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Efficacy and Safety of Once-Weekly Subcutaneous Semaglutide in Overweight or Obese Adults: A Systematic Review with Meta-Analysis

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ABSTRACT

Background To evaluate the efficacy and safety of once-weekly subcutaneous semaglutide treatment in overweight or obese patients without type 2 diabetes.

Methods Randomized clinical trials that assessed the impact of once-weekly semaglutide on body weight and safety outcomes in overweight or obese patients were retrieved from PubMed, EMBASE, and Lilacs up to November 2023. Risk of bias was assessed with RoB 2.0, and certainty of evidence (CoE) with GRADE. A random-effects meta-analysis was conducted.

Results Ten publications, with 22.155 patients, were included. Semaglutide decreased relative body weight (MD: −11.80; 95 %CI: −13.53 to −10.07; CoE: High), absolute body weight (MD: −11.58; 95 %CI: −13.25 to −9.90; CoE: High) and BMI (MD: −4.15; 95 %CI: −4.85 to −3.45; CoE: High). Semaglutide also increased the proportion of patients who achieved 5 %, 10 %, and 15 % of weight loss ([weight loss ≥ 5 %: RR 2.29, 95 % CI: 1.88 to 2.80; CoE: High]; [weight loss ≥ 10 %: RR 4.54, 95 % CI: 3.45 to 5.98; CoE: High]; [weight loss ≥ 15 %: RR 8.29, 95 %CI: 5.54 to 12.39; CoE: High]). Semaglutide leads to small risk to adverse events (RR: 1.03; 95 %CI: 1 to 1.06; CoE: High), no difference in the serious adverse events (RR: 1.07; 95 %CI: 0.70 to 1.62; CoE: Low), but increases in the risk to discontinued treatment (RR: 2.03; 95 %CI: 1.87 to 2.20; CoE: High) and gastrointestinal adverse events (RR: 3.26; 95 %CI: 1.99 to 5.34; CoE: Moderate).

Conclusion This up-to-date systematic review highlights that once-weekly semaglutide treatment resulted in clinically important weight loss, becoming a promising adjuvant therapy for obesity.

Introduction

Overweight and obesity are two major public health issues associated with higher risk of cardiometabolic diseases, such as type 2 diabetes and atherosclerosis, respiratory diseases, stroke, and certain types of cancer [1]. Furthermore, the excess of adiposity also impacts morbidity, lowering the quality of life and wellness of obese people, reducing life expectancy [2]. The estimated overall prevalence of people with excess weight was around 40 %, affecting 650 million adults worldwide [3]. Weight loss is a major goal in the treatment of excess body weight, preventing the progression of obesity-related diseases [1]. However, to date, there are several barriers and issues in treating obesity. In this line, lifestyle changes, mainly by hypocaloric diet and exercise training, are usually recommended as interventions, but their long-term adherence and applicability in modern life are challenging [4]. Moreover, some anti-obesity pharmacological options present low safety profiles and uncertainties regarding their effectiveness [5].

In this line, glucagon-like peptide-1 receptor agonist (GLP-1RA) has been emerging as promising therapies in the pharmacological treatment of metabolic disorders. GLP-1RA has several physiological roles, such as lowering blood glucose, appetite suppression, increasing satiety, and delaying gastric emptying, thus achieving weight reduction [6]. Semaglutide is a GLP-1RA that can be administered subcutaneously once a week with effective impact for the treatment of type 2 diabetes [7]. Evidence indicates that semaglutide treatment lowers blood glucose levels and body weight as well as the risk of major adverse cardiovascular events. The studies that compose the Semaglutide Treatment Effect in Patients with Obesity (STEP) program show the efficacy and safety of the treatment in the management of excess body weight [8–14].

The treatment of obesity with semaglutide has been a focus of previous systematic reviews, exploring the efficacy and safety of subcutaneous semaglutide in patients with excess weight with or without type 2 diabetes [15–17]. Since then, additional publications shed light on the impact of semaglutide as a game changer in the treatment of obesity. There is still a paucity of comprehensive and up-to-date evaluations of the available results that incorporate data from all relevant randomized clinical trials (RCTs) published to date. Therefore, an updated systematic review and meta-analysis were applied to comprehensively and authentically evaluate the efficacy and tolerability of once-weekly subcutaneous semaglutide in overweight or obese patients without type 2 diabetes.

Methods

This systematic review was conducted following the Cochrane Handbook for Systematic Reviews of Interventions and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis [18, 19]. The protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO), under identification number CRD42023451799.

Eligibility criteria

Eligible studies were RCTs of adults (aged > 18 years) with overweight (body mass index [BMI] > 27 to 29.9 kg/m²) or obesity (BMI > 30 kg/m²) without type 2 diabetes evaluating the efficacy and safety of once-weekly subcutaneous semaglutide treatment compared to placebo and at least one of the following outcomes: relative body weight changes, absolute body weight changes, absolute BMI changes, proportions of patients who achieved 5 %, 10 % or 15 % of weight loss, glycated hemoglobin (HbA1c), fasting glucose, systolic and diastolic blood pressure (SBP and DBP), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), triglycerides, C-reactive protein (CRP), adverse events, gastrointestinal events, and serious adverse events. No restrictions were imposed on publication status, language, or methodological quality.

Search strategy

Initially, we systematically searched MEDLINE (via PubMed), Embase, and LILACS from inception to May 2023 for published studies in indexed journals and searched clinicaltrials.gov for potentially available unpublished results. An update search was performed in November 2023 due to the publication of the SELECT trial. The following terms were used: obesity, obese, overweight, semaglutide, Ozempic, and Wegovy combined by Boolean operators with appropriate limiters. We did not include words related to the outcomes of interest to enhance search sensitivity. The search was not restricted by language or publication date filters. We adapted the search terms to fit the requirements of each database. The specific search strategies are referred to in **Supplementary Material 1**.

Study selection and data extraction

Two reviewers independently screened the titles and abstracts identified by the initial search. Studies that did not meet the inclusion criteria were excluded. The full text of selected citations was examined in detail by the two independent reviewers, and studies meeting the prespecified eligibility criteria were included in the review.

The same two reviewers independently extracted relevant data from the included studies using predesigned tables. Data extracted included methodological characteristics of the studies and outcomes of interest. If the study did not report standard deviations, we estimated them from p-values or used the standard deviations provided for the same outcome in other treatment groups in the same study. Disagreements between the two reviewers were resolved by consensus or by consulting a third reviewer for arbitration. We addressed clinically important weight loss of relative weight change by setting a threshold of minimally important difference (MID) of 5 % in the outcome analysis [20].

Risk of bias and certainty of evidence assessment

Two independent reviewers critically appraised the included studies using Risk of Bias (RoB) 2.0 [21]. The overall quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework [22]. Discrepancies in quality assessment were resolved through consensus or by a third reviewer.

Data analysis

Data were synthesized both qualitatively and quantitatively. For qualitative synthesis, we developed a comprehensive summary table containing details of the populations, interventions, compar-

ators, outcomes, and experimental designs. After data extraction, pooled effect estimates were obtained by comparing the change from baseline to study end for each group (mean difference [MD] for continuous outcomes) and relative risk (for categorical outcomes) using a random effects model with the DerSimonian and Laird as variance estimator. We assessed heterogeneity using the I^2 statistic. Results were presented as forest plots with point estimates and 95 % Confidence Intervals (CIs). Meta-analyses were conducted in R statistical software V. 4.1.2 with package meta V.6.5–0. We did not assess publication bias due to the small number of studies included [23].

Results

Search results and included studies

We identified 2428 records in our initial search, and 2243 publications remained for the screening of titles and abstracts after removing duplicates. Then, 2187 publications were excluded after titles and abstracts screening due to unmatching population or intervention eligibility criteria. From the remaining 56 records, 46 were excluded for study design (n = 9), population (n = 3), another intervention (n = 1), outcome (n = 4), and duplicate data (n = 29). Therefore, ten studies met the inclusion criteria, providing data from 22,155 participants [8––12, 24––28] (**Supplementary Fig. 1**). Excluded references from the full-text screening and the reasons for exclusion are provided in **Supplementary Material 2**.

Description of studies

Ten studies involving 22.155 participants with overweight or obesity were included in the systematic review [8–12, 24–28]. The sample size of the included studies ranged between 15 to 17.604 participants. All studies were conducted on non-diabetic overweight or obese individuals with a mean BMI ranging from 33.8 to 45, and all individuals were adults over 18 years of age. Only one study included obese women with polycystic ovary syndrome [26]. Furthermore, Kosiborod and coworkers [27] analyzed the effect of semaglutide on patients with heart failure with preserved ejection fraction and obesity. The proportions of individuals with different types of comorbidities at baseline were presented in all studies, especially the metabolic syndrome, such as dyslipidemia, hypertension, obstructive sleep apnea, and cardiovascular disease. All studies used subcutaneous once-weekly semaglutide, adopting dose escalation throughout, starting with a minimum administered dose of 0.25 mg/week in the first 4 weeks and dose progression every 4 weeks until reaching the maintenance dose. The most frequent maintenance dose of semaglutide was 2.4 mg/week [8–12, 25, 27, 28], but doses of 1.34 mg/week [24] and 1.0 mg/week [26] were also described in the studies. The comparator group used a placebo in all analyzed studies. Lifestyle change co-interventions, consisting of a hypocaloric diet and structured exercise training, were administered in both semaglutide and placebo groups in the STEP program studies [8–12, 27] or SELECT trial [28], while three publications [24–26] did not report co-interventions during the follow-up period. The intervention time in the studies ranged from 12 to 104 weeks. The study of Blundell and colleagues [24] was a cross-over RCT and, due to this reason, was not included in the meta-analysis. (▶ **Table 1**).

Body Weight change

The efficacy of once-weekly subcutaneous semaglutide treatment was assessed by body weight change in people with overweight or obesity and without type 2 diabetes (▶ **Fig. 1**). Seven studies [8–12, 27, 28] evaluated relative body weight changes (% of change) in 22023 patients, indicating superior effects of semaglutide over placebo (MD: −11.80; 95 %CI: −13.53 to - −10.07; p < 0.001; I^2: 98 %; ▶ **Fig. 1a**). Semaglutide treatment had superior effects on absolute body weight changes (kg) (MD: −11.58; 95 %CI: −13.25 to −9.90; p < 0.001; I^2: 83 %; ▶ **Fig. 1b**) in seven studies with 3992 patients [8–12, 25, 26], and on absolute changes of BMI (kg/m²) (MD: −4.15; 95 %CI: −4.85 to −3.45; p < 0.001; I^2: 79 %; ▶ **Fig. 1c**) in five studies conducted with 3709 patients [8–12, 26].

Proportions of participants who achieved 5 %. 10 % and 15 % weight loss

We also assessed the proportion of overweight or obese patients who achieved 5 % (▶ **Fig. 2a**) in five studies involving 3890 patients; and the proportion of patients who achieved 10 % (▶ **Fig. 2b**), and 15 % (▶ **Fig. 2c**) weight loss in six studies involving 4419 patients [8–12, 27]. Notably, participants assigned to once-weekly semaglutide were more likely to reach categorical weight loss targets than those treated with placebo ([weight loss ≥ 5 %: RR 2.29, 95 % CI: 1.88 to 2.80; p < 0.001; I^2: 87 %]; [weight loss ≥ 10 %: RR 4.54, 95 % CI: 3.45 to 5.98; p < 0.001; I^2: 82 %]; [weight loss ≥ 15 %: RR 8.29, 95 %CI: 5.54 to 12.39; p < 0.001; I^2: 75 %]).

The GRADE summary of findings table of efficacy outcomes is fully reported in ▶ **Table 2**. The certainty of evidence was high for efficacy outcomes of weight loss. Thus, semaglutide resulted in a large reduction in body weight (absolute effects of relative weight changes: −11.8 %, 95 %CI: −13.53 to −10.07; absolute effects of absolute weight changes: −11.58 kg, 95 %CI: −9.9 to −13.25) and BMI (absolute effects: −4.15 kg/m², 95 %CI: −3.45 to −4.85). Furthermore, once-weekly subcutaneous semaglutide treatment resulted in large increase in the proportion of participants achieving weight loss of more than 5 % (absolute effect: 46.6 %, 95 %CI: 31.8 to 65.1), 10 % (absolute effect: 53 %, 95 %CI: 36.7 to 74.5), and 15 % (absolute effect: 33.1 %, 95 %CI: 20.6 to 51.7) body weight in overweight or obese patients.

Safety profile

The safety profile of subcutaneous semaglutide treatment was evaluated by the incidence of adverse events (▶ **Fig. 3a**), serious adverse events (▶ **Fig. 3b**), discontinued treatment due to adverse events (▶ **Fig. 3c**) and gastrointestinal adverse events (▶ **Fig. 3d**) (▶ **Fig. 3**). A small increase in the risk relative to adverse events were evaluated in 3987 patients of seven studies (RR: 1.03; 95 %CI: 1–1.06; p = 0.09; I^2:59 %). Seven studies (n = 22.023) identified no difference in the relative risk of serious adverse events (RR: 1.07; 95 %CI: 0.70–1.62; p: 0.75; I^2: 80 %). Semaglutide treatment led to increases in the relative risk treatment discontinuation due to adverse events (RR: 2.03; 95 %CI: 1.87–2.20; p: 0.001; I^2: 0 %). Gastrointestinal adverse events occurred more frequently in the sema-

▶ **Table 1** Characteristics of included studies.

Author, year	NCT number	Intervention comparison	Patient (n)	Female (%)	Age (years)	BMI (kg/m²)	Follow-up (weeks)
Blundell (2017)	NCT02079870	Semaglutide 1.34 mg	30	33.3	42 (36.2)	33.8 (9.1)	12
		Placebo					
Friedrichsen (2020)	NCT03842202	Semaglutide 2.4 mg	36	33.3	40.7 (12.2)	34.2 (3)	20
		Placebo	36	44.4	45 (9.5)	34.6 (3.1)	
Jensterle (2021)	NCT04263415	Semaglutide 1.0 mg	15	100	33.7 (5.3)	36.8 (3.9)	16
		Placebo	15	100		34.8 (3.2)	
Wilding (2021)	NCT03548935	Semaglutide 2.4 mg	1306	73.1	46 (13)	37.8 (6.7)	68
		Placebo	655	76	47 (12)	38 (6.5)	
Wadden (2021)	NCT03611582	Semaglutide 2.4 mg	407	77.4	46 (13)	38.1 (6.7)	68
		Placebo	204	88.2	46 (13)	37.8 (6.9)	
Rubino (2021)	NCT03548987	Semaglutide 2.4 mg	535	80.2	47 (12)	34.5 (6.9)	68
		Placebo	268	76.5	46 (12)	34.1 (7.1)	
Rubino (2022)	NCT04074161	Semaglutide 2.4 mg	126	81	48 (14)	37 (7.4)	68
		Placebo	85	77.6	49 (13)	38.8 (6.5)	
Garvey (2022)	NCT03693430	Semaglutide 2.4 mg	152	80.9	47.3 (11.7)	38.6 (6.7)	104
		Placebo	152	74.3	47.4 (10.3)	38.5 (7.2)	
Koriborod (2023)	NCT04788511	Semaglutide 2.4 mg	263	56.7	70 (9.62)	37.2 (5,3)	52
		Placebo	266	55.6	69 (9.62)	36.9 (6.14)	
Lincoff (2023)	NCT03574597	Semaglutide 2.4 mg	8803	27.8	61.6 (8.9)	33.3 (5.0)	104
		Placebo	8801	27.5	61.6 (8.8)	33.4 (5.0)	

Categorical data presented as percentage. Numeric data presented as mean ± standard deviation. BMI, body mass index; NCT, National Clinical Trial.

glutide treatment group (RR: 3.26; 95 %CI: 1.99–5.34; p: 0.01; I^2: 90 %).

The GRADE summary of findings table of safety outcomes is fully reported in ▶ **Table 3**. The certainty of evidence varied across the safety outcomes. Semaglutide results in little to no difference in adverse events (absolute effects: 2.6 %, 95 %CI: 0 to 5.2; high certainty of evidence;). There is a low certainty of evidence that semaglutide may result in little to no difference in serious adverse events (absolute effects: 0.5 %, 95 %CI: 2.2 to 4.6). However, there is high certainty of evidence that semaglutide increases treatment discontinuation due to adverse events (absolute effects: 7.6 %; 95 %CI: 6.4 to 8.9) and gastrointestinal adverse events (absolute effects: 5.8; 95 %CI: 2.6 to 11.2).

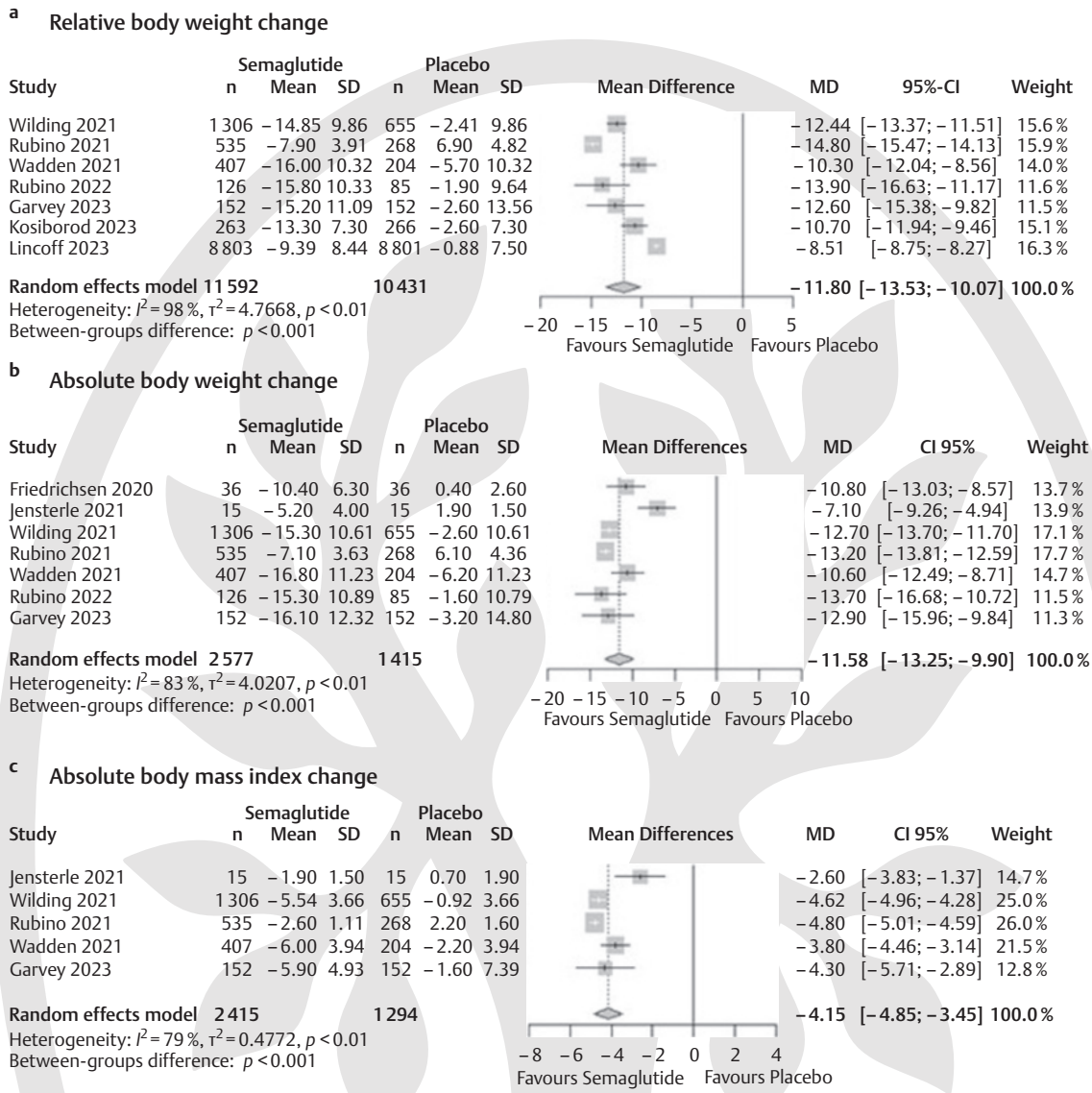
Risk of bias assessment

The risk of bias is shown in **Supplementary Figure 2**. All primary outcomes were considered objective outcomes for the RoB evaluation and presented in a single figure. The study by Jensterle and colleagues [26] raised some concerns about the domains of bias due to deviations in the intended intervention, which was classified as high risk of bias for the domain of assessment of body mass outcomes, BMI, and adverse events. indicating a general high risk of bias. The remaining studies presented low risk of bias for all domains of the RoB 2.0 instrument, indicating a low overall risk of bias [8–12, 25, 27, 28].

The risk of bias of cross-over RCT conducted by Blundell and collaborators [24] was assessed using the RoB 2.0 for cross-over trials tool. The study presented some concerns about the domains "randomization process". and "transition period and effect on outcomes" in the body mass and adverse events outcomes, in addition to high risk for the "missing results data" domain for the outcome of adverse events. The overall judgment indicated "some concerns" for body weight outcome and a high risk of bias for the adverse events.

Subgroup analysis

We performed subgroup analysis related to the treatment duration in relative body weight change, absolute body weight change, serious adverse events, adverse events leading to treatment discontinuation, and gastrointestinal adverse events (▶ **Table 4**). Relative body weight changes (% of change) did not differ between subgroups, but the weight loss peaked at 68 weeks of treatment and slightly attenuate at 104 weeks ([52 weeks: MD: −10.70; 95 %CI: −11.94 to −9.46; 1 study]; [68 weeks: -MD: −12.88; 95 %CI: −14.85 to −10.91; 4 studies]; [104 weeks: MD: −10.31; 95 %CI: −14.29 to −6.33; 2 studies]). Similar patterns were observed in absolute body weight change (kg), 68 weeks of semaglutide treatment showing higher values compared to treatment duration equal or less than 20 weeks ([≤ 20 weeks: MD: −8.94; 95 %CI: −12.56 to −5.31; 2 studies]; [68 weeks: MD: −12.60; 95 %CI: −13.67 to −11.54]; [104 weeks: MD: −12.90; 95 %CI: −15.96 to −9.84]). The incidence of serious adverse events related to semaglutide treatment peaked at 68 weeks and decreased at 104 weeks of treatment ([52 weeks: RR: 0.50; 95 %CI: 0.35 to 0.72; 1 study]; [68 weeks: RR: 1.56; 95 %CI: 1.20 to 2.04; 4 studies]; [104 weeks: RR: 0.92; 95 %CI: 0.88 to 0.95; 2 studies). The incidence of adverse events leading to treatment discontinuation was similar across the treatment duration ([20 weeks: RR: 0.33; 95 %CI: 0.01 to 7.92; 1 study]; [52 weeks: RR: 2.53; 95 %CI: 1.39 to 4.59; 1 study]; [68 weeks: RR: 1.84; 95 %CI: 1.22 to 2.77; 4 studies]; [104 weeks: RR: 2.03; 95 %CI: 1.86 to 2.20; 2 stud-

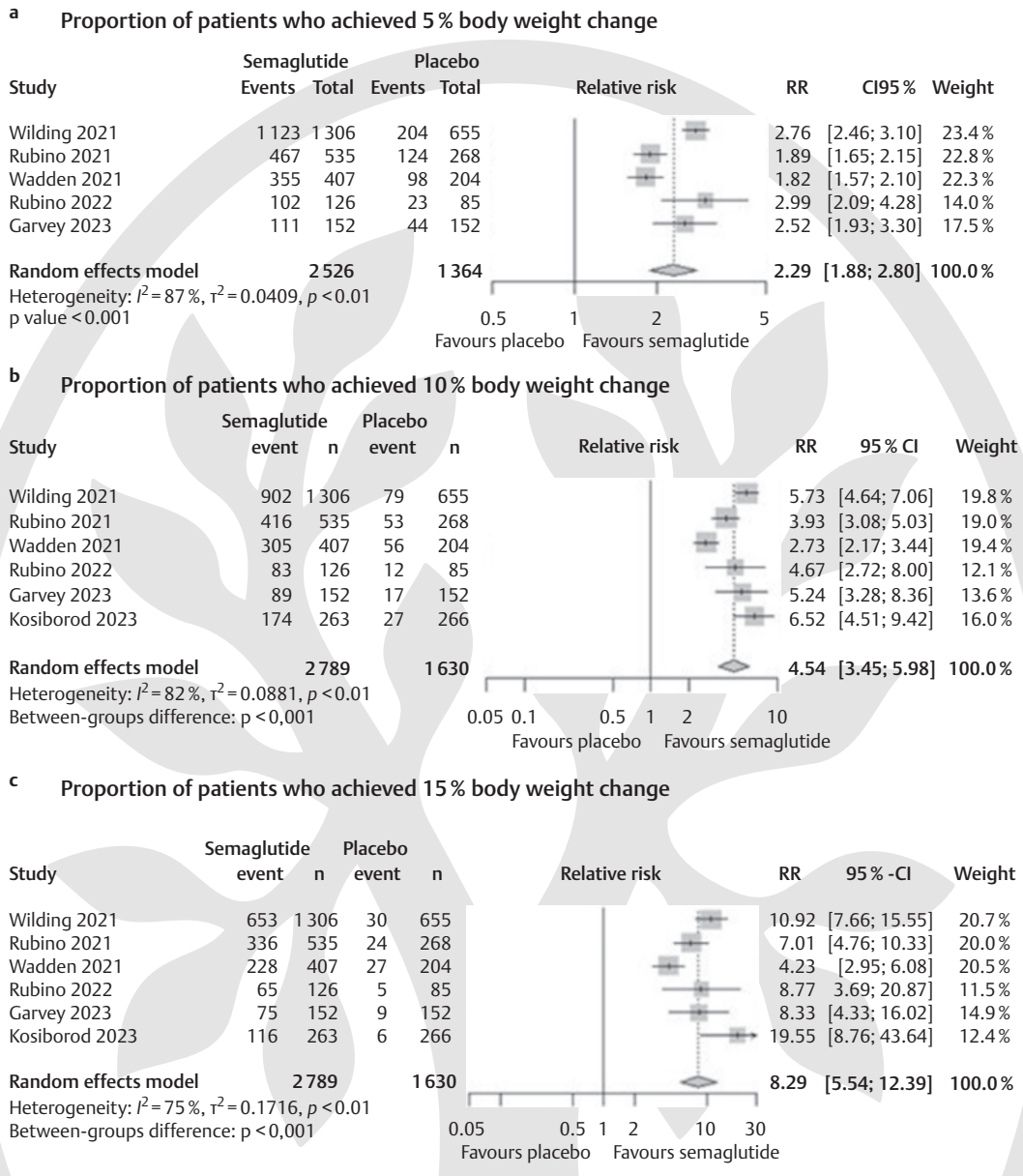


▶ **Fig. 1** Effect of once-weekly semaglutide on body weight variables compared with placebo.

ies]). Gastrointestinal adverse events in semaglutide treatment were higher in all subgroups related to treatment duration, but 104 weeks of treatment lead to the highest relative risk of gastrointestinal events ([< 20 weeks: RR: 2.88; 95%CI: 0.71 to 11.61; 2 studies]; [52 weeks: RR: 3.61; 95%CI: 1.59 to 8.21; 1 study]; [68 weeks: RR: 2.86; 95%CI: 1.02 to 7.98; 4 studies]; [104 weeks: RR: 5.12; 95%CI: 4.36 to 6.01; 2 studies]).

Secondary outcomes

Next, we explored the efficacy of semaglutide on Hb1Ac, fasting glucose, cardiovascular outcomes (SBP and DBP), cholesterol variables (total cholesterol, HDL, LDL, VLDL), triglycerides, and CRP levels in overweight or obese patients without diabetes. ▶ **Fig. 4** shows the overall effect estimate and 95%CI of mean difference of semaglutide versus placebo comparison. Detailed meta-analysis figures are presented in Supplementary Materials. Compared to placebo, semaglutide lowered SBP (MD: −3.98 mmHg; 95%CI: −4.80 to −3.16; 7 studies; 22.023 patients), DBP (MD: −2.14 mmHg; 95%CI: −3.47 to −0.81; 6 studies; 21.494 patients), Hb1Ac (MD: −0.28%; 95%CI: −0.31 to −0.25; 7 studies; 21.524 patients) and fasting glucose (MD: −0,42 mmol/L; 95%CI: −0.48 to −0.36; 6 studies; 3.920 patients) (▶ **Fig. 4a**). Furthermore, semaglutide treatment lowered total cholesterol levels (MD: −4.16%; 95%CI: 5.57 to −2.75; 6 studies; 21.494 patients), LDL (MD: −4.48%; 95%CI: −6.60 to −2.36; six studies; 21.494 patients), VLDL (MD: −16.44%; 95%CI: −16.30 to −14.38; 5 studies; 3.890 patients), triglycerides (MD: −15.34%; 95%CI: −16.30 to −14.38; six studies; 21.494 patients) and CRP levels (MD: −37.14%; 95%CI: −38.70 to −35.58; 6 studies; 21.220 patients), and increased HDL levels (MD: 2.73%; 95%CI: 1.10 to 4.36; six studies; 21.494 patients).



▶ **Fig. 2** Effect of once-weekly semaglutide on the proportion of patients who achieved 5 %, 10 % and 15 % weight loss.

Discussion

The present study is an up-to-date and comprehensive systematic review with a meta-analysis of randomized clinical trials that focused on ascertaining the efficacy of using once-weekly subcutaneous semaglutide treatment on efficacy outcomes and safety profiles in patients with overweight or obesity. Our systematic review of ten studies indicated that once-weekly semaglutide treatment is effective in inducing weight loss in obese and overweight patients without type 2 diabetes. There is a high certainty of evidence that semaglutide treatment reduced body weight by 11.80 % (−11.58 kg), BMI by 4.15 kg/m^2, and achieved more than 5, 10, and 15 % weight loss in a higher proportion of participants compared to placebo. Semaglutide treatment has high efficacy in changing secondary outcomes related to cardiovascular and metabolic risk factors, including SBP/DBP, lipid variables, fasting glucose, Hb1Ac, and inflammation markers. However, semaglutide had more adverse effects than placebo, especially gastrointestinal adverse events, but a non-significant increase in the incidence of serious adverse events. Although these findings must be viewed with caution, they indicate that semaglutide is an important pharmacological adjuvant pharmacotherapy in the treatment of excess body weight.

Previous systematic reviews identified the efficacy and safety profile of semaglutide treatment in both overweight and obese patients with or without type 2 diabetes, reporting the benefits of semaglutide treatment in weight management [6, 15, 17]. How-

▶ **Table 2** A summary of findings table presented in both relative risk and absolute risk differences with 95 % confidence intervals of efficacy outcomes.

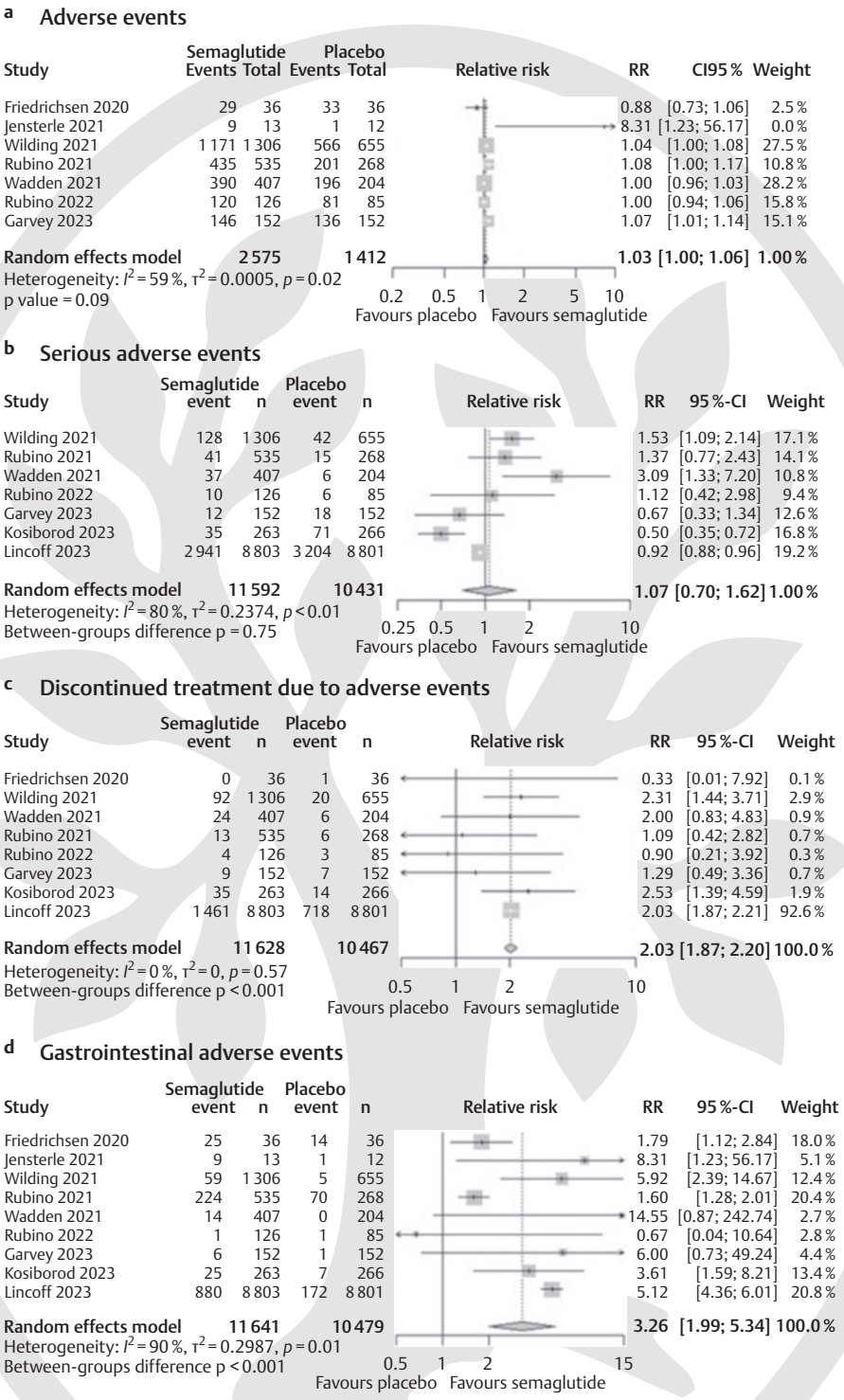
Outcome № of participants (studies)	Relative effect (95 % CI)	Anticipated absolute effects (95 % CI)			Certainty	Planning language
				Difference		
Relative body weight change 22.023 participants (7 RCTs)	-	The mean relative body weight change was **−1,31** %	-	MD **11.8 % lower** (13.53 lower to 10.07 lower)	⊕⊕⊕⊕ High[a,b]	Semaglutide results in a large reduction in relative body weight.
Absolute body weight change 3.992 participants (7 RCTs)	-	The mean absolute body weight change was **−0.74** kg	-	MD **11.58 kg lower** (9.9 lower to 13.25 lower)	⊕⊕⊕⊕ High[a,c]	Semaglutide results in a large reduction in absolute body weight change.
Absolute BMI changes 3.709 (5 RCTs)	-	The mean absolute BMI change was **-0.36** kg/m²	-	MD **4.15 kg/m² lower** (3.45 lower to 4.85 lower)	⊕⊕⊕⊕ High[a,c]	Semaglutide results in a large reduction in absolute BMI changes.
Proportion of participants achieving weight loss of more than 5 % weight loss 3.890 (5 RCTs)	**RR 2.29** (1.88 to 2.80)	36.1 %	**82.8 %** (68 to 100)	**46.6 % more** (31.8 more to 65.1 more)	⊕⊕⊕⊕ High	Semaglutide results in a large increase in the proportion of participants achieving weight loss of more than 5 % weight loss.
Proportion of participants achieving weight loss of more than 10 % weight loss 44.190 (6 RCTs)	**RR 4.54** (3.45 to 5.98)	15 %	**68 %** (51.6 to 89.5)	**53 % more** (36.7 more to 74.5 more)	⊕⊕⊕⊕ High	Semaglutide results in a large increase in the proportion of participants achieving weight loss of more than 10 % weight loss.
Proportion of participants achieving weight loss of more than 15 % weight loss 44.190 (6 RCTs)	**RR 8.29** (5.54 to 12.39)	4.5 %	**37.6 %** (25.2 to 56.2)	**33.1 % more** (20.6 more to 51.7 more)	⊕⊕⊕⊕ High	Semaglutide results in a large increase in the proportion of participants achieving weight loss of more than 15 % weight loss.

*The risk in the intervention group (and its 95 % confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95 % CI). CI: confidence interval; MD: mean difference; RR: risk ratio; BMI, body mass index; RCTs, Randomized Clinical Trials GRADE Working Group grades of evidence. High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. Explanations a. The judgment of the Inconsistency domain indicated "not serious" due to the overlap of the point estimate and low range of 95 %CI related to the sample size and continuous outcome as mentioned by GRADE Guidance 36. b. Imprecision domain was evaluated through a MID of 5 % for relative body weight change. c. The study of Jensterle had a weight of 13.9 % in the overall point estimate.

ever, previous studies included different settings of populations and a variation in the dose and frequency of semaglutide treatment. Since then, the studies of STEP 5 and STEP 8 added new insights into the role of semaglutide treatment effects on overweight/obesity areas. Garvey and coworkers [8] reported the data obtained from STEP 5, which confirms the long-term efficacy, tolerability, and safety profile of semaglutide treatment after 104 weeks. STEP 8 showed a significantly greater average bodyweight reduction of 15.8 % with semaglutide 2.4 mg against the daily injectable GLP-1 RA liraglutide 3 mg and placebo [10]. Recently, Qin and colleagues [29] published an updated systematic review, including the STEP 5 trial reporting the efficacy and safety of semaglutide treatment on overweight and obese patients without type 2 diabetes. Furthermore, recent innovative RCTs using semaglutide have been published.

Here, we presented additional information regarding the safety and efficacy of subcutaneous semaglutide due to the inclusion of STEP-HFpEF and SELECT trials. Kosiborod and coworkers [27] demonstrated the benefits of once-weekly 2.4 mg semaglutide on obese patients with heart failure with preserved ejection fraction (HFpEF) over weight loss and reduced disease-specific symptoms and physical limitations after 52 weeks of treatment. The SELECT trial [28] was a pivotal study that found that after a mean treatment duration of 34.2 months, semaglutide was superior to placebo in reducing the risk of the primary cardiovascular endpoint (a composite of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke), showing the benefits of this treatment to improve not only body composition but also cardiometabolic endpoints. By and large, our study was a comprehensive updated systematic review of RCTs, which fully examined the weight loss effects of different dosages of once-weekly subcutaneous semaglutide compared with placebo in obese or overweight patients without type 2 diabetes.

Semaglutide is a GLP-1 RA initially approved for the treatment of people with type 2 diabetes at weekly doses of up to 1.0 mg [7]. Surprisingly, GLP-1 RA has been reported to reduce body weight through a variety of physiological mechanisms [30]. Semaglutide is the second GLP-1 RA approved for chronic weight management after liraglutide [31]. The results of our study noted that semaglutide reduced body weight by a mean of 11.58 kg (12.85 %) relative to placebo. Preclinical studies suggest that semaglutide decreases body weight by exerting direct and indirect influences on GLP-1 receptors located in the hypothalamus and hindbrain, which play a role in regulating appetite [32–34]. In individuals with obesity, the



▶ **Fig. 3** Meta-analysis results of the proportion with Adverse Events in included trials.

administration of subcutaneous semaglutide at a dosage of 2.4 mg once a week resulted in a significant reduction in appetite and food cravings, leading to an approximately 28.5 % decrease in energy intake compared to the placebo group after a 20-week treatment period [25].

Achieving a consistent weight loss of 5 % brings about meaningful health advantages for individuals experiencing either being overweight with one or more weight-related comorbidities or obesity. Moreover, there is an observable trend suggesting that greater amounts of weight loss may lead to even more substantial ben-

▶ **Table 3** A summary of the findings table presented in both relative risk and absolute risk differences with 95% confidence intervals of safety outcomes.

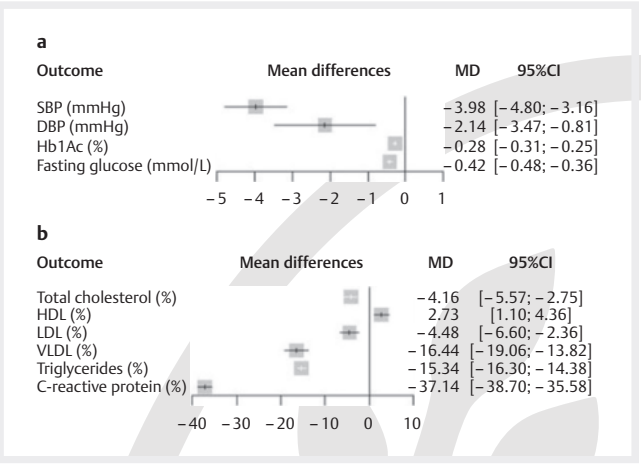
Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
				Difference		
Adverse events 3.987 (7 RCTs)	**RR 1.03** (1.00 to 1.06)	86.0%	**88.6%** (86 to 91.1)	**2.6% more** (0 fewer to 5.2 more)	⊕⊕⊕⊕ High[a]	Semaglutide results in little to no difference in adverse events.
Serious adverse events 22.023 (7 RCTs)	**RR 1.07** (0.70 to 1.62)	7.4%	**7.9%** (5.2 to 12)	**0.5% more** (2.2 fewer to 4.6 more)	⊕⊕◯◯ Low[b,c]	Semaglutide may result in little to no difference in serious adverse events.
Discontinued treatment due to adverse events 22.095 (8 RCTs)	**RR 2.03** (1.87 to 2.20)	7.4%	**15%** (13.8 to 16.3)	**7.6% more** (6.4 more to 8.9 more)	⊕⊕⊕⊕ High[a]	Semaglutide results in an increase in discontinued treatment due to adverse events.
Gastrointestinal adverse events № of participants: 22.120 (8 RCTs)	**RR 3.26** (1.99 to 5.34)	2.6%	**8.4%** (5.1 to 13.8)	**5.8% more** (2.6 more to 11.2 more)	⊕⊕⊕⊕ High[a]	Semaglutide increases gastrointestinal adverse events.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; RR: risk ratio**.** GRADE Working Group grades of evidence. High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. **Explanations** a. The study of Jensterle et al. (2021) was identified as "low weight" in the overall point estimate. b. Serious inconsistency due to low overlap in point estimates. c. Imprecision results are related to null effect and a possible great harm in the semaglutide treatment.

▶ **Table 4** Subgroup analysis of efficacy and safety outcomes in accordance with treatment duration.

Treatment duration	MD	95% CI	I^2	Number of studies	Sample size
Relative body weight change					
52 weeks	−10.70	−11.94 to −9.46	-	1	529
68 weeks	−12.88	−14.85 to −10.91	91%	4	3.586
104 weeks	−10.31	−14.29 to −6.33	88%	2	17.908
Absolute body weight					
<20 weeks	−8.94	−12.56 to −5.31	81.7%	2	102
68 weeks	−12.60	−13.67 to −11.54	58%	4	3.586
104 weeks	−12.90	−15.96 to −9.84	-	1	304
Adverse events					
Treatment duration	RR	95% CI	I^2	Number of studies	Sample size
Serious AE					
52 weeks	0.50	0.35 to 0.72	-	1	529
68 weeks	1.56	1.20 to 2.04	5%	4	3.586
104 weeks	0.92	0.88 to 0.95	0%	2	17.908
AE leading to treatment distontinuation					
<20 weeks	0.33	0.01 to 7.92	-	1	72
52 weeks	2.53	1.39 to 4.59	-	1	529
68 weeks	1.84	1.22 to 2.77	0%	4	3.586
104 weeks	2.03	1.86 to 2.20	0%	2	17.908
GI disorders related adverse events					
<20 weeks	2.88	0.71 to 11.61	57%	2	102
52 weeks	3.61	1.59 to 8.21	-	1	529
68 weeks	2.86	1.02 to 7.98	70%	4	3.586
104 weeks	5.12	4.36 to 6.01	0%	2	17.908

Abbreviations: RR: risk ratio; CI: confidence interval; AEs: Adverse events; GI disorders: Gastrointestinal disorders.



▶ **Fig. 4** Overall effect estimate and 95 % confidence interval (CI) of semaglutide efficacy (versus placebo) on secondary outcomes systolic blood pressure (SBP), diastolic blood pressure (DBP), glycated hemoglobin (Hb1Ac), fasting glucose (all on **a**), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low density lipoprotein (VLDL), triglycerides and C-reactive protein (CRP) levels (**b**).

efits [1, 20]. In our research, the percentages of patients attaining weight loss of ≥ 5 %, ≥ 10 %, or ≥ 15 % within the once-weekly semaglutide treatment cohort were higher compared to the placebo-controlled group. In addition, absolute effects indicate that 46.6 % more patients achieved the MID of 5 % weight loss after semaglutide treatment compared to placebo. More importantly, once-weekly semaglutide increased the weight loss by at least 10 % (53 % more) and 15 % (33 % more) compared with placebo. The significant numbers were notably higher than those observed in previous studies involving other anti-obesity medications within a similar patient population [35, 36].

Taken together, our results pertaining to efficacy outcomes demonstrated that once-weekly subcutaneous semaglutide exhibited marked superiority in managing weight among adults with overweight or obesity without diabetes. It is crucial to emphasize that a consistent and clinically significant reduction in body weight plays a pivotal role in enhancing metabolic health and addressing other comorbidities associated with obesity [36, 37]. Nevertheless, up until now, there has been limited exploration into whether the weight loss induced by semaglutide and other GLP-1 RA drugs can effectively lead to a decrease in complications and diseases associated with obesity. Conversely, the once-weekly subcutaneous administration of semaglutide at a dosage of 2.4 mg demonstrated superiority over the placebo in mitigating the occurrence of cardiovascular complications among patients who were overweight or obese and had preexisting cardiovascular disease [28]. Furthermore, exploratory analysis indicates that semaglutide may attenuate the progression of kidney disease in obese patients [38], as a trial is ongoing to evaluate the effect of semaglutide on kidney outcomes in participants with chronic kidney disease (CKD) and type 2 diabetes [39].

In fact, we found that semaglutide treatment leads to greater improvements in cardiometabolic markers and showed that semaglutide treatment may have positive effects on blood pressure, blood glucose levels, lipid profile, inflammation, and other cardiometabolic risk factors. In this sense, these results may be associated with the potential prevention of obesity-related disease and mortality recently described [28]. Notably, semaglutide has also demonstrated direct cardioprotective effects, including reducing inflammation, improving endothelial function, and reducing arterial stiffness in real-world data [40]. Interestingly, some GLP-1 RA effects on cardiovascular event reduction in overweight or obese patients are associated with an anti-inflammatory mechanism [41]. Furthermore, clinical trials demonstrated that semaglutide lowers the thickness of epicardial fat and significantly reduces the likelihood of major adverse cardiovascular events and stroke compared to placebo [42, 43]. Although the studies were conducted in obese patients with type 2 diabetes, the recently published SELECT trial indicates that semaglutide has the same effectiveness on the protection against cardiometabolic diseases in obese subjects without type 2 diabetes [28].

In this study, we also performed an update on the safety profile of once-weekly subcutaneous semaglutide. Overall, once-weekly semaglutide was well-tolerated and generally deemed safe, with a low incidence of serious adverse events. However, more patients presented adverse events related to treatment discontinuation and gastrointestinal disorders. Gastrointestinal adverse events are commonly associated with semaglutide use. The most frequently reported gastrointestinal side effects include nausea, vomiting, diarrhea, and constipation. These symptoms are generally mild to moderate in severity and tend to diminish over time as the body adjusts to the medication [44, 45]. In terms of other safety considerations, literature data provided reassurance by indicating no overall increase in the incidence of hypoglycemic events, acute pancreatitis, acute renal failure, or malignant neoplasms [46, 47].

According to the European Medicine Agency's (EMA) Methodological Guidelines for the Clinical Evaluation of Technologies and Medicines [48] for weight management, a plateau in the weight loss process is observed after 5 to 6 months (30 weeks) of continuous pharmacological treatment. Here, the data suggest that semaglutide treatment remains highly effective even after 104 weeks, despite the greatest weight loss occurring around 68 weeks. Of note, the point estimate of adverse events leading to treatment discontinuation and gastrointestinal disorders related to adverse events were higher around 104 weeks of treatment than 68 weeks. As treatment duration increases, the total exposure to the GLP-1 drug also increases. This can lead to a higher overall risk of side effects, including GI issues. Additionally, some GLP-1 medications have dose-dependent side effects, meaning higher doses are associated with a greater chance of GI problems. Furthermore, Certain GI side effects, like constipation, may not manifest until later in the treatment course. This can create the impression that they are associated with longer duration rather than simply reflecting individual variability.

Nevertheless, it is important to acknowledge several limitations in our study. Firstly, our meta-analysis relied on study-level data rather than patient-level data. Additionally, due to the limited number of included studies, the potential for publication bias cannot

be ruled out. Lastly, there was notable heterogeneity among the included RCTs, likely stemming from differences in sample sizes, semaglutide dosing, baseline characteristics of patient populations, and trial durations.

In conclusion, once-weekly subcutaneous semaglutide treatment is highly effective in improving the body weight of adults who are overweight or obese without type 2 diabetes. Semaglutide becomes a promising adjuvant therapy, in addition to lifestyle changes such as nutritional support and structured exercise training, in the treatment of excess body weight.

Author Agreement

The manuscript has been seen and approved by all authors; it is not under active consideration for publication, has not been accepted for publication, nor has it been published in full or in part (except in abstract form).

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Gilson Dorneles, Ellen Algeri, Marcelo Pereira and Gehard Lauterbach. The first draft of the manuscript was written by Gilson Dorneles and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Gonzalez-Muniesa P, Martinez-Gonzalez MA, Hu FB et al. Obesity. Nat Rev Dis Primers 2017; 3: 17034. DOI: 10.1038/nrdp.2017.34

[2] Hachula M, Kosowski M, Zielanska K et al. The Impact of various methods of obesity treatment on the quality of life and mental health-A narrative review. Int J Environ Res Public Health 2023; 20. DOI: 10.3390/ijerph20032122

[3] Boutari C, Mantzoros CS. A 2022 update on the epidemiology of obesity and a call to action: As its twin COVID-19 pandemic appears to be receding, the obesity and dysmetabolism pandemic continues to rage on. Metabolism 2022; 133: 155217. DOI: 10.1016/j.metabol.2022.155217

[4] Kim TN. Barriers to obesity management: Patient and physician factors. J Obes Metab Syndr 2020; 29: 244–247. DOI: 10.7570/jomes20124

[5] Muller TD, Bluher M, Tschop MH et al. Anti-obesity drug discovery: Advances and challenges. Nat Rev Drug Discov 2022; 21: 201–223. DOI: 10.1038/s41573-021-00337-8

[6] Wang JY, Wang QW, Yang XY et al. GLP-1 receptor agonists for the treatment of obesity: Role as a promising approach. Front Endocrinol (Lausanne) 2023; 14: 1085799. DOI: 10.3389/fendo.2023.1085799

[7] Singh G, Krauthamer M, Bjalme-Evans M. Wegovy (semaglutide): A new weight loss drug for chronic weight management. J Investig Med 2022; 70: 5–13. DOI: 10.1136/jim-2021-001952

[8] Garvey WT, Batterham RL, Bhatta M et al. Two-year effects of semaglutide in adults with overweight or obesity: The STEP 5 trial. Nat Med 2022; 28: 2083–2091. DOI: 10.1038/s41591-022-02026-4

[9] Rubino D, Abrahamsson N, Davies M et al. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: The STEP 4 Randomized Clinical Trial. JAMA 2021; 325: 1414–1425. DOI: 10.1001/jama.2021.3224

[10] Rubino DM, Greenway FL, Khalid U et al. Effect of weekly subcutaneous semaglutide vs daily liraglutide on body weight in adults with overweight or obesity without diabetes: The STEP 8 Randomized Clinical Trial. JAMA 2022; 327: 138–150. DOI: 10.1001/jama.2021.23619

[11] Wadden TA, Bailey TS, Billings LK et al. Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: The STEP 3 Randomized Clinical Trial. JAMA 2021; 325: 1403–1413. DOI: 10.1001/jama.2021.1831

[12] Wilding JPH, Batterham RL, Calanna S et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med 2021; 384: 989–1002. DOI: 10.1056/NEJMoa2032183

[13] Davies M, Faerch L, Jeppesen OK et al. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): A randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. Lancet 2021; 397: 971–984. DOI: 10.1016/S0140-6736(21)00213-0

[14] Kadowaki T, Isendahl J, Khalid U et al. Semaglutide once a week in adults with overweight or obesity, with or without type 2 diabetes in an east Asian population (STEP 6): A randomised, double-blind, double-dummy, placebo-controlled, phase 3a trial. Lancet Diabetes Endocrinol 2022; 10: 193–206. DOI: 10.1016/S2213-8587(22)00008-0

[15] Gao X, Hua X, Wang X et al. Efficacy and safety of semaglutide on weight loss in obese or overweight patients without diabetes: A systematic review and meta-analysis of randomized controlled trials. Front Pharmacol 2022; 13: 935823. DOI: 10.3389/fphar.2022.935823

[16] He K, Guo Q, Zhang H et al. Once-weekly semaglutide for obesity or overweight: A systematic review and meta-analysis. Diabetes Obes Metab 2022; 24: 722–726. DOI: 10.1111/dom.14612

[17] Zhong P, Zeng H, Huang M et al. Efficacy and safety of once-weekly semaglutide in adults with overweight or obesity: A meta-analysis. Endocrine 2022; 75: 718–724. DOI: 10.1007/s12020-021-02945-1

[18] Higgins JPTTJ, Chandler J, Cumpston M et al. Cochrane Handbook for Systematic Reviews of Interventions: Cochrane; 2023

[19] Moher D, Liberati A, Tetzlaff J et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009; 6: e1000097. DOI: 10.1371/journal.pmed.1000097

[20] Jensen MD, Ryan DH, Apovian CM et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation 2014; 129: S102–138. DOI: 10.1161/01.cir.0000437739.71477.ee

[21] Sterne JAC, Savovic J, Page MJ et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ 2019; 366: l4898. DOI: 10.1136/bmj.l4898

[22] Balshem H, Helfand M, Schunemann HJ et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011; 64: 401–406. DOI: 10.1016/j.jclinepi.2010.07.015

[23] Sterne JA, Sutton AJ, Ioannidis JP et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011; 343: d4002. DOI: 10.1136/bmj.d4002

[24] Blundell J, Finlayson G, Axelsen M et al. Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity. Diabetes Obes Metab 2017; 19: 1242–1251. DOI: 10.1111/dom.12932

[25] Friedrichsen M, Breitschaft A, Tadayon S et al. The effect of semaglutide 2.4 mg once weekly on energy intake, appetite, control of eating, and gastric emptying in adults with obesity. Diabetes Obes Metab 2021; 23: 754–762. DOI: 10.1111/dom.14280

[26] Jensterle M, Ferjan S, Vovk A et al. Semaglutide reduces fat accumulation in the tongue: A randomized single-blind, pilot study. Diabetes Res Clin Pract 2021; 178: 108935. DOI: 10.1016/j.diabres.2021.108935

[27] Kosiborod MN, Abildstrom SZ, Borlaug BA et al. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. N Engl J Med 2023; 389: 1069–1084. DOI: 10.1056/NEJMoa2306963

[28] Lincoff AM, Brown-Frandsen K, Colhoun HM et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med 2023; 389: 2221–2232. DOI: 10.1056/NEJMoa2307563

[29] Qin W, Yang J, Deng C et al. Efficacy and safety of semaglutide 2.4 mg for weight loss in overweight or obese adults without diabetes: An updated systematic review and meta-analysis including the 2-year STEP 5 trial. Diabetes Obes Metab 2023; 26: 911–923. DOI: 10.1111/dom.15386 10.1111/dom.15386

[30] Jensterle M, Rizzo M, Haluzik M et al. Efficacy of GLP-1 RA approved for weight management in patients with or without diabetes: A narrative review. Adv Ther 2022; 39: 2452–2467. DOI: 10.1007/s12325-022-02153-x

[31] Administration. FaD. Wegovy Prescribing Information. In; 2021

[32] Drucker DJ. Mechanisms of action and therapeutic application of glucagon-like peptide-1. Cell Metab 2018; 27: 740–756. DOI: 10.1016/j.cmet.2018.03.001

[33] Gabery S, Salinas CG, Paulsen SJ et al. Semaglutide lowers body weight in rodents via distributed neural pathways. JCI Insight 2020; 5. DOI: 10.1172/jci.insight.133429

[34] Hall S, Isaacs D, Clements JN. Pharmacokinetics and clinical implications of semaglutide: A new glucagon-like peptide (GLP)-1 receptor agonist. Clin Pharmacokinet 2018; 57: 1529–1538. DOI: 10.1007/s40262-018-0668-z

[35] Khera R, Murad MH, Chandar AK et al. Association of pharmacological treatments for obesity with weight loss and adverse events: A systematic review and meta-analysis. JAMA 2016; 315: 2424–2434. DOI: 10.1001/jama.2016.7602

[36] Konwar M, Bose D, Jaiswal SK et al. Efficacy and safety of liraglutide 3.0 mg in patients with overweight and obese with or without diabetes: A systematic review and meta-analysis. Int J Clin Pract 2022; 2022: 1201977. DOI: 10.1155/2022/1201977

[37] Lean ME, Leslie WS, Barnes AC et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): An open-label, cluster-randomised trial. Lancet 2018; 391: 541–551. DOI: 10.1016/S0140-6736(17)33102-1

[38] Heerspink HJL, Apperloo E, Davies M et al. Effects of semaglutide on albuminuria and kidney function in people with overweight or obesity with or without type 2 diabetes: Exploratory analysis from the STEP 1, 2, and 3 trials. Diabetes Care 2023; 46: 801–810. DOI: 10.2337/dc22-1889

[39] Rossing P, Baeres FMM, Bakris G et al. The rationale, design and baseline data of FLOW, a kidney outcomes trial with once-weekly semaglutide in people with type 2 diabetes and chronic kidney disease. Nephrol Dial Transplant 2023; 38: 2041–2051. DOI: 10.1093/ndt/gfad009

[40] Ghusn W, Fansa S, Anazco D et al. Weight loss and cardiovascular disease risk outcomes of semaglutide: A one-year multicentered study. Int J Obes (Lond) 2024; FebL 1 . DOI: 10.1038/s41366-023-01456-5 10.1038/s41366-023-01456-5

[41] Bendotti G, Montefusco L, Lunati ME et al. The anti-inflammatory and immunological properties of GLP-1 receptor agonists. Pharmacol Res 2022; 182: 106320. DOI: 10.1016/j.phrs.2022.106320

[42] Iacobellis G, Villasante Fricke AC. Effects of semaglutide versus dulaglutide on epicardial fat thickness in subjects with type 2 diabetes and obesity. J Endocr Soc 2020; 4: bvz042. DOI: 10.1210/jendso/bvz042

[43] Ji L, Dong X, Li Y et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as add-on to metformin in patients with type 2 diabetes in SUSTAIN China: A 30-week, double-blind, phase 3a, randomized trial. Diabetes Obes Metab 2021; 23: 404–414. DOI: 10.1111/dom.14232

[44] Shu Y, He X, Wu P et al. Gastrointestinal adverse events associated with semaglutide: A pharmacovigilance study based on FDA adverse event reporting system. Front Public Health 2022; 10: 996179. DOI: 10.3389/fpubh.2022.996179

[45] Wharton S, Calanna S, Davies M et al. Gastrointestinal tolerability of once-weekly semaglutide 2.4 mg in adults with overweight or obesity, and the relationship between gastrointestinal adverse events and weight loss. Diabetes Obes Metab 2022; 24: 94–105. DOI: 10.1111/dom.14551

[46] Bergmann NC, Davies MJ, Lingvay I et al. Semaglutide for the treatment of overweight and obesity: A review. Diabetes Obes Metab 2023; 25: 18–35. DOI: 10.1111/dom.14863

[47] Nagendra L, Bg H, Sharma M et al. Semaglutide and cancer: A systematic review and meta-analysis. Diabetes Metab Syndr 2023; 17: 102834. DOI: 10.1016/j.dsx.2023.102834

[48] European Medicines Agency. Guideline on clinical evaluation of medicinal products used in weight management. 2016; https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-evaluation-medicinal-products-used-weight-management-revision-1_en.pdf