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Sara Berg

Hannah Stickle

Suzanne J. Rose

Eric C. Nemec
Sacred Heart University

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Berg, S., Stickle, H., Rose, S. J., & Nemec, E. C. (2025). Discontinuing glucagon-like peptide-1 receptor agonists and body habitus: A systematic review and meta-analysis. *Obesity Reviews*, e13929. Doi: 10.1111/obr.13929

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Received: 27 March 2024 | Revised: 25 February 2025 | Accepted: 26 March 2025

DOI: 10.1111/obr.13929

REVIEW

Clinical Management

OBESITY Reviews WILEY

Discontinuing glucagon-like peptide-1 receptor agonists and body habitus: A systematic review and meta-analysis

Sara Berg[1] | Hannah Stickle[1] | Suzanne J. Rose[2] | Eric C. Nemec[1]

[1]College of Health Professions, Sacred Heart University, Fairfield, Connecticut, USA

[2]Department of Research & Discovery, Stamford Hospital, Stamford, Connecticut, USA

Correspondence
Eric C. Nemec, Sacred Heart University, 5151 Park Ave, Fairfield CT 0682, USA.
Email: nemece@sacredheart.edu

Summary

Research on Glucagon-like peptide 1 receptor agonist (GLP-1RA) has mainly focused on the efficacy of weight loss and not the long-term efficacy of weight loss maintenance. This systematic review and meta-analysis aims to evaluate the sustainability of weight loss of patients taking GLP-1RAs following the discontinuation of the drug. EBSCOhost was used to simultaneously search Academic Search Premier, CINHAL Ultimate, Cochrane Central Register of Controlled Trials, MEDLINE with full text, Cochrane Database of Systematic Reviews, and separate PubMed search was systematically investigated using a predetermined search strategy from inception to February 1st, 2024. The authors extracted data regarding body weight change from baseline on treatment and off treatment, change in waist circumference from baseline on and off treatment, and change in BMI from baseline on and off treatment. Meta-analysis was conducted using RevMan (version 5.4) to calculate pooled mean differences using a Der Simonian-Laird Random Effects model. ResultsThe initial search yielded 497 relevant articles and, after screening, retained 8 randomized controlled trials comprised of 2372 participants, all with a BMI ≥ 27 kg/m^2. After discontinuing GLP-1RA therapy, weight regain was proportional to the original weight loss. Participants who took liraglutide regained 2.20 kg (95% CI 1.69 to 2.70, $P < 0.00001$), and participants taking semaglutide/tirzepatide regained 9.69 kg (95% CI 5.78 to 13.60, $P < 0.00001$). This systematic review and meta-analysis show that significant weight is regained after discontinuing GLP-1RA treatment, which should be discussed when stopping therapy.

Practitioner Points: Question: Does discontinuation of Glucagon-like peptide 1 receptor agonist (GLP-1RA) treatment lead to significant weight gain?
Findings: In this systematic review and meta-analysis, discontinuing GLP-1RA treatment led to a pooled overall mean weight regain of 2.20 kg in participants taking liraglutide and 9.69 kg in those patients prescribed semaglutide/tirzepatide. The proportion of weight regained was proportional to the amount originally lost.

Abbreviations: GLP-1RA, Glucagon-like peptide-1 receptor agonists; kg, kilogram; BMI, Body Mass Index; RevMan, Review Manager; CI, Confidence Interval; GIP, Glucose-dependent insulinotropic polypeptide; FDA, Food and Drug Administration; DDP4, Dipeptidyl peptidase-4; MD, Mean Difference; RoB, Risk of bias; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; A1C, Glycated hemoglobin; ALT, Alanine aminotransferase; AST, Aspartate transferase; CRP, C-reactive protein; LFF, Liver Fat Fraction; mg, milligram.

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Meaning: Discontinuation of GLP-1RA treatment leads to weight regain, regardless of lifestyle interventions, and should therefore be considered a chronic therapy to prevent weight regain and associated undesirable outcomes related to obesity.

KEYWORDS
GLP-1RA, GLP-1RA discontinuation, glucagon-like peptide 1 receptor agonist, obesity, weight gain, weight-reducing drugs

1 | INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1RA) are approved for the treatment of type 2 diabetes mellitus and obesity by the Food and Drug Administration (FDA).[1] Of the GLP-1RAs, semaglutide and liraglutide have the most significant effect on weight loss,[2] with the seminal STEP 8 clinical trial reporting semaglutide at the maximal dose of 2.4 mg had a statistically significant greater effect on reduction in body weight from baseline when compared to the maximal dose of liraglutide (3.0 mg)[3] Tirzepatide is a dual GLP-1RA and glucose-dependent insulinotropic polypeptide (GIP) co-agonist, otherwise known as GIP/GLP-1RA.[4] GIPs have a similar method of action as GLP-1RAs and, when combined, create a synergistic effect resulting in increased weight loss similar in effect to those observed with semaglutide.[4,5]

Roughly, 50% of persons with type 2 diabetes and 68% of those engaging in weight loss care who start a GLP-1RA are reported to discontinue treatment after 1 year.[6,7] For many patients, the reason for stopping the medication is multifactorial. Along with the many potential side effects and injection fatigue, shortages and expenses of GLP-1RAs pose a threat to the continuation of treatments.[8,9] In addition, GLP-1RA therapy can be cost-prohibitive[10] as many insurance companies will not cover GLP-1RAs without an existing diagnosis of type 2 diabetes mellitus or cardiac risk factors.

Studies that have explored weight loss during GLP-1RA treatment have noted a clear need for research focused on the long-term efficacy of weight loss maintenance,[11] as early follow-up studies on GLP-1 treatment have observed that patients regain weight upon discontinuation.[12] Recently, pharmacokinetic/pharmacodynamic modeling, including data from three randomized controlled trials, predicted how much weight one would lose on GLP-1RA treatment and how much a patient would regain after discontinuation.[13] However, there are limited definitive data available to quantify on how much weight a patient will potentially regain following discontinuation of GLP-1RA. Upon careful review of the literature, there are no systematic reviews or meta-analyses evaluating weight loss maintenance following the discontinuation of GLP-1RAs to guide current practice. This systematic review and meta-analysis aims to evaluate the sustainability of weight loss of patients taking GLP-1RAs following the discontinuation of the drug.

2 | METHODS

An ethics statement is not applicable because this study is based exclusively on published literature.

A systematic literature search was performed utilizing EBSCOhost to simultaneously search Academic Search Premier, CINHAL Ultimate, Cochrane Central Register of Controlled Trials, MEDLINE with full text, and Cochrane Database of Systematic Reviews; PubMed was also searched concurrently (See appendix for search strategy) The search was limited to include articles between 2015 and February 1, 2024, based on FDA approval for GLP-1RAs for chronic weight management in December 2014.[14] A gray literature search was performed using similar keyword searches of clinicaltrials.gov and Google Scholar. References of included articles were reviewed for additional articles that may be relevant to this literature. Search results were exported into the Covidence platform to screen for eligibility.

Two independent reviewers (SB and HL) screened titles and abstracts for eligibility based on the following inclusion criteria: written in English, randomized controlled trials, and patients previously taking a GLP-1RA. The exclusion criteria included animal studies, post-bariatric surgery patients, patients taking DDP4 inhibitors, and measured outcomes that did not include weight. Articles that met eligibility were then screened as full text for relevancy.

Full-text articles that met inclusion and exclusion criteria were extracted for systematic review through the Covidence platform by two independent reviewers (SB and HL). Extracted data included article title, study ID, study design, inclusion criteria, intervention, follow-up period length, comorbidities focused on, and secondary outcomes. Statistics including mean, standard deviation, and 95% confidence intervals were provided for age, sample size, baseline body weight, baseline waist circumference, baseline body mass index (BMI), body weight change from baseline on treatment and off treatment, change in waist circumference from baseline on and off treatment, and change in BMI from baseline on and off treatment.

Review Manager (version 5.4) was used to compare mean differences of outcomes using a Der Simonian-Laird Random Effects model.[15] The mean difference (MD) for changes in weight, waist circumference, and BMI was calculated with a 95% confidence interval (CI) for continuous variables to combine trials.[16] The random effects model was applied to estimate the pooled effect for included studies. Outcome measures of $p < 0.05$ were considered statistically

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significant. According to the Cochrane Collaboration recommendations, an I^2 of 50%–75% was classified as substantial heterogeneity, and 75%–100% was classified as considerable heterogeneity.[17]

Risk of bias was evaluated using the Cochrane Risk of Bias tool for randomized controlled trials (RoB 2.0). The articles were judged as low risk, high risk, or with some concerns. Tables of bias risk were generated using the RoB-vis tool.[18] The review protocol was prospectively registered with INPLASY (DOI number: 10.37766/inplasy2024.2.0004).

3 | RESULTS

3.1 | Study selection

The database search yielded 497 results, with 16 full-text articles and 1 conference abstract screened for eligibility. Based on our criteria, 8 randomized controlled trials were retained for this literature review and meta-analysis (see PRISMA Flow in Figure S1).

3.2 | Study characteristics

The eight studies utilized in this review were published between July 2015 and December 2023.[5,12,19–24] Six were randomized, double-blind, controlled trials with 1769 participants in the drug cessation group.[12,20–24] These studies randomized participants to continue treatment with GLP-1RA or a placebo injection with subsequent patient follow-up. Two articles were randomized, double-blind withdrawal studies with 603 participants in the drug cessation group.[5,19] These studies had a run-in period where all participants received GLP-1RA treatment followed by randomization to either continue GLP-1RA treatment or receive a placebo with a specific follow-up period to evaluate the outcomes of stopping a GLP-1RA. All studies used weight loss dosing for the GLP-1RA intervention, which are 3.0 mg for liraglutide in five studies,[20–24] 2.4 mg for semaglutide in two studies,[5,12] and 10 mg or 15 mg for tirzepatide in one study.[19]

The length of treatment ranged from 20 to 160 weeks before GLP-1RA treatment ended. All studies used lifestyle changes such as a low-calorie diet and increased physical activity with the treatment and placebo groups. During the off-treatment periods, one study stopped all lifestyle modifications in addition to the interventions.[12,23] All other studies continued lifestyle modifications during the off-treatment periods.[5,19–21,23,24] Follow-up periods for all studies were 12,[20–22] 26,[23,24] 48,[5,12] or 52[19] weeks. The studies were assigned to subgroups for analysis based on weight reduction efficacy and the follow-up period post-discontinuation of GLP-1RAs.

Outcome groups were defined as the liraglutide group[3] and a pooled analysis of semaglutide/tirzepatide group based upon percentage of weight initially lost by participants.[5,25] The subgroups were categorized as short-term and long-term outcomes. The short-term subgroup was defined as 12 weeks for the liraglutide group[20–22] The long-term subgroup was defined as 26 weeks for the liraglutide group[23,24] and 48–52 weeks for the semaglutide/tirzepatide group.[12,19] The age range for the articles was wide and included both pediatric[23] and adult[5,12,19–22,24] participants.

While all articles had participants who were obese or overweight, each article focused on a specific comorbidity, which included either type 2 diabetes,[20] pre-diabetes,[21] obesity,[5,12,19,22,23] or obesity with non-alcoholic fatty liver disease.[24] The baseline mean weight of all studies ranged from 99.3 kg to 107.5 kg. Body size outcomes included weight in all eight studies,[5,12,19–24] waist circumference in six studies,[5,19–22,24] and body mass index (BMI) in six studies.[5,12,19,20,23,24] Study characteristics of the articles included are summarized in Table 1.

3.3 | Risk of bias

The risk of bias of included articles was evaluated using the Cochrane Risk of Bias tool for randomized controlled trials (RoB 2.0)[26] and assessed as low for all studies[5,12,19–24] (see Figure S2).

3.4 | GLP-1 receptor agonist treatment vs discontinuation: mean weight

Mean weight regain was assessed after discontinuing semaglutide/tirzepatide in 3 studies that included 800 participants[5,12,19](Figure 1). The pooled overall mean weight regain after semaglutide/tirzepatide discontinuation was a significant finding at 9.69 kg. Before discontinuation, mean weight loss ranged from 11.1 to 21.1 kg. Pooled data on semaglutide/tirzepatide discontinuation had considerable heterogeneity ($I^2 = 97\%$) (Figure 1a). Mean weight regain after discontinuation of liraglutide was 2.20 kg based on data from 5 studies, inclusive of 1572 participants.[20–24] Before discontinuation, mean weight loss ranged from 2.7 to 9.34 kg. Pooled data for liraglutide discontinuation were homogonous ($I^2 = 0\%$) (Figure 1b).

3.5 | GLP-1 receptor agonist treatment VS discontinuation: mean waist circumference

The mean change in waist circumference from baseline after semaglutide/tirzepatide discontinuation was measured in 2 studies and included 603 participants who originally lost between 10.1 and 17.4 cm (Figure 2a).[5,19] The pooled overall increase for waist circumference between weeks 48 and 52 of semaglutide/tirzepatide discontinuation, was significant at 5.78 cm[5,19] though pooled data for semaglutide/tirzepatide had considerable heterogeneity ($I^2 = 97\%$) (Figure 2a). The mean change in waist circumference from baseline after liraglutide discontinuation was measured in 4 studies and included 1473 participants who originally lost between 5.6 and 9.4 cm (Figure 2b).[20–22,24] After Liraglutide discontinuation, the pooled overall waist circumference regain was significant at 1.37 cm and homogonous ($I^2 = 0\%$) (Figure 2b).[20–22,24]

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TABLE 1 Summary of study characteristics (abbreviations: A1C = glycated hemoglobin, ALT = alanine aminotransferase, AST = aspartate transferase, BMI = body mass index, CRP = C-reactive protein, kg = kilogram, LFF = liver fat fraction, mg = milligram).

Follow up	Author, publication date study design	Intervention and drug cessation sample size	Comorbidity	Mean age of drug cessation group	Baseline mean weight of drug cessation group	Body size outcomes	Secondary outcomes
Semaglutide/Tirzepatide							
Long term (48–52 weeks)	Rubino, 2021.[5] Randomized Controlled Withdrawal Study	Semaglutide 2.4 mg N = 268	Obesity	46 (12)	107.2 (22.7)	1) weight (kg) 2) waist circumference (cm) 3) BMI (kg/m^2)	Waist circumference, systolic blood pressure, physical functioning
	Wilding, 2022.[12] Randomized Controlled Trial	Semaglutide 2.4 mg N = 197	Obesity	48 (12)	105.6 (21.8)	1) weight (kg) 2) BMI (kg/m^2)	Blood pressure, lipid panel, hemoglobin A1C%, CRP
	Aronne, 2024.[19] Randomized Controlled Withdrawal Study	Tirzepatide 10 or 15 mg N = 335	Obesity	48 (12)	107.3 (22.3)	1) weight (kg) 2) waist circumference (cm) 3) BMI (kg/m^2)	Blood pressure, maintenance of 80% of weight loss in patients at week 88, lipid panel, fasting glucose, hemoglobin A1C%, quality of life
Liraglutide							
Short-term (12 weeks)	Davies, 2015.[20] Randomized Controlled Trial	Liraglutide 3.0 mg N = 324	Type 2 diabetes	55.0 (10.8)	105.7 (21.9)	1) weight (kg) 2) waist circumference (cm) 3) BMI (kg/m^2)	Blood pressure, lipid panel, fasting glucose, hemoglobin A1C%, cardiovascular biomarkers, quality of life
	le Roux, 2017.[21] Randomized Controlled Trial	Liraglutide 3.0 mg N = 783	Pre-diabetes	47.5 (11.7)	107.5 (21.6)	1) weight (kg) 2) waist circumference (cm)	Blood pressure, lipid panel, fasting glucose, hemoglobin A1C%, quality of life, cardiovascular biomarkers
	Pi-Sunyer, 2015.[22] Randomized Controlled Trial	Liraglutide 3.0 mg N = 351	Obesity	45.2 (12.1)	106.2 (21.2)	1) weight (kg) 2) waist circumference (cm)	Blood pressure, lipid panel, fasting glucose, hemoglobin A1C%, quality of life cardiovascular biomarkers
Long-term (26 weeks)	Kelly, 2020.[23] Randomized Controlled Trial	Liraglutide 3.0 mg N = 99	Obesity	14.6 (1.6)	99.3 (19.7)	1) weight (kg) 2) BMI (kg/m^2)	Body weight (kg), waist circumference, blood pressure, lipid panel, fasting insulin, CRP, quality of life
	Khoo, 2019.[24] Randomized Controlled Trial	Liraglutide 3.0 mg N = 15	Obesity w/non-alcoholic fatty liver disease	38.6 (8.2)	102.7 (16.2)	1) weight (kg) 2) waist circumference (cm) 3) BMI (kg/m^2)	Lipid panel, liver stiffness, ALT, AST, LFF, CRP

3.6 | GLP-1 receptor agonist treatment VS discontinuation: mean body mass index (BMI)

The mean change in BMI after semaglutide/tirzepatide treatment discontinuation was measured in 3 studies and included 800 participants who originally lost between 4 and 7.9 kg/m^2 (Figure 3a).[5,12,19] The pooled overall mean increase of BMI after semaglutide/tirzepatide discontinuation was highly significant at 3.59 (kg/m^2). The pooled data on semaglutide/tirzepatide discontinuation had considerable heterogeneity (97%) (Figure 3a). The mean change in BMI after liraglutide discontinuation was measured in 3 studies and included 438 participants who originally lost between 1 and 2.5 kg/m^2 (Figure 3b).[20,23,24] The pooled overall mean increase of BMI after liraglutide discontinuation was highly significant at 0.73 (kg/m^2). The pooled data on liraglutide discontinuation was homogonous (I^2 = 10%) (Figure 3b).

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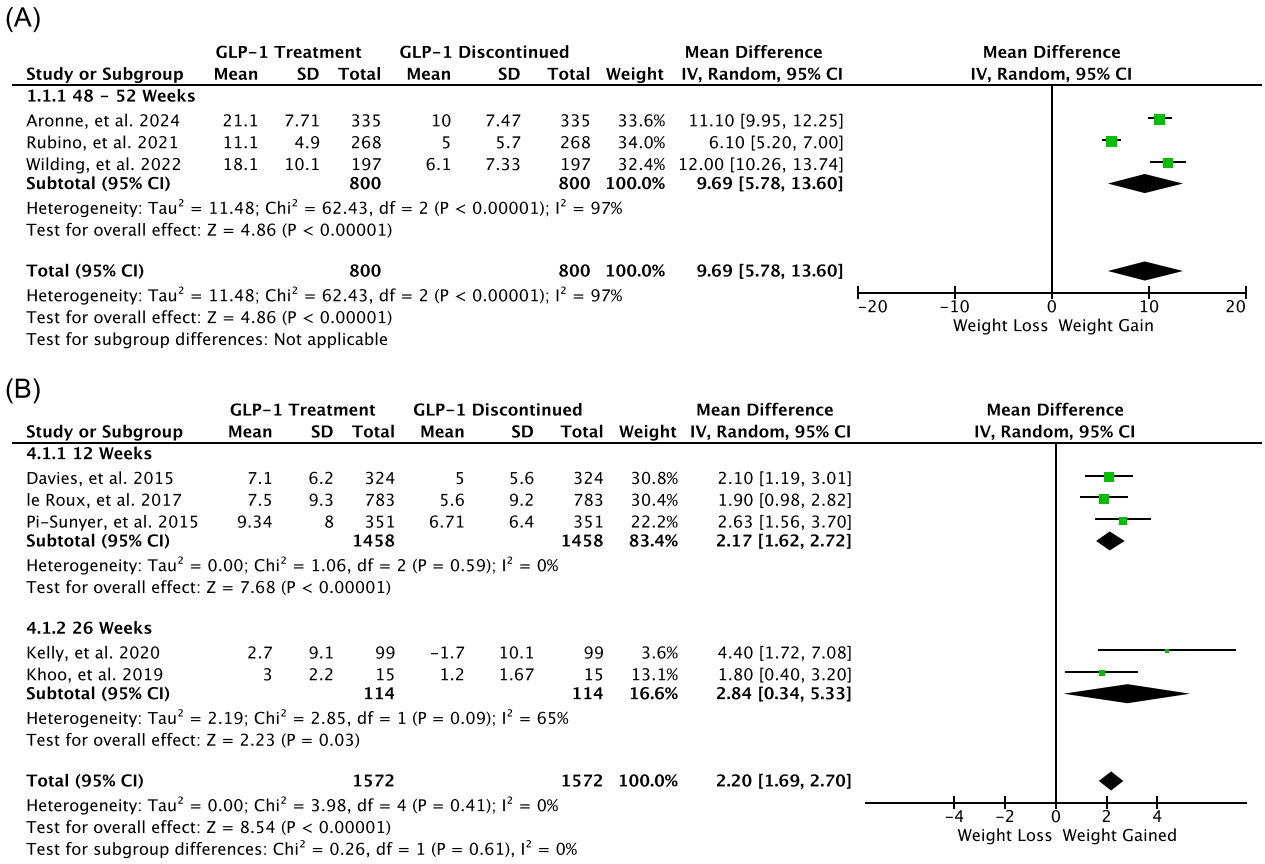


FIGURE 1 Mean difference of change in weight from baseline weight loss after GLP-1RA initiation versus regain after discontinuation. **a.** Mean difference of change in weight (kg) from baseline of semaglutide/tirzepatide treatment versus discontinuation. **b.** Mean difference of change in weight (kg) from baseline of liraglutide treatment versus discontinuation.

4 | DISCUSSION

4.1 | Summary of key findings

The percentage of weight and BMI that is regained from what was originally lost predictably increased between the short-term and long-term subgroups of liraglutide. In the short-term, after liraglutide discontinuation, participants regained between 25.3% and 29.6% of the weight that they lost on GLP-1 treatment, and in the long-term, between 60.0% and 163.0% of the weight was regained. Similarly, after semaglutide/tirzepatide discontinuation, participants regained between 52.6% and 63.5% of weight lost on treatment.

The percentage of BMI regained that was lost on GLP-1RA treatment was almost equal to corresponding weight regain in all but one study.[23] As time passes after the cessation of GLP-1RA treatment, the mean weight and BMI regain also increase, regardless of the GLP-1RA used. The weight regain shown, in addition to lifestyle modifications being continued in six[5,19–21,23,24] of the eight studies, shows that weight loss was not sustainable with long-term discontinuation of GLP-1RA therapy. All studies except Kelly et al (who had personalized nutrition counseling) employed the World Health Organization exercise and diet guidelines for lifestyle interventions and provided advice from a dietician or nutritionist; additionally, participants were encouraged to engage in 150 minutes of high-intensity exercise per week, and except for Wilding et al, to continue these after stopping GLP-1RA therapy. Thus, if participants continued lifestyle modifications as they were encouraged to do, they theoretically should have been able to keep the weight off. Yet, they still regained a significant portion of the weight lost. Meta-analysis shows calorie deficit is the primary weight loss driver, followed by macronutrient composition, and in these data, without the use of GLP-1RA, these dietary suggestions became challenging to adhere to.[27]

Overall, the proportion of waist circumference regained from the cessation of treatment to the end of the study was not similar to the proportion of weight and BMI regained. This was particularly true for GLP-1RA's liraglutide and semaglutide. After liraglutide discontinuation, between 16.1% and 18.4% of waist circumference was regained in the short term, and 19.6% was regained in the long term. 32.7% of waist circumference was regained in the semaglutide study. These percentages are smaller when compared to the percentages of regain of weight and BMI. Tirzepatide did not have the same effect and participants regained 47.7% of the waist circumference that was originally lost which was proportional to the weight and BMI regain.

Since waist circumference is not proportional to weight and BMI regain for semaglutide and liraglutide, this could mean that although weight is regained, the adipose tissue may be dispersed in other

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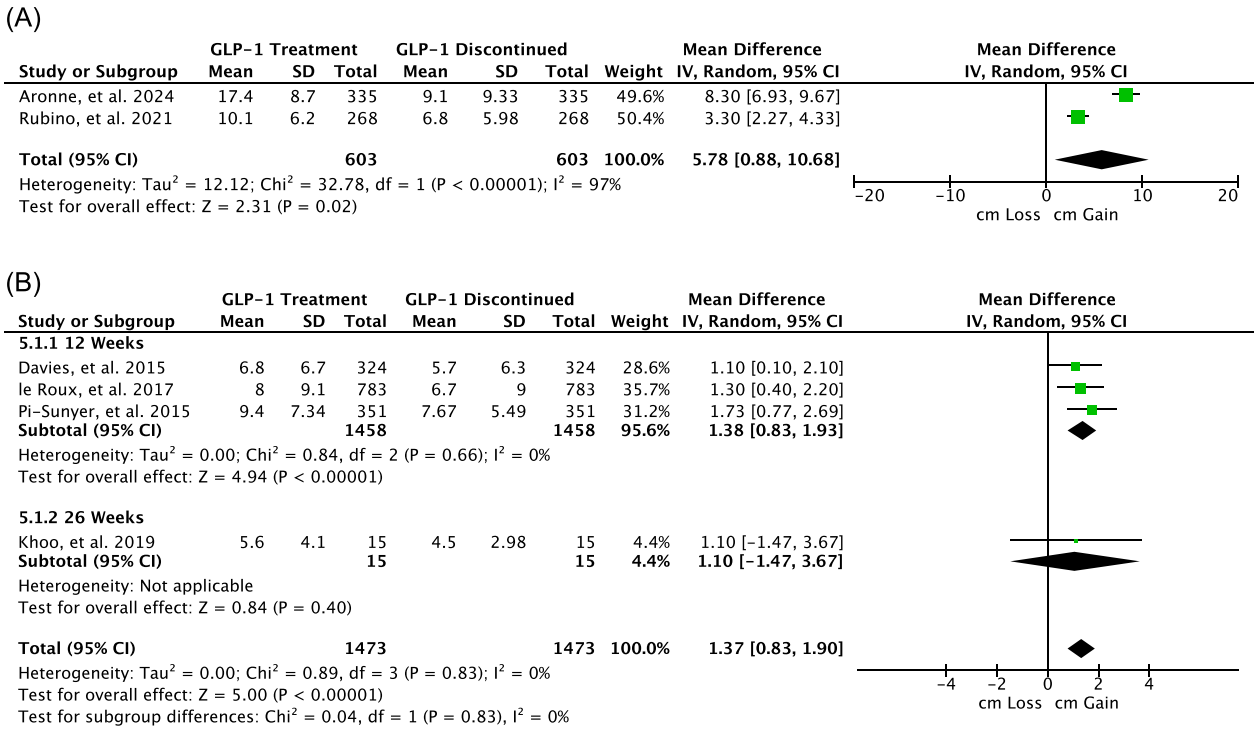


FIGURE 2 Mean difference of change in waist circumference from baseline weight loss after GLP-1RA initiation versus regain after discontinuation. **a.** Mean difference of change in waist circumference (cm) from baseline of semaglutide/tirzepatide treatment versus discontinuation. **b**. Mean difference of change in waist circumference (cm) from baseline of liraglutide treatment versus discontinuation.

forms, for instance as visceral, not subcutaneous, causing the appearance of waist circumference gain to be less apparent.[28] Excess visceral adipose tissue can pose a threat to cardiovascular health and is linked to worsening cardiovascular biomarkers.[28,29] Although cardiovascular biomarkers were not an outcome in this review, two studies did observe worsening of cardiovascular biomarkers after discontinuing GLP-1RA therapy.[5,12] Further studies are needed to assess changes in cardiovascular biomarkers and their relation to weight regain after discontinuation of therapy.

The corollary of the FDA's definition of clinical significance for weight loss was used to determine that gaining 5% of body weight from the end of treatment was clinically significant.[30] Weight regain was proportional to weight loss. Data from other meta-analyses suggest that semaglutide yields a mean weight reduction of 11.62 kg, tirzepatide 12.47 kg, and liraglutide 5.04 kg for liraglutide.[11,31,32] Similarly, readers can review original body habitus changes to compare outcomes by examining the "GLP-1 Treatment" columns of each forest plot. Semaglutide/tirzepatide showed a clinically significant percentage of body weight regain throughout all studies, ranging from 6.4% to 13.1%. The percentage of weight regained in the Liraglutide studies was not clinically significant, ranging from 1.9% to 2.7% short-term and 1.8 to 4.6% long-term. Interestingly, in the long-term subgroup, the percentage of body weight lost on treatment was not considered clinically significant according to the FDA's definition. It is possible that minimal weight loss affected the clinical significance of long-term weight regain, and due to this, further long-term studies are needed to determine if clinically significant weight regain occurs with liraglutide.

A recent study found that participants who engaged in supervised exercise during GLP-1RA treatment maintained weight loss more effectively one year after discontinuation than those who received GLP-1RA without an exercise intervention.[33] These findings support the intuitive conclusion that physical activity may be crucial in mitigating weight regain post-treatment. While our meta-analysis included studies where lifestyle interventions were part of the treatment phase, adherence data were unavailable, making it difficult to determine the long-term impact of exercise. Future studies should further explore the role of sustained exercise in preventing weight regain following GLP-1RA cessation.

This systematic review and meta-analysis show that body habitus outcomes (mean weight, waist circumference, and BMI) increased overall after cessation of GLP-1RA treatment regardless of lifestyle intervention, which continued in six of the eight included studies. After discontinuation, participants will regain some, if not all, of the weight they were able to lose while on GLP-1RA treatment. In contrast, it is seen in long-term efficacy studies that weight loss is maintained if GLP-1RA therapy is continued.[21,34] Therefore, these data support that GLP-1RA therapy should be considered chronic therapy.

Addressing Obstacles of Chronic Therapy.

These data show that the body habitus benefits of GLP-1RA therapy are lost without continued treatment; continued treatment has also been shown to maintain the benefits.[21,34] However, limitations

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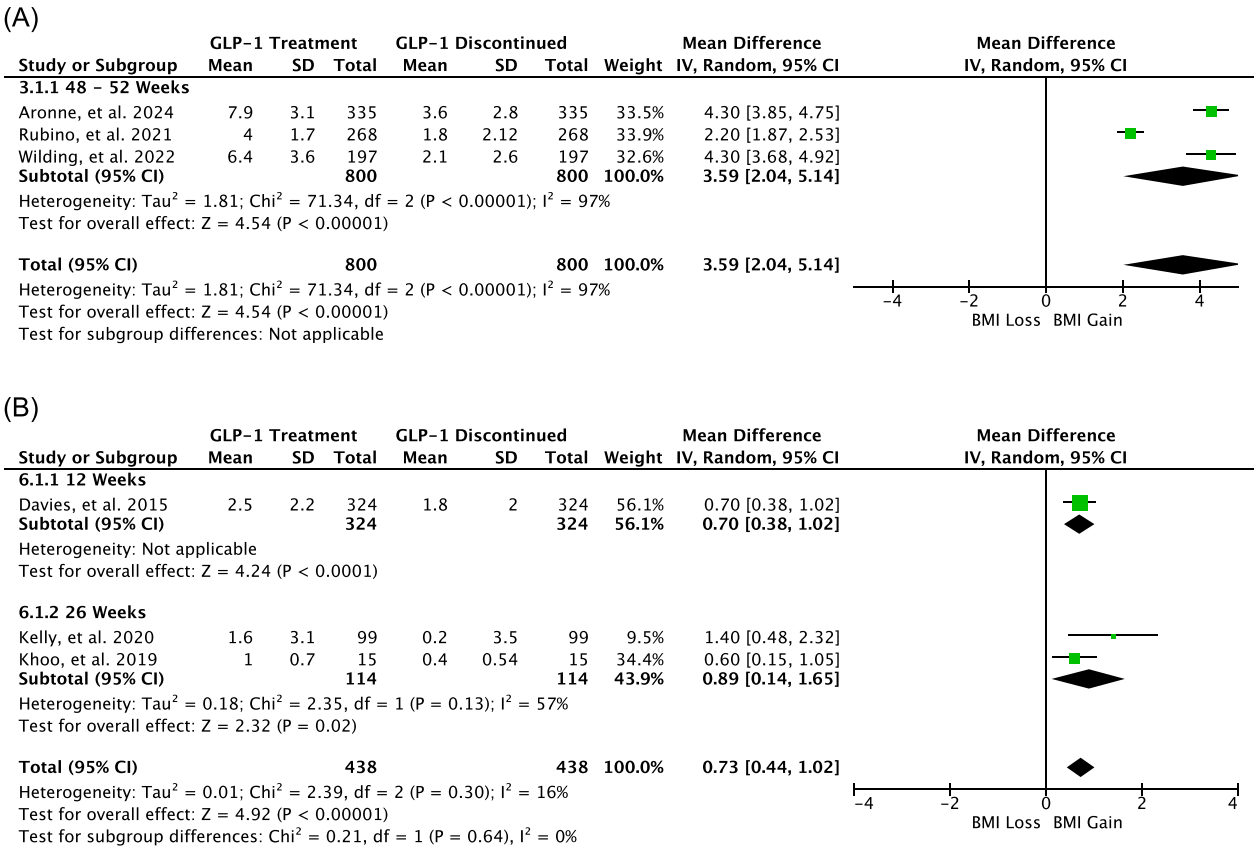


FIGURE 3 Mean difference of change in BMI from baseline weight loss after GLP-1RA initiation versus regain after discontinuation. **a.** Mean difference of change in BMI (kg/m^2) from baseline of semaglutide/tirzepatide treatment versus discontinuation. **b**. Mean difference of change in waist circumference (cm) from baseline of liraglutide treatment versus discontinuation.

such as cost, adverse effects, and route of administration have caused chronic treatment to be less attainable.[11] Currently, liraglutide, semaglutide, and tirzepatide cost (in United States Dollars) roughly $1325.00, $951.96, and $1041.75 for a 28-day supply, respectively.[10] This can be an out-of-pocket expense because many states' Medicaid programs do not cover GLP-1RA treatment for weight loss.[35] Currently, there are 16 states that cover GLP-1RA treatment for weight loss; however, many public insurance programs are moving to cease coverage.[35] The Centers for Medicare and Medicaid Services announced in 2024 that it would allow coverage of semaglutide under its Part D drug program for overweight patients with preexisting heart disease.[36] In Europe, insurance coverage of weight loss drugs varies widely by country and depends on national healthcare policies and the specific medications involved. German health authorities have traditionally categorized weight-loss drugs as lifestyle products, meaning they were not covered under statutory health insurance, although this stance is evolving, particularly for specific cases like stroke prevention.[37] In contrast, in the United Kingdom, the National Health Service (NHS) has approved the limited use of semaglutide for specific patients who meet certain criteria related to obesity and related conditions, but it is not universally available.[38]

The route of administration may also limit the ability to continue long-term treatment as currently GLP-1RAs for weight loss are administered through subcutaneous injection.[39] Semaglutide and tirzepatide are administered once weekly, while liraglutide is administered once daily.[1] The frequency of injections required makes adherence to the prescription more difficult. Currently, trials are being conducted exploring oral semaglutide for weight loss.[40] The hope is to increase long-term compliance with oral medication by eliminating the adverse effects of subcutaneous injection. Another common adverse effect, gastrointestinal upset, was unresolved with oral administration, and in some studies, the symptoms were more severe.[41]

Guidelines for addressing side effects include improving eating habits, adapting food composition to personal requirements, increasing exercise, and keeping a food diary to identify trigger foods.[42] This contributed to similar adherence rates between oral semaglutide, subcutaneous semaglutide, and liraglutide in the PIONEER and SUSTAIN trials.[41] Future long-term studies are necessary to determine if increased adherence can be achieved with oral therapy. Overcoming these barriers to treatment is needed to allow for long-term therapy of GLP-1RA.

4.2 | Strengths and Limitations of our study

This review had a robust sample size, including studies with a low risk of bias; however, despite similar efficacy, heterogeneity was

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seen in the pooled semaglutide and tirzepatide data. A stepwise removal of studies was performed to identify causes of heterogeneity. Rubino et al[5] had the largest influence, and when removed, the I^2 was 0% for both the weight regain and BMI pooled analyses. Given that Aronne et al and Wilding et al were homogenous ($I^2 = 0\%$) despite their investigating tirzepatide (a GLP-1RA/GIP co-agonist) and semaglutide (GLP1-RA), respectively, authors speculate this difference to be based on time of follow-up (52 vs. 48 weeks).[5,12,19] We did not expect 6 weeks to make a clinically significant difference. In addition, the unequal representation of semaglutide and tirzepatide compared to liraglutide was also a limitation. Only two studies of semaglutide and tirzepatide included waist circumference; therefore, outcomes related to the amount of time off-treatment could not be assessed in the meta-analysis. Finally, the Der Simonian and Laird meta-analysis methodology cannot reliably estimate heterogeneity when analyzing only a few studies.[43] However, no satisfactory universal method is currently available to perform meta-analyses in the case of very few studies, and other studies have suggested that given the sample size of these data, the random effects model as employed is among the best methodology.[43,44] Finally, while the included studies implemented structured lifestyle interventions, adherence data were not consistently reported. This is a significant limitation, as adherence to prescribed lifestyle changes likely influences weight regain after GLP-1RA discontinuation. Future research should focus on assessing adherence to lifestyle components and their impact on long-term weight maintenance to better inform clinical recommendations.

5 | CONCLUSION

This systematic review and meta-analysis detail the result of body habitus outcomes post GLP-1RA treatment cessation, demonstrating that discontinuation of GLP-1RA treatment leads to increased body size outcomes, regardless of lifestyle interventions. As more time passes off the drug regimen, the larger the body habitus outcomes increase; therefore, long-term studies are needed to quantify a trend in weight regain plateaus. Semaglutide or tirzepatide discontinuation causes a clinically meaningful weight regain, which was proportional to the original weight loss. GLP-1RA should be considered chronic therapy to prevent weight regain and associated undesirable outcomes related to obesity and type 2 diabetes.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

The authors declare that we have no relevant or material financial interests that relate to the research described in this paper.

ORCID

Suzanne J. Rose https://orcid.org/0000-0001-5770-826X
Eric C. Nemec https://orcid.org/0000-0001-7794-6732

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How to cite this article: Berg S, Stickle H, Rose SJ, Nemec EC. Discontinuing glucagon-like peptide-1 receptor agonists and body habitus: A systematic review and meta-analysis. *Obesity Reviews*. 2025;26(8):e13929. doi:10.1111/obr.13929

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