like peptide-1; PICO, Patient-Intervention-Comparison-Outcome; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RA, Receptor agonist; ROB 2, Cochrane Risk-Of-Bias Tool for Randomized Trials Version 2; SD, Standard deviation; SEM, Standard error of the mean; STEP, Semaglutide Treatment Effect in People with Obesity; WHO, World Health Organization.

1 | INTRODUCTION

The prevalence of overweight and obesity has almost tripled since the 1970s[1] and contributes to a major health care burden.[2] Obesity increases the risk of developing comorbidities, such as cardiovascular disease, type 2 diabetes, and certain forms of cancer, and is also associated with reduced life expectancy and quality of life.[3–5]

Weight loss of at least 5% is associated with improved blood glucose, blood lipids, and blood pressure.[6] Larger weight losses have greater benefits on the risk of developing obesity-related comorbidities, and weight loss of more than 10% may be needed in the presence of comorbidities.[7–9] Clinical obesity guidelines recommend lifestyle changes as a first-line treatment of obesity. Lifestyle changes refer to increased physical activity, decreased energy intake, and behavioral techniques for adopting dietary and physical activity changes.[9–11] Weight losses with lifestyle changes are typically up to 8% after 1 year, with 3%–5% weight loss sustained in the following years.[12,13] A low-calorie diet followed by dietary support can induce 1-year weight losses of 7 to 10 kilograms (kg).[14–16] Exercise interventions typically result in modest weight losses of about 0 to 4 kg but with reduced fat mass and preserved lean mass, improving body composition.[17] Importantly, exercise can effectively maintain diet-induced weight loss and improve body composition for at least 1 year.[18,19]

Weight loss decreases energy expenditure, increases sedentary behavior, and may affect appetite[20,21] with observations of increased appetite at least a year after diet-induced weight loss in some studies,[22–24] which makes sustained weight loss difficult. For people with a BMI ≥30 kg/m^2 or ≥27 kg/m^2 with at least one obesity-related comorbidity who have not experienced sustained weight loss with lifestyle changes alone, the addition of pharmacotherapy as an adjunct to lifestyle intervention may be an option. The glucagon-like peptide-1 receptor agonists (GLP-1 RA) once-daily subcutaneous liraglutide improves glycemic control and cardiovascular outcomes in people with type 2 diabetes.[25] Liraglutide 3.0 mg was the first GLP-1 RA approved specifically for weight loss. It was approved for weight loss in 2014[26] and demonstrated an average weight loss of 5–6 kg.[27] Since then, considerable advances have been made within incretin-based therapies for the treatment of obesity. Compared with liraglutide, semaglutide is a longer-acting GLP-1 RA administered once weekly that is more potent in terms of weight loss and glycemic control.[28–30] Subcutaneous semaglutide was initially approved for the treatment of type 2 diabetes. In 2021 and 2022, respectively, once-weekly subcutaneous semaglutide 2.4 mg was approved by the US Food and Drug Administration and the European Medicines Agency for chronic weight management in adults with obesity or overweight with at least one weight-related comorbidity adjunct to lifestyle modification.[31,32] Subsequently, the cardiovascular outcome trial of semaglutide 2.4 mg, the SELECT study, found that semaglutide 2.4 mg reduces the incidence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in people with established cardiovascular disease with overweight or obesity with no prior history of diabetes.[33]

Tirzepatide, a novel dual-agonist of receptors for the incretin hormones GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), has shown promising potential for improving glycemic control and decreasing body weight in people with type 2 diabetes.[34,35] In 2022, tirzepatide was approved for treating type 2 diabetes,[36] and in the following year, November 2023, the medication was also approved for treating obesity at doses of up to 15 mg once weekly.[37]

Meta-analyses on the efficacy of subcutaneous semaglutide in people with overweight or obesity without diabetes have been published.[38–41] However, these meta-analyses included studies with lower doses than the doses approved for obesity treatment, studies of once-daily semaglutide, and studies with durations of less than half a year. Since weight loss with semaglutide seems to continue for at least a year,[42,43] studies of shorter duration could underestimate the treatment efficacy. In addition, recently published semaglutide and tirzepatide studies have not been included in previous meta-analyses, and systematic reviews of tirzepatide have so far focused mostly on people with type 2 diabetes.[44,45] Furthermore, while the body mass index (BMI, body weight [kg] divided by the squared height [m]) is useful to define obesity at a population level, BMI does not consider body composition or fat distribution. In contrast, visceral fat located inside the abdomen is an important risk factor, which is why additional measurements of body composition, such as waist circumference and fat and lean mass, are useful to determine abdominal obesity and obesity-related metabolic risks.[46,47]

Therefore, we conducted a systematic review and meta-analysis to assess the efficacy and safety of subcutaneous semaglutide and tirzepatide in the doses approved for obesity on body weight and waist circumference reduction in people with overweight or obesity without diabetes, treated for a least 1 year.

2 | METHODS

The conduct of the current systematic review and meta-analysis conforms to the Cochrane Handbook for Systematic Reviews of Interventions.[48] It is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Table S1).

2.1 | Data sources and search strategies

The search was completed in PubMed, Embase, and Cochrane Library by two independent reviewers (A. L. O. M. & R. M. S.) from the inception of each database to the 14th of November, 2023. The search string was built on the concept of P-I-C-O (Patient, Intervention, Comparison, Outcome) and combined with Boolean operators (AND, OR). It used text and medical subject headings, including but not limited to (Obesity OR Overweight) AND (Semaglutide OR Wegovy OR Tirzepatide OR Mounjaro OR Cagrisema) AND (Placebo) AND (Body weight OR Waist circumference). The entire search strings from each database can be seen in Tables S2–S4.

2.2 | Study selection

The digital screening tool Covidence,[49] was used to screen the studies yielded from the search. The selection criteria for inclusion into the systematic review were (i) randomized controlled trial, (ii) inclusion of patients with overweight or obesity without diabetes, (iii) treatment of obesity with subcutaneous potent incretin-based therapy versus placebo for at least 1 year (semaglutide 2.4 mg or tirzepatide 15 mg), (iv) percentage body weight change or waist circumference change in cm as outcome, and (v) reporting of adverse events. Two authors (A. L. O. M. and R. M. S.) independently screened titles, abstracts, and full texts based on the selection criteria presented above. Potential discrepancies in selecting studies were resolved through consensus-based discussions or, if necessary, the inclusion of a third reviewer (S. B. K. J).

2.3 | Data extraction and outcomes

This systematic review and meta-analysis primarily focused on the efficacy of potent incretin-based obesity therapy on the outcome of body weight change in percent and change in waist circumference in centimeters and, secondarily, body weight change in kg. The data collected from each article were: characteristics of the study (design, number of participants, and dropout), the participants (sex, age, and degree of obesity), the intervention (dose, frequency, duration, and sort of lifestyle component), changes from baseline to follow-up (expressed as mean ± standard deviation [SD] when available). In studies where the results were expressed as mean and confidence interval (CI), the CI was converted to SD ($SD = (\frac{(\text{upper limit} - \text{lower limit})}{4}) * \sqrt{n}$), and where results were expressed as the mean and standard error of the mean (SEM), the SEM was converted to SD ($SD = SEM * \sqrt{n}$). Furthermore, safety was investigated by summarizing the number of individuals with ≥1 of any adverse event and ≥1 serious adverse event, the most common adverse events (>10% frequency), and adverse events of particular interest to incretin-based therapy, including gallbladder-related disorders such as cholelithiasis, pancreatitis, hypoglycemia, cardiovascular disorders, renal failure, neoplasms, psychiatric disorders, and allergic and injection site reactions. Attention to these particular adverse events has previously been raised by clinical trials of incretin mimetic drugs and medical agencies.[42,50–52] In the included studies, adverse events were any untoward medical occurrence to a participant, regardless of whether it was related to the investigated drug or treatment. Adverse events ranged from mild, moderate, to severe, and could also be caused by events other than the drug or therapy itself. Serious adverse events include hospitalization, life-threatening events, disability or incapacity, or death.

2.4 | Quality assessment

Each study was quality assessed using the second version of Cochrane's tool for assessing the risk of bias (RoB2).[53] Studies were assessed individually in the RoB2 suitable for randomized, controlled trials. RoB2 is divided into five domains of bias, focusing on different aspects of study design, conduct, and reporting. The domains are the risk of bias due to (i) randomization process, (ii) deviations from intended intervention, (iii) missing outcome data, (iv) measurement of the outcome, and (v) selection of the reported result. Each domain is assessed as "*Low*" or "*High*" risk of bias or as "*Some concerns*".

2.5 | Statistical analyses

Statistical analyses were carried out using Cochrane's statistic tool for meta-analyses, Review Manager version 5.4.1.[54] For all outcomes, efficacy analyses were based on the intention-to-treat population. The treatment policy estimate (traditional intention-to-treat analysis) was extracted from the studies, which quantified the treatment response for all randomized participants regardless of treatment discontinuation or rescue intervention. The pooled effects of semaglutide and tirzepatide alone and together on body weight change in percent and change in waist circumference in cm were estimated through fixed-effect or random-effects meta-analysis, depending on the heterogeneity. The heterogeneity between the studies was assessed using the I^2 statistic. I^2 statistic exceeding 50% was interpreted as substantial heterogenic.[48] The level of significance was set at 0.05.

3 | RESULTS

3.1 | Study selection

For an overview of the study selection process, see the flowchart in Figure 1. The search yielded 744 results across the three databases. Duplicates were removed by both Covidence and manually, and 417 articles remained for screening. The 400 studies were excluded due to non-relevance based on title and abstract. The 17 articles were extracted for full-text reading, of which 10 articles were excluded due to being an abstract, journal club, or trial registration, or the inclusion of participants with type 2 diabetes, or duplicate sample. Thus, seven articles that fulfilled the selection criteria were included in the systematic review and meta-analysis.[29,42,43,55–58]

3.2 | Study characteristics

The study characteristics of the included studies are summarized in Table 1. The included studies were all phase 3 randomized controlled trials investigating either the effect of subcutaneous semaglutide (five studies[29,42,43,55,56]) or tirzepatide (two studies[57,58]). Five of the seven included studies were part of the global phase 3 trial: Semaglutide Treatment Effect in People with Obesity (STEP). The program aims to evaluate the efficacy and safety of subcutaneous semaglutide in

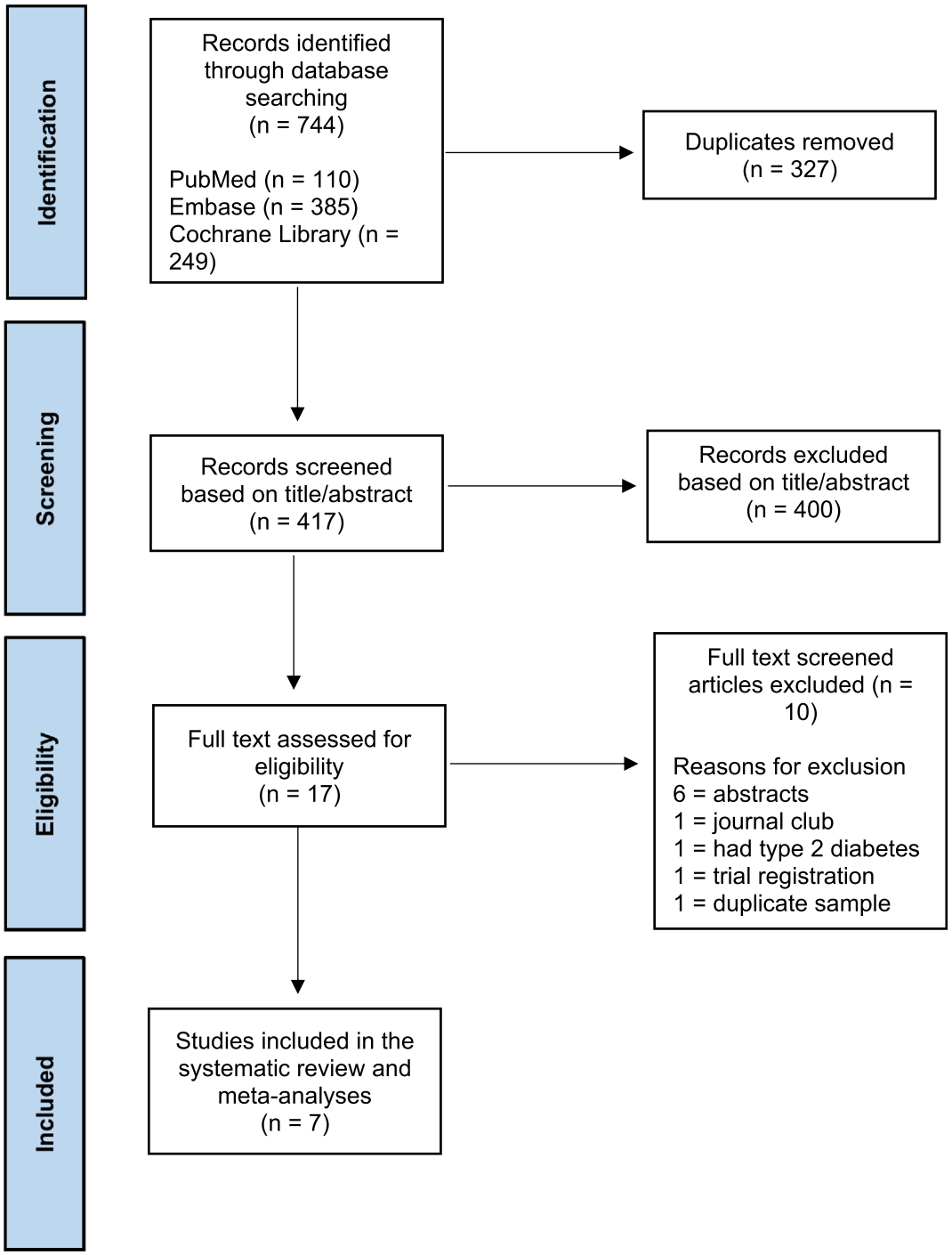

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of the study selection process.

people with overweight or obesity, with body weight change as the primary outcome.[59] The STEP 1 trial by Wilding et al.[42] investigated the effect of subcutaneous semaglutide 2.4 mg versus placebo in adults with overweight or obesity for 68 weeks, while the STEP 3 trial by Wadden et al.[55] investigated the effect of subcutaneous semaglutide 2.4 mg versus placebo as an adjunct to intensive behavioral therapy in adults with overweight or obesity for 68 weeks. The STEP 5 trial by Garvey et al.[43] investigated the efficacy and safety of once-weekly subcutaneous semaglutide 2.4 mg versus placebo in adults with overweight or obesity for 104 weeks. The STEP 8 trial by Rubino et al.[29] investigated the effect of subcutaneous semaglutide versus subcutaneous liraglutide 3.0 mg and matching placebo in adults with overweight or obesity for 68 weeks. The STEP TEENS trial by Weghuber et al.[56] assessed the efficacy and safety of once-weekly subcutaneous semaglutide 2.4 mg versus placebo among adolescents with obesity for 68 weeks. The remaining STEP trials have not yet

TABLE 1 Characteristics of the included studies.

Study	Design	Sample size		Dropout (%)		Duration
		Intervention	Placebo	Intervention	Placebo	
Wilding 2021 (STEP 1) Investigated the efficacy and safety of semaglutide versus placebo for reducing body weight in adults with overweight or obesity	Phase 3, randomized, multi-center, double-blind, placebo-controlled trial	1306	655	5.1	7.0	68 weeks
Wadden 2021 (STEP 3) Investigated semaglutide versus placebo for weight management as an adjunct to intensive behavioral therapy in adults with overweight or obesity.	Phase 3, randomized, multi-center, double-blind, placebo-controlled trial	407	204	7.6	6.4	68 weeks
Garvey 2022 (STEP 5) Investigated the efficacy and safety of semaglutide versus placebo for long-term treatment of adults with overweight or obesity	Phase 3, randomized, multi-center, double-blind, placebo-controlled trial	152	152	2.6	11.8	104 weeks
Rubino 2022 (STEP 8) Investigated the efficacy and safety of semaglutide versus liraglutide or placebo in adults with overweight or obesity	Phase 3, randomized, multi-center, open-label (semaglutide versus liraglutide), double-blind (active versus placebo), controlled trial	126	85	4.8	4.7	68 weeks
Weghuber 2022 (STEP TEENS) Investigated the efficacy and safety of semaglutide versus placebo among adolescents with obesity	Phase 3, randomized, multi-center, double-blind, parallel-group, placebo-controlled trial	134	67	1.0	4.0	68 weeks
Jastreboff 2022 (SURMOUNT-1) Investigated the efficacy and safety of tirzepatide in adults with overweight or obesity	Phase 3, randomized, multi-center, double-blind, placebo-controlled trial	5 mg: 630 10 mg: 636 15 mg: 630	643	5 mg: 11.0 10 mg: 11.6 15 mg: 10.2	23.0	72 weeks
Wadden 2023 (SURMOUNT-3) Investigated the effect of tirzepatide on weight reduction after a successful intensive lifestyle intervention in adults with overweight or obesity	Phase 3, randomized, multi-center, double-blind, placebo-controlled trial	287	292	12.2	22.3	84 weeks (72 weeks of treatment with tirzepatide or placebo after ≥5.0% body weight reduction)

Abbreviations: d, day; kcal, kilocalories; mg, milligram; min, minutes; NR, not reported; wk, week.

TABLE 1 (Continued)

Study	Intervention and comparator (dose, frequency)	Concomitant treatment	Primary/co-primary outcome
Wilding 2021 (STEP 1) Investigated the efficacy and safety of semaglutide versus placebo for reducing body weight in adults with overweight or obesity	2.4 mg subcutaneous semaglutide once a week versus placebo	Lifestyle intervention: Individual counseling sessions every 4 weeks to help adherence to a reduced-calorie diet (500-kcal deficit/day relative to the energy expenditure estimated at the time they underwent randomization) and increased physical activity (150 min/wk was encouraged)	Percentage change in body weight and weight reduction of at least 5%
Wadden 2021 (STEP 3) Investigated semaglutide versus placebo for weight management as an adjunct to intensive behavioral therapy in adults with overweight or obesity.	2.4 mg subcutaneous semaglutide once a week versus placebo	Intensive lifestyle intervention: Low-calorie diet (1000–1200 kcal/d) for the first 8 weeks. Participants were transitioned to a hypocaloric diet (1200–1800 kcal/d) for the remainder of the trial. Participants were prescribed 100 min of physical activity per week, which increased by 25 min every 4 weeks to reach 200 min per week. Furthermore, they received intensive behavioral therapy (30 counseling visits) throughout the intervention period	Percentage change in body weight and weight reduction of at least 5%
Garvey 2022 (STEP 5) Investigated the efficacy and safety of semaglutide versus placebo for long-term treatment of adults with overweight or obesity	2.4 mg subcutaneous semaglutide once a week versus placebo	Lifestyle intervention: Participants received counseling by a dietitian or similarly qualified healthcare professional every 4 weeks via in-person visits or telephone to adhere to a reduced-calorie diet (500-kcal deficit a day relative to the energy expenditure estimated at randomization) and increased physical activity (150 min a week encouraged)	Percentage change in body weight and weight reduction of at least 5%
Rubino 2022 (STEP 8) Investigated the efficacy and safety of semaglutide versus liraglutide or placebo in adults with overweight or obesity	2.4 mg subcutaneous semaglutide once a week versus liraglutide or placebo	Lifestyle intervention: Participants received individual counseling sessions every 4 weeks to help adhere to a reduced-calorie diet (500-kcal/day relative to energy expenditure estimated at randomization) and increased physical activity (150 min/wk was encouraged)	Percentage change in body weight
Weghuber 2022 (STEP TEENS) Investigated the efficacy and safety of semaglutide versus placebo among adolescents with obesity	2.4 mg subcutaneous semaglutide once a week versus placebo	Lifestyle intervention: Participants and parents or guardians received behavioral lifestyle therapy (defined as counseling about healthy nutrition and physical activity for weight loss) throughout the trial	Percentage change in body mass index

TABLE 1 (Continued)

Study	Intervention and comparator (dose, frequency)	Concomitant treatment	Primary/co-primary outcome
Jastreboff 2022 (SURMOUNT-1) Investigated the efficacy and safety of tirzepatide in adults with overweight or obesity	Once-weekly, subcutaneous tirzepatide (5, 10, or 15 mg) or placebo	Lifestyle intervention: Participants received lifestyle counseling delivered by a dietitian or a qualified health care professional to help participants adhere to healthful, balanced meals, with a deficit of 500 cal per day and at least 150 min of physical activity per week	Percentage change in body weight and weight reduction of at least 5%
Wadden 2023 (SURMOUNT-3) Investigated the effect of tirzepatide on weight reduction after a successful intensive lifestyle intervention in adults with overweight or obesity	Once-weekly, subcutaneous tirzepatide (10 or 15 mg) or placebo	The study started with a 12-week lead-in period during which participants received intensive lifestyle intervention (including meal replacements) to achieve ≥5.0% body weight reduction. This was followed by the 72-week placebo-controlled treatment period. Lifestyle intervention: Participants continued to consult with a dietitian or other qualified healthcare professional following the lead-in period. Lifestyle counseling sessions occurred every 12 weeks and focused on consumption of a healthy balanced diet, with a 500 kcal per day deficit and continuation of physical activity of at least 150 min per week.	Percentage change in body weight and weight reduction of at least 5%

Abbreviations: d, day; kcal, kilocalories; mg, milligram; min, minutes; NR, not reported; wk, week.

been published (STEP 7, 9, and 10), have focused on patients with type 2 diabetes (STEP 2 and 6), or had a placebo group that was initially treated with semaglutide (STEP 4), and thereby not eligible for inclusion in this study.

The remaining two studies were part of the global phase three trial: SURMOUNT. The program aims to evaluate the efficacy and safety of subcutaneous tirzepatide compared with placebo for chronic weight management in adults with overweight or obesity. The SURMOUNT-1 trial by Jastreboff et al.[57] investigated the efficacy and safety of tirzepatide (5, 10, and 15 mg) in adults with overweight or obesity without diabetes versus placebo for 72 weeks. The SURMOUNT-3 trial by Wadden et al.[58] investigated the efficacy and safety of tirzepatide (10 or 15 mg) versus placebo on weight reduction after a successful intensive lifestyle intervention for a total of 72 weeks.

All included trials used double-blinding for their placebo-controlled analyses. In STEP 8,[29] due to the necessary daily versus weekly dosing, participants knew whether they were in the arm comparing (daily) liraglutide vs. daily placebo or in the arm comparing (weekly) semaglutide versus weekly placebo. However, they were blinded to active drug versus placebo in their arm.

3.3 | Participants

The baseline participant characteristics are summarized in Table 2. The seven included studies consist of a total of 5140 participants. The participants were primarily women (ranging from 62% to 81%) with a mean age range between 44 and 49 years, except for STEP TEENS,[56] where the participants had a mean age of 15.4 years. In six studies, participants were included if they had a BMI ≥ 30 or ≥27 kg/m^2 with 1 or more weight-related comorbidities, without diabetes.[29,42,43,55,57,58] In STEP TEENS,[56] participants were included if they had a BMI in the 95th percentile or higher or a BMI in the 85th percentile or higher and at least one weight-related comorbidity. In STEP TEENS,[56] a minority of participants had type 2 diabetes (4%) at baseline. The baseline body weight ranged from a mean of 101.9 to 107.5 kg. The baseline mean BMI ranged from 35.9 to 38.8 kg/m^2.

TABLE 2 Baseline characteristics of patients in the included studies.

Study	Sex (male) (%)		Age (years)		Body weight (kg)		Body mass index (kg/m^2)		Waist circumference (cm)	
Semaglutide 2.4 mg										
Wilding 2021 (STEP 1)	25.45		46.5 (12.5)		105.3 (21.8)		37.8 (6.7)	38.0 (6.5)	114.6 (14.8)	114.8 (14.4)
Wadden 2021 (STEP 3)	19.0		46 (13)		105 (22.9)		38.1 (6.7)	37.8 (6.9)	113.6 (15.1)	111.8 (16.2)
Garvey 2022 (STEP 5)	19.1	25.7	47.3 (11.7)	47.4 (10.3)	105.6 (20.8)	106.5 (23.1)	38.6 (6.7)	38.5 (7.2)	115.8 (14.3)	115.7 (15.5)
Rubino 2022 (STEP 8)	21.60		49 (13)		104.5 (23.8)		37.0 (7.4)	38.8 (6.5)	111.8 (16.3)	115.4 (15.1)
Weghuber 2022 (STEP TEENS)	38.0		15.4 (1.6)		107.5 (24.5)		37.0 (6.4)		110.4 (16.0)	
Tirzepatide 10 or 15 mg[a]										
Jastreboff 2022 (SURMOUNT-1)[b]	32.5		44.9 (12.5)		104.8 (22.12)		38.0 (6.81)		114.1 (15.16)	
Wadden 2023 (SURMOUNT-3)[c]	37.1		45.6 (12.2)		101.9 (21.4)		35.9 (6.3)		109.4 (15.0)	

Data are presented as mean (standard deviation). Where cells are split in two, the left represents the baseline characteristics of the intervention group, and the right represents the baseline characteristic of the placebo group.
Abbreviation: NR, not reported.
[a]Data from SURMOUNT-1 is 15 mg, while SURMOUNT-3 is 10 or 15 mg.
[b]Data from the intervention group are from the tirzepatide 15-mg group ($n = 630$).
[c]Data are from randomization (week 0, end of lead-in period [from week -12 to 0]).

The baseline mean waist circumference ranged from 109.4 to 115.8 cm.

3.4 | Interventions

The majority of the included studies, the STEP trials, investigated the effect of subcutaneous semaglutide 2.4 mg once-weekly for 68 weeks (STEP 1,[42] STEP 3,[55] STEP 8,[29] and STEP TEENS[56]) or 104 weeks (STEP 5[43]) for the treatment of overweight or obesity. The remaining two trials, the SURMOUNT trials,[57,58] investigated the effect of subcutaneous tirzepatide 5, 10, or 15 mg once weekly for 72 weeks.

All studies mentioned the use of lifestyle components in combination with the active treatment and placebo, which is summarized in Table 1. In all studies, the lifestyle component consisted of individual nutritional and physical activity counseling by qualified professionals. Five studies build their nutritional counseling on a reduced-calorie diet (500-kcal deficit/day relative to the energy expenditure estimated at the time they underwent randomization) and increased physical activity to at least 150 min/week without specifying exercise intensity.[29,42,43,57,58] In these five studies, participants were encouraged to record food intake and physical activity to assist counseling sessions. In STEP 3,[55] all participants received a total meal-replacement low-calorie diet (1000–1200 kcal/day) for the first 8 weeks after randomization. Participants were then transitioned to a hypocaloric diet (1200–1800 kcal/day depending on randomization body weight) of conventional food for the rest of the trial. Participants were encouraged to do 100 min of physical activity/week, which increased by 25 min every 4 weeks to reach 200 min/week. Participants were provided 30 individual intensive behavioral therapy visits with a registered dietitian, which also included behavioral strategies to facilitate diet and activity changes. Participants received activity trackers and were encouraged to register food intake. In STEP TEENS,[56] participants and their parents or guardians received counseling on healthy nutrition and were encouraged to perform 60 min of moderate-to-high-intensity physical activity per day. Activity trackers could be provided to help achieve this goal. SURMOUNT-3[58] was initiated with a 12-week lead-in period during which participants received an intensive lifestyle intervention consisting of frequent in-person counseling sessions by a qualified professional, including instruction on daily caloric intake (1200 kcal for women and 1500 kcal for men) and weekly physical activity (at least 150 min of moderate-intensity physical activity). The goal was to achieve ≥5.0% body weight reduction before the placebo-controlled treatment period. None of the seven studies included information on adherence to the lifestyle component of the study during the placebo-controlled treatment period.

3.5 | Quality assessment

Figure 2 presents the overall risk of bias in the included studies assessed using the RoB2 tool. Bias was evaluated in the five domains presented as low (green), moderate (yellow), or high (red) risk of bias. All included studies were found to have a low risk of bias in each of the five domains due to their high-quality randomization process, low deviations from intended intervention, low missing outcome data, high-quality measurement of outcome, and low risk of bias in the selection of the reported result. Thereby, they were all deemed to have an overall low risk of bias.

3.6 | Results of included studies

All included studies had significant changes in body weight and waist circumference in the intervention groups compared to the placebo group at follow-up (<0.00001). The changes in body weight in percent and in kg, BMI, and waist circumference from baseline to follow-up in the included studies are presented in Table 3.

3.7 | Change in body weight in percent

The synthesis showed a heterogeneity of 93%; thus, a random-effects model was chosen for the analysis. Based on the analysis, the pooled estimate of the mean difference in body weight in the five STEP trials was −12.9% (95% CI, −14.7 to −11.1, $p < 0.001$) compared with placebo. The SURMOUNT trials showed a mean difference of −19.2% (95% CI, −22.2 to −16.2, $p < 0.001$) in body weight compared with placebo. The total mean difference in body weight for all seven trials was −15.0% (95% CI, −17.8 to −12.2, $p < 0.001$) compared with placebo. The results are presented in Figure 3.

3.8 | Change in waist circumference

The synthesis showed a heterogeneity of 89%; thus, a random-effects model was chosen for the analysis. Based on the analysis, the pooled estimate of the mean difference in waist circumference in the five STEP trials was −9.7 cm (95% CI, −10.8 to −8.5, $p < 0.001$) compared with placebo. The SURMOUNT trials showed a mean difference of −14.6 cm (95% CI, −15.8 to −13.4, $p < 0.001$) compared with placebo. The total mean difference in waist circumference for all seven trials was −11.4 cm (95% CI, −13.7 to −9.2, $p < 0.001$) compared with placebo. The results are presented in Figure 4.

3.9 | Change in fat mass and lean mass

Two studies used dual-energy X-ray absorptiometry to assess changes in fat mass and lean mass in study subpopulations.[42,57] In STEP 1,[42] 140 participants were scanned before and after treatment. Reductions in total fat mass were −8.4 kg with semaglutide and −1.4 kg with placebo (mean difference: −7.0 kg, 95% CI, −9.8 to −4.2). Total lean mass was reduced with −5.3 kg with semaglutide and −1.8 kg with placebo (mean difference: −3.4 kg, 95% CI, −4.7 to −2.1). Semaglutide reduced the proportion of fat mass relative to total body weight compared with placebo.

In SURMOUNT-1,[57] 160 participants were scanned before and after the intervention. Total fat mass was reduced by −33.9% with pooled tirzepatide (5 mg, 10 mg, and 15 mg) and −8.2% with placebo (mean difference: −25.7%, 95% CI, −31.4 to −20.0). Total lean mass was reduced by −10.9% for pooled tirzepatide and −2.6% for placebo (mean difference: −8.3%, 95% CI, −10.6 to −6.1).

3.10 | Change in body weight in kilogram

The synthesis showed a heterogeneity of 97%; thus, a random-effects model was chosen for the analysis. Based on the analysis, the pooled estimate of the mean difference in body weight was −13.0 kg (95% CI, −14.8 to −11.2, $p < 0.001$) compared with placebo in the five STEP trials. Measures of the variance of body weight change in kg were not accessible from the SURMOUNT-1 study and, therefore, not included in the analysis. SURMOUNT-3 showed a mean difference in body weight of −25.0 kg (95% CI, −27.0 to −23.1, $p < 0.001$) compared with placebo. The total mean difference in body weight for all six trials was −15.5 kg (95% CI, −20.2 to −10.8, $p < 0.001$) compared with placebo. The results are presented in Figure 5.

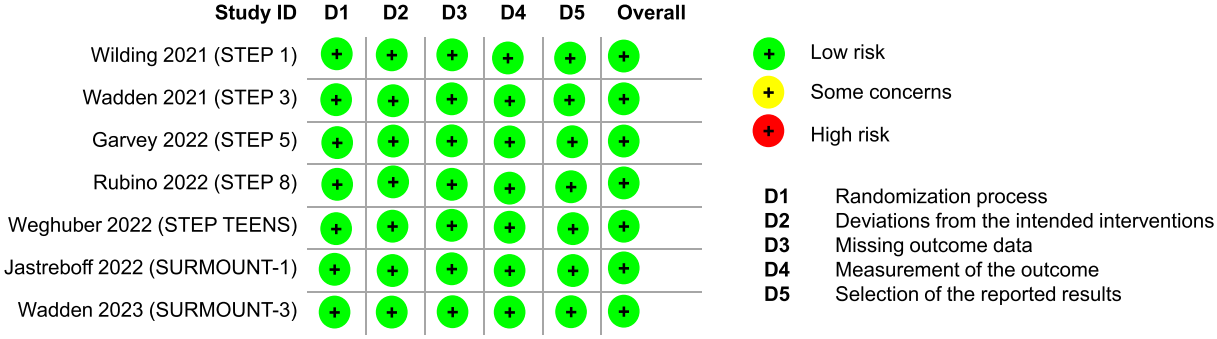

FIGURE 2 Risk of bias assessment of the included studies.

TABLE 3 Results of the included studies.

Study	Body weight (%)			Body weight (kg)			*p*-value[a]
	Intervention	Placebo	Difference	Intervention	Placebo	Difference	
Semaglutide 2.4 mg							
Wilding 2021 (STEP 1)	−14.9 (9.4)	−2.4 (9.1)	−12.5 (19.5)	−15.3 (10.7)	−2.6 (10.7)	−12.7 (22.6)	<0.001
Wadden 2021 (STEP 3)	−16.0 (10.1)	−5.7 (10.1)	−10.3 (21.4)	−16.8 (11.3)	−6.2 (11.3)	−10.6 (24.0)	<0.001
Garvey 2022 (STEP 5)	−15.2 (15.7)	−2.6 (19.2)	−12.6 (28.9)	−16.1 (17.4)	−3.2 (20.9)	−12.9 (28.0)	<0.001
Rubino 2022 (STEP 8)	−15.8 (10.6)	−1.9 (9.9)	−13.9 (21.1)	−15.3 (11.3)	−1.4 (9.9)	−13.9 (21.5)	<0.001
Weghuber 2022 (STEP TEENS)	−14.7 (12.6)	2.7 (12.6)	−17.4 (26.8)	−15.3 (14.0)	2.4 (14.0)	−17.7 (29.3)	<0.001
Tirzepatide 10 or 15 mg[b]							
Jastreboff 2022 (SURMOUNT-1)[c]	−20.9 (12.2)	−3.1 (15.5)	−17.8 (27.3)	−24.4 (NR)	−2.4 (NR)	−22.0 (NR)	<0.001
Wadden 2023 (SURMOUNT-3)[d]	−18.4 (11.9)	2.5 (17.1)	−20.9 (28.3)	−21.5 (11.9)	3.5 (12.0)	−25.0 (22.3)	<0.001

Data are presented as mean (standard deviation). Changes are presented as means (standard deviation). The *p*-values represent the difference between the intervention group and the control group within the reported outcomes. Standard deviations are extracted directly from the articles or calculated in Review Manager version 5.4.1.

Abbreviations: NR, not reported; kg, kilogram; cm, centimeters.

[a]The *p*-values shown are from all four outcomes.

[b]Data from SURMOUNT-1 is 15 mg, while SURMOUNT-3 is 10 or 15 mg.

[c]Data from the intervention group is from the tirzepatide 15 mg group ($n = 630$).

[d]Data are from randomization (week 0, end of lead-in period [from week −12 to 0]) to end of intervention (week 72).

TABLE 3 (Continued)

Study	Body mass index (kg/m^2)			Waist circumference (cm)			*p*-value[a]
	Intervention	Placebo	Difference	Intervention	Placebo	Difference	
Semaglutide 2.4 mg							
Wilding 2021 (STEP 1)	−5.5 (3.6)	−0.9 (3.6)	−4.6 (7.6)	−13.5 (9.5)	−4.1 (9.5)	−9.4 (20.1)	<0.001
Wadden 2021 (STEP 3)	−6.0 (3.6)	−2.2 (3.6)	−3.8 (9.9)	−14.6 (10.7)	−6.3 (10.7)	−8.3 (22.7)	<0.001
Garvey 2022 (STEP 5)	−5.9 (7.0)	−1.6 (10.5)	−4.3 (12.5)	−14.4 (15.7)	−5.2 (20.9)	−9.2 (26.7)	<0.001
Rubino 2022 (STEP 8)	NR	NR	NR	−13.2 (10.2)	−1.7 (9.2)	−11.5 (19.7)	<0.001
Weghuber 2022 (STEP TEENS)	−5.8 (NR)	0.1 (NR)	−6.0 (9.8)	−12.7 (11.9)	−0.6 (11.9)	−12.1 (25.0)	<0.001
Tirzepatide 10 or 15 mg[b]							
Jastreboff 2022 (SURMOUNT-1)[c]	NR	NR	NR	−18.5 (10.9)	−4.0 (14.9)	−14.5 (26.4)	<0.001
Wadden 2023 (SURMOUNT-3)[d]	−7.7 (3.4)	−1.2 (3.4)	−8.9 (7.8)	−14.6 (11.9)	0.2 (17.1)	−14.8 (28.3)	<0.001

Data are presented as mean (standard deviation). Changes are presented as means (standard deviation). The *p*-values represent the difference between the intervention group and the control group within the reported outcomes. Standard deviations are extracted directly from the articles or calculated in Review Manager version 5.4.1.

Abbreviations: NR, not reported; kg, kilogram; cm, centimeters.

[a]The *p*-values shown are from all four outcomes.

[b]Data from SURMOUNT-1 is 15 mg, while SURMOUNT-3 is 10 or 15 mg.

[c]Data from the intervention group is from the tirzepatide 15 mg group ($n = 630$).

[d]Data are from randomization (week 0, end of lead-in period [from week −12 to 0]) to end of intervention (week 72).

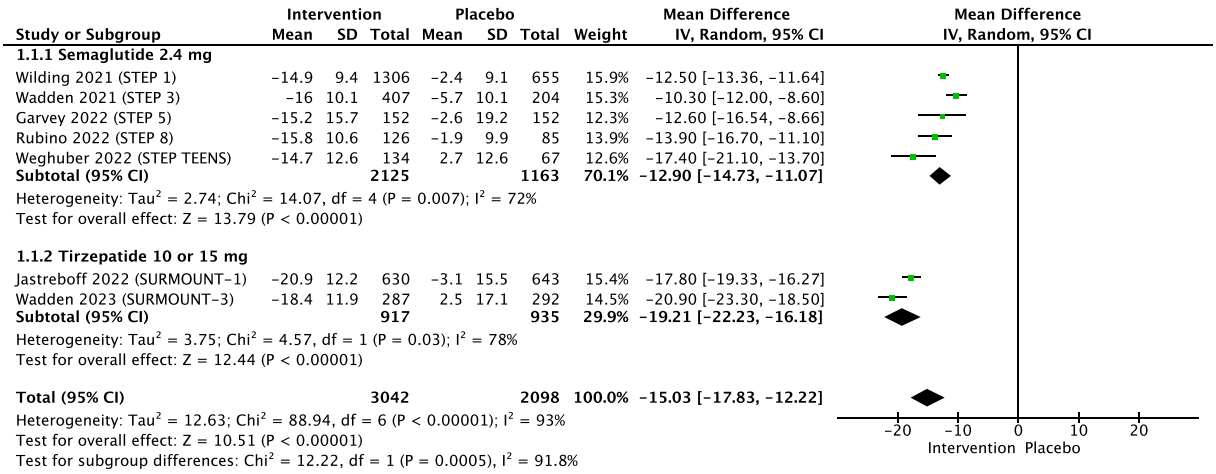

FIGURE 3 Forest plots are of the pooled effects (random-effects model) of semaglutide 2.4 mg versus placebo, tirzepatide 10 or 15 mg versus placebo, and the pooled effect of semaglutide 2.4 mg and tirzepatide 10 or 15 mg versus placebo on percent change in body weight. Data are presented as mean (standard deviation) and mean difference (95% confidence interval). A *p*-value below 0.05 is considered significant. SD, standard deviation; CI, confidence interval. Analysis performed in Review Manager version 5.4.1.

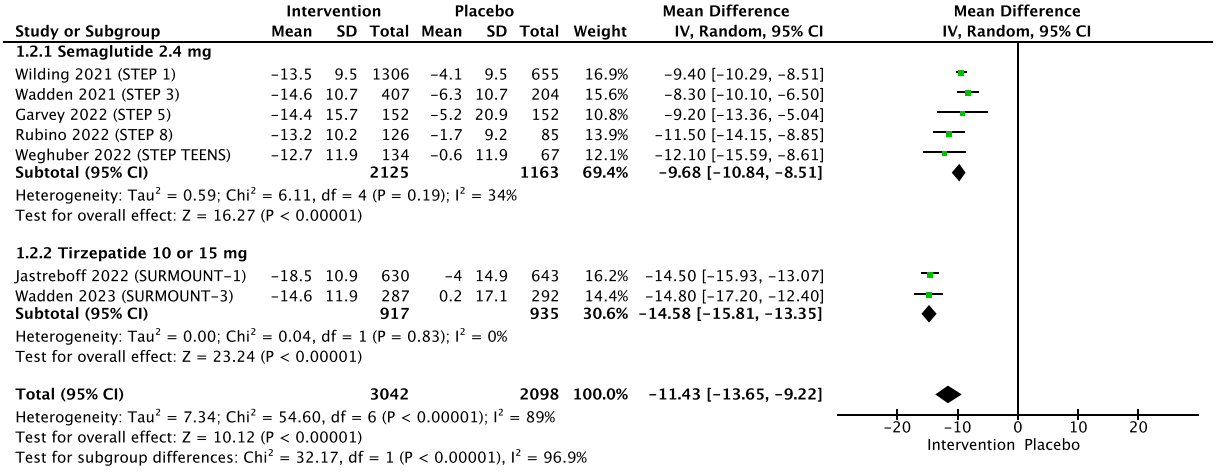

FIGURE 4 Forest plots are of the pooled effects (random-effects model) of semaglutide 2.4 mg versus placebo, tirzepatide 10 or 15 mg versus placebo, and the pooled effect of semaglutide 2.4 mg and tirzepatide 10 or 15 mg versus placebo on change in waist circumference. Data are presented as mean (standard deviation) and mean difference (95% confidence interval). A *p*-value below 0.05 is considered significant. SD, standard deviation; CI, confidence interval. Analysis performed in Review Manager version 5.4.1.

3.11 | Safety

The number of adverse events expressed as the percentage of individuals experiencing at least one given event is presented in Table 4 (STEP trials) and Table 5 (SURMOUNT trials). In the included STEP trials, an average of 91.0% of 2124 participants treated with semaglutide 2.4 mg and 88.9% of 1163 participants with placebo experienced at least one adverse event (Table 4). The most common adverse events were gastrointestinal disorders, including nausea, diarrhea, constipation, and vomiting, which occurred more frequently with semaglutide 2.4 mg compared with placebo (76% vs. 52%, respectively). All STEP trials reported that these common gastrointestinal adverse events were more frequent during the dose-titration period, mild-to-moderate, and decreased throughout the treatment period. Adverse events leading to discontinuation of trial medication were also higher in the semaglutide groups compared with placebo (6.4% vs. 3.4%, respectively), where the common reason for discontinuation in the semaglutide groups was gastrointestinal disorders (3.9% vs. 0.7% with placebo). On average, more serious adverse events were reported with semaglutide compared with placebo (9.5% vs. 6.7%, respectively). Serious adverse events were more often reported with semaglutide treatment than with placebo in STEP 1, STEP 3, and STEP TEENS. STEP 5 reported more serious adverse events in the placebo group than in the semaglutide group (11.8% vs. 7.9%, respectively).

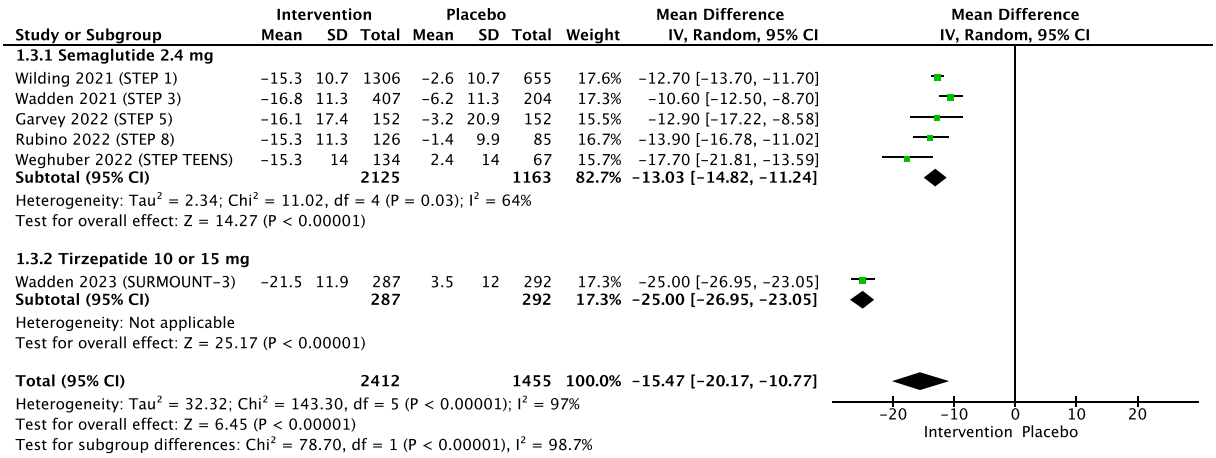

FIGURE 5 Forest plots are of the pooled effects (random-effects model) of semaglutide 2.4 mg versus placebo and the pooled effect of semaglutide 2.4 mg and tirzepatide 10 or 15 mg versus placebo on change in body weight in kilograms. Since only the SURMOUNT-3 study was included for tirzepatide 10 or 15 mg, meta-analysis was not performed on the effect of tirzepatide 10 or 15 mg versus placebo. Data are presented as mean (standard deviation) and mean difference (95% confidence interval). A *p*-value below 0.05 is considered significant. SD, standard deviation; CI, confidence interval. Analysis performed in Review Manager version 5.4.1.

STEP 8 reported a similar frequency of serious adverse events between the groups (7.9% with semaglutide vs. 7.1% with placebo). Regarding adverse events of particular interest to incretin-based therapy, more gallbladder-related disorders, such as gallstones (cholelithiasis), were reported with semaglutide treatment compared with placebo (3.0% vs. 1.2%, respectively) in all STEP trials, except for STEP 8 in which a more even number of events were seen (0.8% with semaglutide vs. 1.2% with placebo). On average, in the STEP trials, cardiovascular disorders were less frequently reported with semaglutide than with placebo (8.9% vs. 12.5%, respectively). No apparent differences in hepatic disorders, pancreatitis, hypoglycemia, acute renal failure, malignant neoplasms, psychiatric disorders, and allergic and injection site reactions were seen in the STEP trials.

In the included SURMOUNT trials, 81.5% of participants experienced at least one adverse event with tirzepatide and 73.5% with placebo, and 5.3% of participants treated with tirzepatide and 6.2% with placebo had a serious adverse event (Table 5). Similar to the STEP trials, the most common adverse events reported with tirzepatide were gastrointestinal disorders, including nausea, diarrhea, vomiting, and constipation. These events were described as transient, mild-to-moderate, and primarily occurred in the dose-titration period. More participants discontinued treatment due to adverse events with tirzepatide than with placebo (7.5% vs. 2.5%, respectively). In the SURMOUNT trials, hypoglycemia and injection-site reactions were reported more frequently with tirzepatide (1.1% and 6.7%, respectively) compared with placebo (0.1% and 0.5%, respectively). No apparent differences were seen regarding gallbladder disease, hepatic events, pancreatitis, major depressive disorder or suicidal ideation, cancer, and major adverse cardiovascular events, and few events were generally reported (frequencies between 0% and 1.1%); however, more severe or serious gastrointestinal events were reported with tirzepatide (4.0%) compared with placebo (1.3%).

4 | DISCUSSION

In the present systematic review and meta-analysis of randomized controlled trials, we investigated the effects of potent incretin-based pharmacotherapy compared with placebo for treating obesity in people without diabetes. Of the 744 records identified, seven randomized controlled trials ($n = 5140$) were included. The analyses showed that semaglutide and tirzepatide produce clinically relevant reductions in body weight with a mean reduction of body weight of 15.0% and a mean reduction of waist circumference of 11.4 cm compared with placebo. The adverse events related to the study drugs were primarily mild to moderate in severity and mostly gastrointestinal and occured more frequently during the dose-titration period and leveled off during the treatment period.

The meta-analysis of the five studies that investigated once-weekly semaglutide 2.4 mg ($n = 2125$ for semaglutide and $n = 1163$ for placebo) showed a mean difference in body weight of −12.9% (13.0 kg) compared with placebo. This estimated treatment effect is slightly larger than the mean difference in body weight of 10.1% to 11.9% reported in most previous meta-analyses.[38–40] The present meta-analysis was restricted to studies that investigated the efficacy compared with placebo when the medications were taken in a manner that reflects best practice; thus, at the highest dose approved for obesity treatment for at least a year to obtain the full weight loss. Therefore, the analyses differ from previously reported meta-analyses by not including once-daily semaglutide,[38–40] studies with a duration of less than a year,[38,41] and the STEP 4 study,[60] in which the control group switched to placebo after a 20-week semaglutide treatment phase.[39,41] In addition, two studies were included that have not been included in previous meta-analyses[38–41]; the STEP 5 study[43] investigated the 2-year effects of semaglutide 2.4 mg versus placebo, and the STEP TEENS study[56] investigated semaglutide 2.4 mg versus placebo for 68 weeks in adolescents (12 to 18 years of age) with obesity.

TABLE 4 Adverse events in the included STEP studies.

Adverse events of included studies	Wilding 2021 STEP 1		Wadden 2021 STEP 3		Garvey 2022 STEP 5		Rubino 2022 STEP 8		Weghuber 2022 STEP TEENS		STEP studies total	
Duration, weeks	68		68		104		68		68			
Participants, *N*	1306	655	407	204	152	152	126	85	133	67	2124	1163
Parameter, *n* (%)	Semaglutide 2.4 mg	Placebo	Semaglutide 2.4 mg	Placebo	Semaglutide 2.4 mg	Placebo	Semaglutide 2.4 mg	Placebo	Semaglutide 2.4 mg	Placebo	Semaglutide 2.4 mg	Placebo
Any adverse event	1171 (89.7)	566 (86.4)	390 (95.8)	196 (96.1)	146 (96.1)	136 (89.5)	120 (95.2)	81 (95.3)	105 (79)	55 (82)	1932 (91.0)	1034 (88.9)
Serious adverse events	128 (9.8)	42 (6.4)	37 (9.1)	6 (2.9)	12 (7.9)	18 (11.8)	10 (7.9)	6 (7.1)	15 (11)	6 (9)	202 (9.5)	78 (6.7)
Discontinuation due to adverse events	92 (7.0)	20 (3.1)	24 (5.9)	6 (2.9)	9 (5.9)	7 (4.6)	4 (3.2)	3 (3.5)	6 (5)	3 (4)	135 (6.4)	39 (3.4)
Discontinuation due to GI-disorders	59 (4.5)	5 (0.8)	14 (3.4)	0 (0.0)	6 (3.9)	1 (0.7)	1 (0.8)	1 (1.2)	3 (2)	1 (1)	83 (3.9)	8 (0.7)
Common (>10%) adverse events[a]												
Nausea	577 (44.2)	114 (17.4)	237 (58.2)	45 (22.1)	81 (53.3)	33 (21.7)	77 (61.1)	19 (22.4)	56 (42)	12 (18)	1028 (48.4)	223 (19.2)
Diarrhea	412 (31.5)	104 (15.9)	147 (36.1)	45 (22.1)	53 (34.9)	36 (23.7)	35 (27.8)	22 (25.9)	29 (22)	13 (19)	676 (31.8)	220 (18.9)
Vomiting	324 (24.8)	43 (6.6)	111 (27.3)	22 (10.8)	46 (30.3)	7 (4.6)	32 (25.4)	5 (5.9)	48 (36)	7 (10)	561 (26.4)	84 (7.2)
Constipation	306 (23.4)	62 (9.5)	150 (36.9)	50 (24.5)	47 (30.9)	17 (11.2)	49 (38.9)	20 (23.5)	8 (6)	1 (1)	560 (26.4)	150 (12.9)
Nasopharyngitis	281 (21.5)	133 (20.3)	90 (22.1)	49 (24.0)	24 (15.8)	23 (15.1)	10 (7.9)	9 (10.6)	16 (12)	7 (10)	421 (19.8)	221 (19.0)
Headache	198 (15.2)	80 (12.2)	78 (19.2)	20 (9.8)	16 (10.5)	16 (10.5)	20 (15.9)	10 (11.8)	22 (17)	11 (16)	334 (15.7)	137 (11.8)
Dyspepsia	135 (10.3)	23 (3.5)	NR	NR	20 (13.2)	7 (4.6)	11 (8.7)	5 (5.9)	NR	NR	166 (10.5)	35 (3.9)
Abdominal pain	130 (10.0)	36 (5.5)	54 (13.3)	10 (4.9)	20 (13.2)	4 (2.6)	NR	NR	20 (15)	4 (6)	224 (11.2)	54 (5.0)
Upper respiratory tract infection	114 (8.7)	80 (12.2)	85 (20.9)	44 (21.6)	20 (13.2)	23 (15.1)	9 (7.1)	18 (21.2)	NR	NR	228 (11.5)	165 (15.1)
Gastrointestinal disorders[b]	969 (74.2)	314 (47.9)	337 (82.8)	129 (63.2)	125 (82.2)	82 (53.9)	106 (84.1)	47 (55.3)	82 (61.7)	28 (41.8)	1619 (76.2)	600 (51.6)
Safety focus areas[c]												
Gallbladder-related disorders	34 (2.6)	8 (1.2)	20 (4.9)	3 (1.5)	4 (2.6)	2 (1.3)	1 (0.8)	1 (1.2)	5 (3.8)	0 (0.0)	64 (3.0)	14 (1.2)
Hepatobiliary disorders[b]	33 (2.5)	5 (0.8)	10 (2.5)	0 (0.0)	4 (2.6)	2 (1.3)	NR	NR	5 (3.8)	0 (0.0)	52 (2.6)	7 (0.6)
Cholelithiasis	23 (1.8)	4 (0.6)	13 (3.2)	2 (1.0)	3 (2.0)	2 (1.3)	1 (0.8)	1 (1.2)	3 (2.3)	0 (0.0)	43 (2.0)	9 (0.8)

(Continues)

TABLE 4 (Continued)

Adverse events of included studies	Wilding 2021 STEP 1		Wadden 2021 STEP 3		Garvey 2022 STEP 5		Rubino 2022 STEP 8		Weghuber 2022 STEP TEENS		STEP studies total	
Duration, weeks	68		68		104		68		68			
Participants, *N*	1306	655	407	204	152	152	126	85	133	67	2124	1163
Parameter, *n* (%)	Semaglutide 2.4 mg	Placebo	Semaglutide 2.4 mg	Placebo	Semaglutide 2.4 mg	Placebo	Semaglutide 2.4 mg	Placebo	Semaglutide 2.4 mg	Placebo	Semaglutide 2.4 mg	Placebo
Hepatic disorders	31 (2.4)	20 (3.1)	8 (2.0)	4 (2.0)	3 (2.0)	3 (2.0)	2 (1.6)	3 (3.5)	10 (7.5)	1 (1.5)	54 (2.5)	31 (2.7)
Acute pancreatitis[d]	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)	0 (0.0)
Cardiovascular disorders	107 (8.2)	75 (11.5)	40 (9.8)	22 (10.8)	17 (11.2)	32 (21.1)	16 (12.7)	9 (10.6)	10 (7.5)	7 (10.4)	190 (8.9)	145 (12.5)
Malignant neoplasms	14 (1.1)	7 (1.1)	3 (0.7)	1 (0.5)	2 (1.3)	4 (2.6)	3 (2.4)	1 (1.2)	0 (0.0)	1 (1.5)	22 (1.0)	14 (1.2)
Acute renal failure	3 (0.2)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	1 (1.2)	0 (0.0)	0 (0.0)	4 (0.2)	3 (0.3)
Psychiatric disorders	124 (9.5)	83 (12.7)	60 (14.7)	24 (11.8)	26 (17.1)	25 (16.4)	7 (5.6)	9 (10.6)	9 (6.8)	10 (14.9)	226 (10.6)	151 (13.0)
Allergic reactions	96 (7.4)	54 (8.2)	35 (8.6)	19 (9.3)	23 (15.1)	8 (5.3)	9 (7.1)	10 (11.8)	12 (9.0)	4 (6.0)	175 (8.2)	95 (8.2)
Injection-site reactions	65 (5.0)	44 (6.7)	22 (5.4)	12 (5.9)	10 (6.6)	15 (9.9)	0 (0.0)	5 (5.9)	4 (3.0)	3 (4.5)	101 (4.8)	79 (6.8)
Hypoglycemia	8 (0.6)	5 (0.8)	2 (0.5)	0 (0.0)	4 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	14 (0.7)	5 (0.4)

Abbreviation: GI, gastrointestinal.

[a]List of common adverse events by preferred term in MedDRA reported in 10% or more of participants in either treatment group.

[b]System organ class. Regarding gallbladder-related disorders, hepatobiliary disorders is system organ class and cholelithiasis preferred term.

[c]Adverse events of particular interest to incretin-based therapy from experience from glucagon-like peptide 1 studies and regulatory agencies (see Outcomes for details) based on Medical Dictionary for Regulatory Activities (MedDRA).

[d]Pancreatitis decided by an adjudication committee.

TABLE 5 Adverse events in the included SURMOUNT studies.

Adverse events of included studies	JASTREBOFF 2022 SURMOUNT-1		Wadden 2023 SURMOUNT-3		SURMOUNT studies total	
Duration, weeks	72		72			
Participants, *N*	630	643	287	292	917	935
Parameter, *n* (%)	Tirzepatide 15 mg	Placebo	Tirzepatide 10 or 15 mg	Placebo	Tirzepatide 10 or 15 mg	Placebo
Any adverse event	497 (78.9)	463 (72.0)	250 (87.1)	224 (76.7)	747 (81.5)	687 (73.5)
Serious adverse events	32 (5.1)	44 (6.8)	17 (5.9)	14 (4.8)	49 (5.3)	58 (6.2)
Discontinuation due to adverse events	39 (6.2)	17 (2.6)	30 (10.5)	6 (2.1)	69 (7.5)	23 (2.5)
Nausea	12 (1.9)	2 (0.3)	24 (8.4)	4 (1.4)	36 (3.9)	6 (0.6)
Diarrhea	3 (0.5)	0 (0.0)	3 (1.0)	0 (0.0)	6 (0.7)	0 (0.0)
Abdominal pain	3 (0.5)	0 (0.0)	NR	NR	3 (0.5)	0 (0.0)
Vomiting	NR	NR	6 (2.1)	0 (0.0)	6 (2.1)	0 (0.0)
Dyspepsia	NR	NR	3 (1.0)	0 (0.0)	3 (1.0)	0 (0.0)
Constipation	NR	NR	2 (0.7)	0 (0.0)	2 (0.7)	0 (0.0)
Common (>10%) adverse events[a]						
Nausea	195 (31.0)	61 (9.5)	114 (39.7)	41 (14.0)	309 (33.7)	102 (10.9)
Diarrhea	145 (23.0)	47 (7.3)	89 (31.0)	27 (9.2)	234 (25.5)	74 (7.9)
Vomiting	77 (12.2)	11 (1.7)	52 (18.1)	4 (1.4)	129 (14.1)	15 (1.6)
Constipation	74 (11.7)	37 (5.8)	66 (23.0)	20 (6.8)	140 (15.3)	57 (6.1)
Nasopharyngitis	NR	NR	NR	NR	NR	NR
Headache	41 (6.5)	42 (6.5)	27 (9.4)	22 (7.5)	68 (7.4)	64 (6.8)
Dyspepsia	71 (11.3)	27 (4.2)	27 (9.4)	9 (3.1)	98 (10.7)	36 (3.9)
Abdominal pain	31 (4.9)	21 (3.3)	30 (10.5)	7 (2.4)	61 (6.7)	28 (3.0)
Upper respiratory tract infection	NR	NR	25 (8.7)	21 (7.2)	25 (8.7)	21 (7.2)
Gastrointestinal disorders[b]	NR	NR	NR	NR	NR	NR
Safety focus areas[c]						
Severe or serious gastrointestinal events	21 (3.3)	7 (1.1)	16 (5.6)	5 (1.7)	37 (4.0)	12 (1.3)
Severe or serious acute gall bladder diseases	6 (1.0)	5 (0.8)	2 (0.7)	0 (0.0)	8 (0.9)	5 (0.5)
Cholelithiasis	4 (0.6)	6 (0.9)	4 (1.4)	3 (1.0)	8 (0.9)	9 (1.0)
Severe or serious hepatic events	0 (0.0)	0 (0.0)	NR	NR	0 (0.0)	0 (0.0)
Pancreatitis[d]	1 (0.2)	1 (0.2)	1 (0.3)	1 (0.3)	2 (0.2)	2 (0.2)
Major adverse cardiovascular events[d]	0 (0.0)	5 (0.8)	1 (0.3)	1 (0.3)	1 (0.1)	6 (0.6)
Cancer/malignancies[e]	5 (0.8)	7 (1.1)	5 (1.7)	3 (1.0)	10 (1.1)	10 (1.1)
Severe or serious renal events	2 (0.3)	1 (0.2)	1 (0.3)	0 (0.0)	3 (0.3)	1 (0.1)
Severe or serious major depressive disorder or suicidal behavior and ideation	2 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	3 (0.3)	0 (0.0)
Hypersensitivity	1 (0.2)	0 (0.0)	NR	NR	1 (0.2)	0 (0.0)
Injection-site reactions	29 (4.6)	2 (0.3)	32 (11.1)	3 (1.0)	61 (6.7)	5 (0.5)
Severe hypoglycemia	10 (1.6)	1 (0.2)	0 (0.0)	0 (0.0)	10 (1.1)	1 (0.1)

[a]List of common adverse events by preferred term in MedDRA reported in 10% or more of participants in either treatment group.
[b]System organ class.
[c]Adverse events of particular interest to incretin-based therapy from experience from glucagon-like peptide 1 studies and regulatory agencies (see Outcomes for details) based on Medical Dictionary for Regulatory Activities (MedDRA). In the SURMOUNT trials, gallbladder-related disorders were reported as gallbladder disease, hepatic disorders as hepatic events, psychiatric disorders as major depressive disorder or suicidal behavior/ideation, allergic reactions as hypersensitivity, and cardiovascular disorders as major cardiovascular events, and these categories counted severe or serious adverse events.
[d]Pancreatitis and major cardiovascular events decided by an adjudication committee.
[e]In SURMOUNT-1 and SURMOUNT-3, malignant neoplasms were reported as cancer or malignancies, including medullary thyroid cancer, and no cases of medullary thyroid cancer were reported.

The meta-analysis of the two studies that investigated once-weekly tirzepatide 10 or 15 mg ($n = 917$ for tirzepatide and $n = 935$ for placebo) showed a mean difference in body weight of 19.2% (23.5 kg) compared with placebo.[57,58] While this weight loss with tirzepatide seems higher than with semaglutide, no studies have directly compared tirzepatide with semaglutide in doses indicated for obesity. In people with type 2 diabetes, tirzepatide 15 mg was superior to semaglutide 1.0 mg once weekly, regarding improvements in both glycated hemoglobin and weight loss.[34] However, some of this difference may be explained by different doses of medication. Therefore, whether tirzepatide is superior to semaglutide for treating obesity awaits more trials. Treatment with tirzepatide 10 or 15 mg led to fewer serious adverse events than with placebo, despite the larger weight loss observed with tirzepatide compared with semaglutide in the STEP trials, which generally reported more serious adverse events with semaglutide 2.4 mg than with placebo. In contrast, more hypoglycemic events seemed to occur with tirzepatide 10 or 15 mg than with semaglutide 2.4 mg compared with placebo. The US Food and Drug Administration and European Medicines Agency have raised safety concerns of thyroid neoplasms with incretin-based therapy;[61,62] however, no increased risk of malignant neoplasms or cancer were observed in the included STEP or SURMOUNT trials.

The weight loss seen with semaglutide and tirzepatide is markedly larger than other approved obesity medications, which have shown treatment effects of −3.07 kg (95% CI -3.76 to −2.37) with orlistat, −4.39 kg (95% CI 5.05 to −3.72) with bupropion-naltrexone, and −5.25 kg (95% CI −6.17 to −4.32) with liraglutide.[63]

The meta-analysis of changes in waist circumference showed that semaglutide and tirzepatide resulted in a mean reduction of 11.4 cm compared with placebo. These results indicate a marked reduction in abdominal adiposity and, thus, improved body composition. Two studies included data on fat and lean mass in subpopulations.[42,57] In a subpopulation of STEP 1, total fat mass was reduced by 8.4 kg, and the proportion of fat relative to total mass was reduced.[42] However, lean mass loss accounted for 39% of total body weight loss. In a subpopulation of SURMOUNT-1, total fat mass was reduced by 34%, and total lean mass was reduced by 11%. Thus, lean mass loss is a concern with weight loss induced by incretin-based pharmacotherapy. However, increased physical activity can preserve lean mass during weight loss,[64,65] and obesity medications are usually approved by medicines agencies as an adjunct to recommendations of lifestyle modifications. All seven studies included in this review investigated the active treatment compared with placebo in conjunction with a lifestyle component involving recommendations on increased physical activity and dietary calorie restriction. However, none of the trials reported adherence or monitoring of the lifestyle components. Thus, whether physical activity was increased during the trials is unknown. A recent randomized placebo-controlled trial investigated the efficacy of a moderate-to-vigorous–intensity exercise program, liraglutide 3.0 mg per day, or the combination of both after a diet-induced weight loss.[18] In this study, the combination of exercise and liraglutide reduced body weight and body fat percentage approximately twice as much as the single-treatment strategies, strongly indicating that exercise is important during obesity pharmacotherapy to reduce fat mass while preserving lean mass. The combination of exercise and liraglutide was associated with additional health benefits, including improved glycated hemoglobin level, insulin sensitivity, cardiorespiratory fitness, physical functioning, and emotional well-being. This study supports the importance of adhering to lifestyle modifications such as increased physical activity while taking obesity medications.[66]

Major advances have been made in the pharmacological treatment of obesity in recent years. Results from the cardiovascular outcome trial of semaglutide 2.4 mg, the SELECT study, including more than 17,000 participants with preexisting cardiovascular disease and overweight or obesity but without type 2 diabetes show that semaglutide 2.4 mg compared with placebo, reduced the incidence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (the primary cardiovascular composite endpoint) by 20% (hazard ratio: 0.80,95% CI, 0.72 to 0.90, $p < 0.001$) in addition to its benefits in weight management and glycemic control.[33] Also, in the SELECT study, serious adverse events were reported less frequently in the semaglutide 2.4 mg group (33.4%) than in the placebo group (36.4%).[33] Furthermore, instances of serious adverse events of particular interest to GLP-1 RAs did not occur more frequently with semaglutide compared with placebo, namely gastrointestinal disorders, acute kidney failure, pancreatitis, cancers, or psychiatric disorders.[33]

Numerous new treatments for obesity are currently being investigated. Subcutaneous semaglutide is currently being investigated at a higher dose of 7.2 mg once weekly compared with the 2.4-mg dose and placebo for the indication of obesity in the STEP UP trial.[67] Subcutaneous cagrilintide, an amylin analog, in combination with semaglutide, has shown weight losses of up to 17% after 20 weeks in the phase 1b trial,[68] and once-weekly cagrilintide 2.4 mg and semaglutide 2.4 mg, CagriSema, is investigated in the REDEFINE phase 3 program (e.g., REDEFINE 1, clinicaltrial.org identifier: NCT05567796). Subcutaneous retatrutide, a triple agonist of the GIP, GLP-1, and glucagon receptors, has shown weight losses of 24.2% after 48 weeks in the 12-mg group in the phase 2 trial.[69] Oral semaglutide has been found effective for treating type 2 diabetes,[70,71] and now also for obesity. In the OASIS-1 phase 3 trial, oral semaglutide 50 mg once daily showed weight losses of 15.1% after 68 weeks.[72] Also, orforglipron, an oral GLP-1 RA, has demonstrated weight losses of up to 14.7% after 36 weeks in the Phase 2 trial.[73] Thus, the efficacy of novel obesity pharmacotherapies is challenging the 25% weight losses that can be sustained on average after bariatric surgery,[74] with the advantage that medications can be paused or stopped and have no inherent surgical risks. However, an extension study conducted in a subpopulation of the STEP 1 trial investigated weight changes 1 year after semaglutide discontinuation.[75] Two-thirds of the weight loss achieved with semaglutide was regained 1 year after treatment discontinuation, highlighting that the benefits of obesity pharmacotherapy depend on continued usage.[75,66]

The present review has several strengths. The meta-analysis included the most recent published trials with a duration of more than 1 year and investigated potent incretin-based therapies for treating obesity. All studies were of high quality and low risk of bias, and the

meta-analysis included a large sample size. Therefore, the included studies provided robust evidence regarding the efficacy of potent incretin-based obesity treatment. Focusing on body composition and not solely body weight is also a strength, as healthy weight loss should comprise loss of fat mass and preservation of lean mass. The review also has limitations related to the number of existing studies. Only two studies investigated the effects of tirzepatide; thus, the evidence so far may be more robust for semaglutide than tirzepatide. Only two studies investigated changes in fat and lean mass in subpopulations. Finally, the reporting of design and adherence to the concomitant lifestyle components were not detailed in most available studies.

In conclusion, this systematic review and meta-analysis shows that among people living with obesity without diabetes, subcutaneous semaglutide 2.4 mg or tirzepatide 10 or 15 mg causes substantial and clinically relevant reductions in body weight and waist circumference.

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CONFLICT OF INTEREST STATEMENT

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SUPPORTING INFORMATION

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

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