Trajectory of weight regain after cessation of GLP-1 receptor agonists: a systematic review and nonlinear meta-regression

Brajan Budini,[a,*,e] Steven Luo,[a,e] Martin Tam,[a] Isabel Stead,[a] Andrew Lee,[a] Angelica Akrami,[a] Antonio Vidal-Puig,[b,c,f] and Adrian Park[d,f]

[a]School of Clinical Medicine, University of Cambridge, Cambridge, UK
[b]Centro de Investigación Príncipe Felipe, CIBERDEM, Valencia, Spain
[c]Institute of Metabolic Science, University of Cambridge, Cambridge, UK
[d]Addenbrooke's Hospital, NIHR Cambridge Biomedical Research Centre, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

eClinicalMedicine
2026;93: 103796

Published Online 4 March 2026
https://doi.org/10.1016/j.eclinm.2026.103796

Summary

Background Glucagon-like peptide 1 receptor agonists (GLP-1RAs) have emerged as breakthrough agents for weight loss. However, discontinuation is common, and clinical trials have demonstrated significant weight regain following cessation. In this systematic review, we aimed to characterise the trajectory of weight regain after GLP-1RA cessation.

Methods This systematic review and meta-regression analysis followed Cochrane and PRISMA guidelines. We searched MEDLINE, Embase, Cochrane Library, Scopus and Web of Science from inception to August 28, 2025 for randomised controlled trials (RCTs), non-randomised interventional studies and observational studies reporting weight outcomes after cessation of GLP-1RAs in adults with overweight or obesity. Weight regain was the primary outcome and was modelled using nonlinear regression. Secondary, exploratory outcomes included HbA1c and systolic blood pressure. The study protocol is registered with PROSPERO (CRD420250631751).

Findings A total of 48 relevant studies were included. Weight consistently rebounded after cessation of GLP-1RAs. Six RCTs with 3236 participants were included in the nonlinear meta-regression, which utilised a mixed-effect exponential recovery model with random effects applied to the rate constant. At 1 year post-cessation, 60% of the weight lost during treatment was regained. Beyond 52 weeks, weight trajectories were extrapolated, with weight regain estimated to plateau at 75.3% (95% CI 68.9–81.6) of the weight lost on treatment. The rate constant was 0.0302 per week (95% CI 0.0202–0.0401), corresponding to a half-life of 23.0 weeks (95% CI 17.3–34.3). Most studies were assessed to have a moderate risk of bias.

Interpretation GLP-1RA cessation is associated with a predictable and decelerating pattern of weight regain, which appears to plateau below pre-treatment levels, suggesting that partial weight-loss benefit may persist long-term but is substantially attenuated.

Funding None.

Copyright © 2026 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Keywords: GLP-1RAs; Weight regain; Obesity; Treatment discontinuation; Anti-obesity pharmacotherapy; Meta-regression

Introduction

The increasing prevalence of obesity represents a significant public health concern. Worldwide, more than one billion individuals are living with obesity.[1] At the individual level, obesity has been linked to poor health outcomes and is associated with comorbidities including type 2 diabetes, cardiovascular disease, and metabolic dysfunction-associated steatotic liver disease.

Weight loss of 5–10% can mitigate obesity-related health complications.[2] For patients with a body mass index (BMI) of 35 kg/m^2 or higher, evidence-based guidance[3] recommends a greater weight loss of

*Corresponding author.
E-mail address: bb616@cam.ac.uk (B. Budini).
[e]These authors contributed equally to this work. (co-first authors).
[f]These authors contributed equally to this work. (co-senior authors).

Research in context

Evidence before this study

Glucagon-like peptide 1 receptor agonists (GLP-1RAs) have emerged as highly effective weight loss medications for individuals with overweight or obesity. However, rates of discontinuation are high due to cost and poor tolerability. The risk of weight regain following cessation remains a pressing question for patients on GLP-1RA treatment. Randomised controlled trials such as STEP 4 and SURMOUNT-4 have demonstrated that significant weight regain occurs after cessation, but no large-scale trials have tracked weight beyond 1 year after treatment discontinuation. To evaluate the existing literature, we searched PubMed for systematic reviews using search terms including 'GLP-1RA', 'cessation', 'discontinuation' and 'weight regain'. We identified two reviews that reported point estimates of weight regain, with one of these also providing a graphical trajectory of weight regain based on pooled weighted mean differences at specific time points post-cessation. However, neither review applied modelling analysis to characterise the trajectory of weight regain or extrapolate the temporal profile beyond reported post-cessation time points in trials.

Added value of this study

This review represents the most comprehensive collection of evidence on post-GLP-1RA weight outcomes to date. To our knowledge, this is the first systematic review to parametrically model the trajectory of weight regain over time after discontinuation of GLP-1RA therapy. We identified a regain curve in which 60% of the weight lost during treatment is regained 1 year after cessation. Extrapolation of our model provides novel insights into weight outcomes beyond 1 year, predicting that weight regain plateaus at 75% of the weight lost during treatment.

Implications of all the available evidence

The findings of this study demonstrate that individuals who discontinue GLP-1RA therapy will regain a majority of the weight lost during treatment. Currently, prescribing guidelines for GLP-1RAs are inconsistent and largely inadequate in addressing the risk of weight regain following treatment cessation. In the UK, for example, the National Institute for Health and Care Excellence recommends that semaglutide be prescribed for weight loss for a maximum duration of 2 years, but no such limit is set for tirzepatide. Given the growing reliance on GLP-1RAs for weight management and the high discontinuation rates reported in previous studies, physicians and regulatory bodies must utilise alternative dosing strategies to help mitigate the risk of weight regain. Current evidence suggests that adopting an individualised dose-tapering approach can limit weight regain, but more research is needed to develop strategies for reliable long-term weight management after GLP-1RA cessation.

15–20% for sustained improvement in comorbidity. Lifestyle modifications, primarily diet and exercise, have historically been the cornerstone of weight management. However, despite being widely recommended, lifestyle modification alone is generally ineffective.[4]

Until recently, pharmacological options for weight loss were limited, with either poor efficacy or tolerability.[5] In the past few years, however, glucagon-like peptide 1 receptor agonists (GLP-1RAs) have emerged as highly effective weight loss drugs; clinical trials have demonstrated substantial weight losses of 15–20% with agents such as semaglutide and tirzepatide.[6,7] In addition, patients treated with GLP-1RAs experience improvements in cardiometabolic parameters, including blood pressure, HbA1c, LDL, and triglycerides.[6]

Despite the successes of GLP-1RAs, approximately half of patients who initiate them discontinue within the first year,[8] likely due to their potential gastrointestinal side effects as well as limited access under insurance coverage policies and national prescribing guidelines.

Outcomes after discontinuing GLP-1RAs have been underexplored in the literature. Two reviews[9,10] reported weight regain after GLP-1RA cessation but neither modelled the trajectory of weight over time. While clinical trials such as STEP 4[11] and SURMOUNT-4[12] have provided insights into post-cessation outcomes, additional relevant data exist across a wider body of trials with greater diversity in drugs and populations. Understanding the nature of weight regain could aid the development of strategies to maintain weight loss after cessation. Therefore, this review aimed to synthesise existing evidence and characterise the typical trajectory of weight regain following cessation of GLP-1RA treatment.

Methods

Search strategy and selection criteria

This systematic review and meta-regression followed the Cochrane Handbook for Systematic Reviews. Findings were reported according to PRISMA guidelines. The protocol is registered with PROSPERO (CRD420250631751).

SL conducted a systematic search in MEDLINE, Embase, Cochrane Library, Scopus and Web of Science from their inception to Aug 28, 2025. We aimed to identify studies which tracked weight outcomes in patients following discontinuation of GLP-1RA therapy. A

broad search strategy was used because post-cessation outcomes were often absent from abstracts despite being reported in full texts or supplements.

The search queries comprised variations of the term 'glucagon-like peptide 1 receptor agonist' in combination with keywords related to weight regain and treatment cessation. In addition, supplementary searches were conducted by SL in Google Search and Google Scholar to identify further relevant studies not included in the primary databases. Conference abstracts and other grey literature were included if they met the inclusion criteria. Protocol papers and conference abstracts were followed up for full-text publications which, if eligible, were subsequently included in the review. Non-English studies and reviews were excluded from the search results. The complete search strategy is provided in the Appendix (p. 2).

Citations were imported into EndNote, deduplicated and then uploaded to Rayyan for screening. Six authors conducted title and abstract screening as well as full-text screening. Two reviewers independently screened each record and conflicts were resolved through discussion.

Studies were eligible for inclusion if they were randomised controlled trials (RCTs), non-randomised interventional studies or observational studies that reported weight outcomes following cessation of GLP-1RA treatment in adults with overweight or obesity, defined as a BMI of $\geq$25 kg/m^2 or $\geq$23 kg/m^2 for specific populations. Studies were required to have a treatment period of at least 8 weeks and a post-cessation follow-up period of at least 4 weeks, and could not include co-treatment with other FDA-approved weight loss drugs. Case reports, protocol-only publications, reviews, editorials and non-English publications were excluded.

Outcomes

The primary outcome was percentage weight regain, defined as the percentage of weight regained after treatment cessation relative to the weight lost at the end of treatment. This was calculated using end-of-treatment weight loss data and the weight reported at any post-cessation time point for which data were available. We adopted this approach to normalise for differences in the absolute amount of weight lost, which varied between studies. Secondary outcomes included post-cessation changes in HbA1c and systolic blood pressure (SBP). These outcomes were exploratory and studies were not required to report them for inclusion in the review.

Data extraction and risk of bias assessment

Risk of bias was assessed using the Cochrane RoB 2 tool for RCTs and the Cochrane ROBINS-I tool for non-randomised studies. Risk of bias assessments were performed by BB, IS and SL, with each study being independently assessed by two reviewers. Conflicts were resolved through discussion. Additionally, the quality of evidence for the six RCTs included in the meta-regression was evaluated using the GRADE approach.

Structured data extraction was performed using Google Sheets. Extracted variables included weight, HbA1c and SBP at baseline and follow-up at all available time points. Data values were independently extracted by two reviewers with discrepancies resolved by discussion. For each observation, we recorded the sample size, mean and standard error of the mean (SEM). Where data were presented graphically, we used WebPlotDigitizer to extract numerical values.

Statistical analysis

In this meta-regression, we aimed to characterise the trajectory of weight regain following GLP-1RA treatment cessation. To ensure reliable modelling, we filtered down the 48 included studies to include only those high-quality publications which comprehensively reported on post-cessation weight data. Our criteria required that studies be randomised, enrol a sufficient sample size in the treatment arm (n $\geq$ 100), report substantial on-treatment weight loss ($\geq$3 kg) and have at least two post-cessation data points or one data point after 12 weeks. Studies that did not meet these criteria introduced noise into the modelled weight trajectories and were deemed less reliable for interpretation. Two outlier studies were excluded to preserve comparability: one[13] which focused on a population with type 2 diabetes, and another[14] which investigated beinaglutide, a short-acting GLP-1RA with limited regulatory approval and markedly distinct pharmacokinetics.[15] Ultimately, six studies[6,7,11,12,16,17] were included in the meta-regression (Table 1).

Due to significant variability in reported post-cessation time points between studies, we opted to model weight regain as a continuous trajectory using all available time points. In major trials assessing weight following cessation, namely STEP 1,[6] STEP 4[11] and SURMOUNT-4,[12] we noted that weight regain resembled an exponential recovery curve approaching an asymptote. This observation is consistent with established first-order kinetic models of weight change, which predict rapid early changes followed by a gradual plateau as a new steady state is reached.[18] Therefore, we adopted an exponential recovery function for use in regression analysis.

Percentage weight regain was modelled as a function of time with the following formula:

$$R(t) = A\left(1 - e^{-kt}\right)$$

where $R(t)$ is the percentage of weight regained at time t weeks, A is the asymptotic maximum weight regain, and k is the recovery rate constant. A was modelled with

	STEP 1[6]	STEP 4[11]	STEP 10[17]	SURMOUNT-1[7]			SURMOUNT-4[12]	SCALE obesity[16]
GLP-1RA	Semaglutide	Semaglutide	Semaglutide	Tirzepatide			Tirzepatide	Liraglutide
Dosing[a]	2.4 mg once-weekly	2.4 mg once-weekly	2.4 mg once-weekly	5 mg once-weekly	10 mg once-weekly	15 mg once-weekly	10 or 15 mg once-weekly	3 mg once-daily
Cohort size[b]	228	268	138	247	262	253	335	1505
Treatment length (weeks)	68	20	52	176	176	176	36	160
Follow-up length (weeks)	52	48	28	17	17	17	52	12
Age	48 (12)	46 (12)	53 (11)	49 (12)	47 (12)	48 (12)	48 (12)	48 (12)
Sex (% female)	66.7	76.5	72.5	64.8	64.1	63.6	70.7	75.8
BMI (kg/m^2)	37.6 (7.0)	38.4 (6.9)	39.9 (6.6)	37.8 (6.6)	39.0 (7.2)	39.2 (7.4)	38.4 (6.6)	38.8 (6.4)
Weight (kg)								
Baseline	105.6 (21.8)	107.2 (22.7)	111.9 (21.5)	104.6 (21.9)	108.9 (23.9)	108.6 (25.4)	107.3 (22.3)	107.5 (21.6)
Change[c]	−17.1	−11.0	−13.9	−15.4	−19.9	−22.9	−20.0	−6.1
Baseline HbA1C (%)	5.7 (0.3)	5.7 (0.3)	5.9 (0.3)	5.8 (0.3)	5.7 (0.3)	5.8 (0.4)	5.5 (0.4)	5.8 (0.3)
Baseline SBP (mmHg)	129 (14)	127 (14)	131 (15)	127 (12)	125 (13)	125 (13)	126 (13)	125 (13)

Data are reported as mean (standard deviation). GLP-1RA, glucagon-like peptide 1 receptor agonist; BMI, body mass index; SBP, systolic blood pressure. [a]All drugs were administered via subcutaneous injection. [b]Includes only those patients in the treatment arm who discontinued GLP-1RA therapy. [c]Percentage of weight lost at the end of the treatment period.

Table 1: **Baseline characteristics for the trials included in the meta-regression analysis.**

a fixed effect across all studies. k was modelled with fixed and study-level random effects to estimate the mean effect across all studies and account for between-study heterogeneity respectively. Inverse-variance weighting was applied using the SEM of each observation. Additionally, between-study heterogeneity in k was quantified as the standard deviation of the random effects, τ. Model fit was assessed using the root mean square error (RMSE) and Akaike information criterion (AIC). Multiple sensitivity analyses were performed and are presented in the Appendix (pp. 11–19), including alternative random effects models, leave-one-study-out analysis, and Monte Carlo simulation of digitisation error. Key findings were robust across all analyses.

Data analysis and visualisation were conducted using R (version 4.3.2) with the *nlme* and *ggplot2* packages.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and was responsible for the final decision to submit the manuscript for publication.

Results

The study selection process is outlined in Fig. 1. The initial search yielded 6574 records. After deduplication and screening, 48 relevant studies were included in the review, comprising 36 RCTs and 12 non-randomised studies.

All studies reported post-cessation weight data in overweight and obese populations, with some focussing on comorbidities such as type 2 diabetes. Treatment durations ranged from 10 to 104 weeks, and post-cessation follow-up durations spanned from 4 to 104 weeks. Interventions included liraglutide, semaglutide, tirzepatide, and other GLP-1RAs. A complete summary of the included studies is provided in the Appendix (pp. 3–6).

Six RCTs were included in a mixed-effects exponential recovery regression to characterise the trajectory of weight regain. These trials included a total of 3236 participants with longitudinal data on weight regain up to 52 weeks after discontinuation of GLP-1RAs. The baseline characteristics of these trials are summarised in Table 1.

The estimated fixed effects were a maximum percentage weight regain (A) of 75.3% (95% CI 68.9–81.6) and a recovery rate constant (k) of 0.0302 per week (95% CI 0.0202–0.0401), corresponding to a half-life of 23.0 weeks (95% CI 17.3–34.3). The standard deviation (τ) of the study-level random effects on k was 0.0101. Model fit was acceptable, with an RMSE of 7.54 percentage points based on fixed-effect predictions.

The fitted trajectories are shown in Fig. 2. The model estimated a rapid initial rate of weight regain which progressively slowed and began to plateau at around 60 weeks. At 52 weeks, the weight regain was 60% of the original weight loss or 79% of the estimated maximum weight regain. Weight regain trajectories appeared broadly similar across trials of liraglutide, semaglutide and tirzepatide.

In our broader review, all studies reported weight reductions after treatment with GLP-1RAs; however, the magnitude of weight loss ranged from approximately 1 to 20% of the pre-treatment baseline. Variation

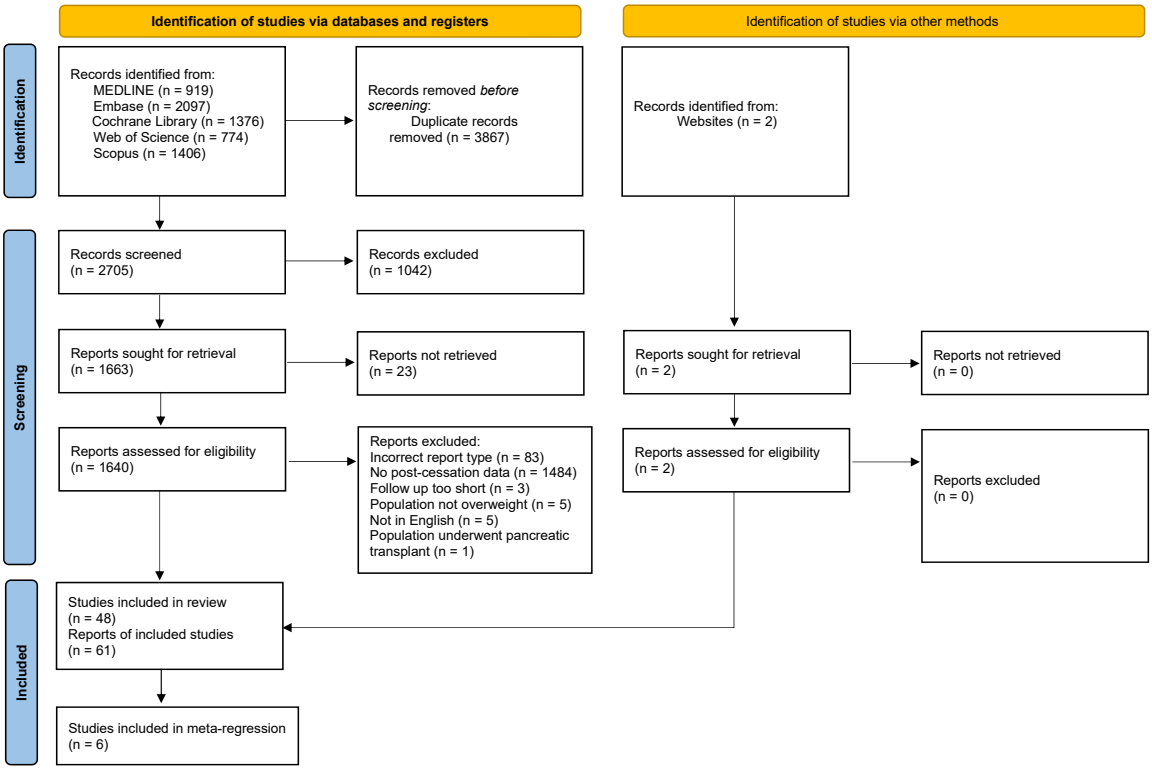


Fig. 1: PRISMA 2020 flow diagram of study selection.

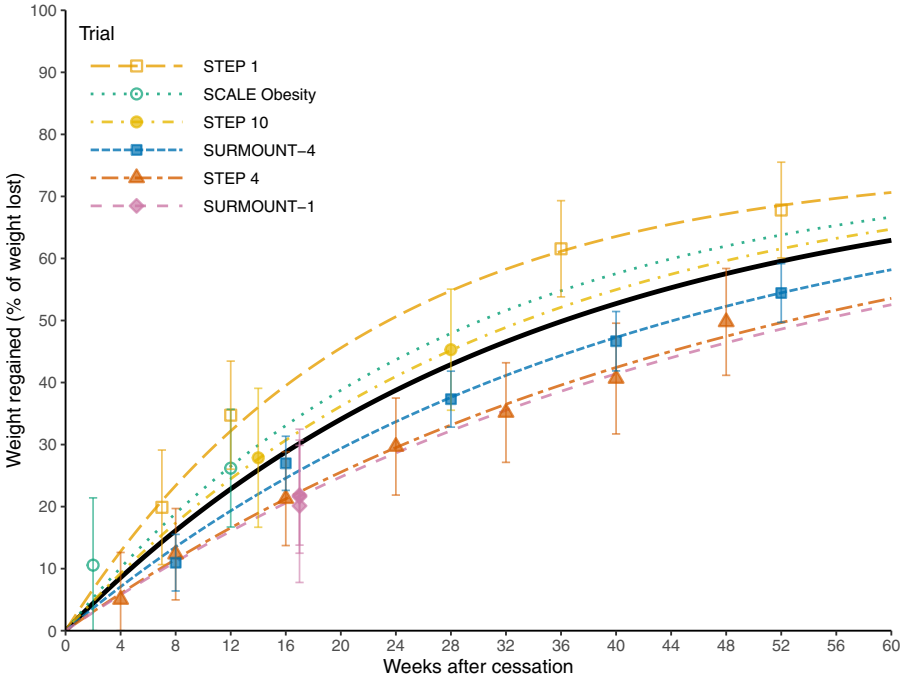


Fig. 2: Fitted trajectories of weight regain following cessation of glucagon-like peptide 1 receptor agonists (GLP-1RAs), based on clinical trial data. Regression was conducted with an exponential recovery function. Semaglutide was given in STEP 1,[6] STEP 4[10] and STEP 10[15]; tirzepatide was given in SURMOUNT-1[7] and SURMOUNT-4[11]; liraglutide was given in SCALE Obesity.[12] The black line indicates the pooled fitted trajectory.

was primarily driven by differences in drug efficacy—newer drugs including semaglutide and tirzepatide produced greater weight loss than older drugs such as exenatide and liraglutide.

Almost all studies observed some degree of weight regain after cessation of GLP-1RA treatment, although the extent varied significantly. Across studies with sufficient initial weight loss for meaningful interpretation, defined here as over 3 kg, the weight regained at or around 12 weeks post-cessation ranged from approximately 10 to 80% of the treatment-induced weight loss. Studies in which participants lost less than 3 kg during treatment were considered less reliable for interpretation. In one such study,[19] post-cessation weight exceeded the pre-treatment baseline weight, likely due to participants switching to insulin therapy, resulting in an apparent weight regain of over 100%.

Post-cessation HbA1c was reported by 17 RCTs and non-randomised studies. HbA1c typically decreased by 0.5–1.5 percentage points while on GLP-1RA treatment, with some outliers falling outside this range. Virtually all studies which tracked this outcome observed post-cessation increases in HbA1c. In most cases, around half of the initial HbA1c reduction appeared to be regained by 8–12 weeks after treatment cessation. However, the extent and timing of this rebound varied significantly between studies. HbA1c rarely returned fully to pre-treatment baseline levels, even after one year off treatment.

Post-cessation SBP was reported by 16 RCTs and three non-randomised studies. During treatment, SBP typically showed reductions ranging from around 1 to 10 mmHg, although some studies fell outside this range. After cessation of treatment, SBP typically rebounded towards the pre-treatment baseline, with most studies reporting that around 70–80% of the initial SBP reduction was regained within 12 weeks.

Inadequate data and the lack of a clear or consistent temporal trajectory precluded further analysis of HbA1c and SBP.

Outcome reporting varied widely across studies. Most trials were not explicitly designed to measure post-cessation outcomes and only extended data collection beyond treatment cessation for exploratory or safety reasons, typically for 4–12 weeks with a single data point taken at the end. Some trials, such as STEP 4[11] and SURMOUNT-4,[12] were designed to measure post-cessation outcomes and often included longer follow-up durations of up to 52 weeks, with data collected at multiple intervening time points. This variability in follow-up timing prompted us to choose a time-based regression approach rather than grouping data into discrete time windows.

Study populations showed heterogeneity in health conditions. 18 studies looked at overweight or obese patients with no specific comorbidities. 17 studies focused specifically on patients with type 2 diabetes. Other comorbidities included metabolic dysfunction-associated steatotic liver disease, polycystic ovary syndrome, chronic kidney disease and chronic obstructive pulmonary disease. We were unable to determine whether comorbidities influenced the dynamics of post-cessation weight regain.

Some studies included additional interventions to GLP-1RAs, mainly lifestyle counselling or standard antidiabetic medications like metformin for patient populations with type 2 diabetes. Two studies[20,21] used liraglutide to maintain weight loss induced by prior intensive low-calorie diets. After stopping liraglutide, weight typically rebounded toward baseline, a finding consistent with other studies.

Three studies[22–24] reported little to no weight regain after substantial weight loss during treatment. Seier et al.[22] implemented a dose tapering protocol and reported that patients' mean weight did not increase after they reduced their dose of semaglutide. While the protocol allowed for complete cessation, many remained on some dose of semaglutide and it is unclear how many stopped entirely. In another study,[23] patients were maintained on a carbohydrate-restricted diet after cessation and experienced negligible weight regain. One study[24] only reported categorical weight outcomes; while the distribution suggested no substantial changes in the average weight after drug cessation, details were limited, and the absence of mean values restricted interpretation.

In one study of exenatide,[25] patients underwent two treatment phases—52 weeks followed by 104 weeks—with a 12-week off-treatment period after each phase. Weight regain during the second off-treatment period was attenuated compared to the first, suggesting that GLP-1RA-induced weight loss may become more durable with prolonged exposure. However, we were unable to explore this hypothesis further due to insufficient data.

Most studies were judged to have a moderate risk of bias, primarily due to the absence of pre-specified post-cessation outcomes in study protocols or analysis plans. Full risk of bias assessments are given in the Appendix (p. 7). In addition, a GRADE summary of findings table is provided in the Appendix (p. 20).

In summary, the majority of studies found partial weight regain after cessation of GLP-1RA therapy, with significant variation in magnitude and timing. Our regression model supported an exponential recovery trajectory, with a weight regain plateau at 75% of the original weight loss. Secondary outcomes of HbA1c and SBP generally showed rebound, but data were insufficient for modelling.

Discussion

The findings of this review indicate that there is significant weight regain following cessation of GLP-1RAs.

The meta-regression shows that after 1 year of treatment withdrawal, participants regain 60% of the weight they lost during treatment. The trajectory of regain is nonlinear and decelerating in nature, with an initial rapid recovery followed by a gradual tapering off and eventual plateauing. Notably, the estimated plateau is below the pre-treatment baseline weight, indicating that some beneficial effects may persist at the population level beyond 1 year after cessation, potentially indefinitely based on model extrapolation.

Weight regain poses a major challenge to the long-term efficacy of GLP-1RAs after treatment cessation, which is particularly relevant as around half of patients discontinue treatment within the first year.[8] Discontinuation is often due to gastrointestinal side effects, financial constraints, and limited access through insurance or prescribing guidelines. Despite this, public health bodies have yet to provide clear and coherent guidance on the use of GLP-1RAs in long-term weight management. In the UK, the National Institute for Health and Care Excellence (NICE) recommends that semaglutide should be prescribed for weight loss for a maximum of 2 years,[26] but no strict limit is set for tirzepatide.[27] This inconsistency highlights a blind spot in long-term obesity management as the benefits of GLP-1RAs risk being negated by subsequent weight regain.

While our model predicts considerable weight regain, it also suggests that 25% of the initial weight loss may be sustained in the long term. This residual weight loss corresponds approximately to a 4–5% reduction in body weight relative to the pre-treatment baseline, assuming an initial weight loss of 15–20% as seen in trials of semaglutide and tirzepatide.[6,7] Notably, we observed that the residual weight loss was consistently greater than that seen in placebo groups. Clinically significant weight loss for individuals with a BMI of less than 35 kg/m^2 has been defined as a 5–10% reduction in body weight,[2] with the predicted residual weight loss of 4–5% falling just below this threshold. Nonetheless, GLP-1RAs may confer modest long-term metabolic benefits for some patients even after cessation.

If weight regain does indeed persist, this may be explained by sustained behavioural or physiological adaptations. By reducing appetite, GLP-1RAs may help facilitate the development of healthier eating habits, such as reduced portion sizes or improved nutritional quality, which may persist even after treatment is discontinued. GLP-1RAs may also facilitate long-term physiologic adaptations, such as altering hormone levels and hypothalamic resetting.[28]

When deprescribing GLP-1RAs, physicians and patients should be aware of the potential for weight regain and consider strategies to mitigate this risk. One possible option is individualised dose tapering. This approach was explored by Seier et al.,[22] who treated patients with semaglutide until they reached their target weight loss, then gradually reduced the dosage to the minimum dose that maintained their weight. This strategy may improve long-term tolerability, however patients may be unable to stop treatment entirely. Another study[29] is currently investigating whether weight regain after total discontinuation can be mitigated by interventions that include tailored meals and a mobile application tracking food intake and exercise.

Our results are subject to certain limitations and should be interpreted with caution. Most importantly, the trial data used to fit our model only extend to 52 weeks after cessation. No large-scale trials have reported weight regain data beyond this point; thus predictions made outside of this window are extrapolations. Longer-term trials are necessary to confirm that our predictions hold beyond one year.

We restricted our meta-regression analysis to studies reporting at least 3 kg on-treatment mean weight loss. This was a pragmatic threshold chosen to enable reliable estimation of post-cessation weight regain trajectories whilst also reflecting the typical weight loss seen in most GLP-1RA users. We acknowledge, however, that patients achieving more modest weight loss are a clinically important subgroup and their post-cessation weight trajectories may not mirror those presented in our analysis.

We were unable to run sensitivity analyses to determine the extent to which other variables such as concomitant medications, weight maintenance strategies or comorbidities affected the trajectory of weight regain. This was because data were typically not reported in sufficient detail, often only with broad summary statistics or not at all. In particular, reporting and implementation of post-cessation weight maintenance strategies was inconsistent amongst studies included in the meta-regression.

Assessment of publication bias was not feasible as the meta-regression included only six studies; funnel plot methods typically require at least ten studies for reliable interpretation.

We initially aimed to model trajectories of HbA1c and SBP following cessation, as exploratory outcomes, but this proved infeasible due to inconsistent reporting and the lack of a clearly defined trajectory. As a result, insights into these parameters were limited, mainly confirming expected post-cessation rebound trends. We note, however, that study inclusion was primarily based on the availability of post-cessation weight data. Consequently, the HbA1c and SBP results in this review may not capture a fully representative sample of post-cessation outcomes in these variables.

The topic of weight regain after GLP-1RA cessation has been largely underexplored in the literature. There are relatively few major trials investigating weight regain after cessation of GLP-1RAs; we identified only two large-scale RCTs that were designed to measure weight regain as a primary outcome: STEP 4[11] and

SURMOUNT-4.[12] Most of our included trials, including STEP 1[6] and SURMOUNT-1,[7] measured weight regain as a secondary, often exploratory outcome; even these represent a small subset of all GLP-1RA trials, which generally do not report any post-cessation outcomes.

Beyond weight regain, there are significant concerns about the long-term consequences of GLP-1RAs on body composition. Studies indicate that 40–60%[30] of the weight lost during treatment is lean mass, with newer agents such as semaglutide and tirzepatide being less effective in preserving lean mass.[31] In patients who discontinue treatment, it is unknown whether the same proportion of lean mass is recovered as no studies have specifically assessed post-treatment changes in body composition. We recommend that future trials investigate further the effect of GLP-1RAs on the composition of weight loss during and after treatment cessation and how these changes compare to other weight loss modalities.

Our findings paint a nuanced picture regarding long-term post-GLP-1RA outcomes. Although a significant proportion of the weight is regained after cessation, the results of our modelling suggest that some benefit is maintained for at least 1 year; however there is likely significant variation at the individual level. As Seier et al.[22] demonstrated, while some patients may require long-term therapy at the full dose for weight maintenance, others can taper their dose to a reduced maintenance level, and some may be able to discontinue therapy entirely while maintaining their desired weight. These considerations underscore the importance of a flexible, individualised approach to weight management when using GLP-1RAs. Blanket guidelines such as NICE's 2-year limit for semaglutide may fail to accommodate patients' individual needs and risk undermining long-term effectiveness.

The landscape of weight loss medications is rapidly evolving as new agents are brought to market. Although included here as a GLP-1RA, tirzepatide is a dual agonist that also targets the glucose-dependent insulinotropic polypeptide (GIP) receptor, likely contributing to its superior efficacy.[32] Even more potent agents are on the horizon. Currently undergoing clinical trials is retatrutide, a triple agonist of the GLP-1, GIP and glucagon receptors, which has produced weight loss of 24% after 48 weeks of treatment.[33] If the weight dynamics in this review hold for newer agents, greater on-treatment efficacy may translate to sizeable residual weight loss even after discontinuation.

In the face of high discontinuation rates and policy-imposed treatment duration limits, our findings underscore the need for an urgent re-evaluation of prescribing guidelines. Individualised cessation strategies and long-term support are essential to sustain treatment benefits and prevent the reversal of clinical progress. As newer and more potent agents emerge, understanding the trajectory of discontinuation outcomes will be pivotal in shaping future obesity care.

Contributors

BB and SL conceived the study and co-wrote the first draft of the manuscript. BB, SL, MT, and AA co-designed the study. SL conducted the systematic search. AA, AL, BB, IS, MT, and SL conducted literature screening. AL, BB, IS, and SL carried out data extraction. SL performed the data analysis. BB, IS, and SL conducted risk of bias assessments. AVP and AP supervised the project, aided data interpretation and contributed to the final manuscript. BB and SL had full access to all underlying data and verified its accuracy. All authors had the final responsibility for the decision to submit for publication.

Data sharing statement

Data for this study were extracted from the published literature. The dataset and scripts used for analysis are available at https://github.com/stevenluo1/glp1_weight_regain_analysis.

Declaration of interests

AP has received payments from Eli Lilly and Novo Nordisk for lecturers/presentations and meetings. AP has also served as Principal Investigator for GLP-1RA trials conducted by Eli Lilly and Novo Nordisk. AVP currently sits on the strategic science advisory committee of Hisun Pharmaceutical.

Acknowledgements

ChatGPT was used to verify grammar, refine the English phrasing in our text and for coding assistance in data analysis. All output was manually reviewed and the authors take full responsibility for the accuracy and quality of the publication.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2026.103796.

References

1 Phelps NH, Singleton RK, Zhou B, et al. Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. *Lancet*. 2024;403(10431):1027–1050.
2 Jung RT. Obesity as a disease. *Br Med Bull*. 1997;53(2):307–321.
3 *Management of Obesity: a National Clinical Guideline*. Edinburgh: Scottish Intercollegiate Guidelines Network; 2010.
4 Ge L, Sadeghirad B, Ball GDC, et al. Comparison of dietary macronutrient patterns of 14 popular named dietary programmes for weight and cardiovascular risk factor reduction in adults: systematic review and network meta-analysis of randomised trials. *BMJ*. 2020;369:m696.
5 Benedictus B, Pratama VK, Purnomo CW, Tan K, Febrinasari RP. Efficacy of oral medication in weight loss management: a systematic review and network meta-analysis. *Clin Ther*. 2025;47(4):316–329.
6 Wilding JPH, Batterham RL, Davies M, et al. Weight regain and cardiometabolic effects after withdrawal of semaglutide: the STEP 1 trial extension. *Diabetes Obes Metab*. 2022;24(8):1553–1564.
7 Jastreboff AM, le Roux CW, Stefanski A, et al. Tirzepatide for obesity treatment and diabetes prevention. *N Engl J Med*. 2025;392(10):958–971.
8 Rodriguez PJ, Zhang V, Gratzl S, et al. Discontinuation and reinitiation of dual-labeled GLP-1 receptor agonists among US adults with overweight or obesity. *JAMA Netw Open*. 2025;8(1):e2457349.
9 Berg S, Stickle H, Rose SJ, Nemec EC. Discontinuing glucagon-like peptide-1 receptor agonists and body habitus: a systematic review and meta-analysis. *Obes Rev*. 2025;26:e13929.
10 Wu H, Yang W, Guo T, Cai X, Ji L. Trajectory of the body weight after drug discontinuation in the treatment of anti-obesity medications. *BMC Med*. 2025;23(1):398.
11 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(14):1414–1425.
12 Aronne LJ, Sattar N, Horn DB, et al. Continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity: the SURMOUNT-4 randomized clinical trial. *JAMA*. 2024;331(1):38–48.
13 Davies MJ, Bergenstal R, Bode B, et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial. *JAMA*. 2015;314(7):687–699.
14 Chen K, Chen L, Shan Z, et al. Beinaglutide for weight management in Chinese individuals with overweight or obesity: a phase 3 randomized controlled clinical study. *Diabetes Obes Metab*. 2024;26(2):690–698.
15 Lin P, Li C, Liu Y, et al. Pharmacokinetics and safety profiles of beinaglutide injection, a recombinant human GLP-1, in adults with overweight/obesity: results from a phase I clinical trial. *Front Pharmacol*. 2024;15 [cited 2025 June 7]. Available from: https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2024.1433587/full.
16 le Roux CW, Astrup A, Fujioka K, et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. *Lancet*. 2017;389(10077):1399–1409.
17 McGowan BM, Bruun JM, Capehorn M, et al. Efficacy and safety of once-weekly semaglutide 2·4 mg versus placebo in people with obesity and prediabetes (STEP 10): a randomised, double-blind, placebo-controlled, multicentre phase 3 trial. *Lancet Diabetes Endocrinol*. 2024;12(9):631–642.
18 Hall KD, Sacks G, Chandramohan D, et al. Quantification of the effect of energy imbalance on bodyweight. *Lancet*. 2011;378(9793):826–837.
19 D'Alessio D, Häring HU, Charbonnel B, et al. Comparison of insulin glargine and liraglutide added to oral agents in patients with poorly controlled type 2 diabetes. *Diabetes Obes Metab*. 2015;17(2):170–178.
20 Jensen SBK, Blond MB, Sandsdal RM, et al. Healthy weight loss maintenance with exercise, GLP-1 receptor agonist, or both combined followed by one year without treatment: a post-treatment analysis of a randomised placebo-controlled trial. *eClinicalMedicine*. 2024;69:102475.
21 Wadden TA, Hollander P, Klein S, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. *Int J Obes*. 2013;37(11):1443–1451.
22 Seier S, Stamp-Larsen K, Jensen SBK, Torekov SS, Gudbergsen H. *Treat to Target in Weight Management with Semaglutide: Real-World Evidence from an eHealth Clinic*. Rochester, NY: Social Science Research Network; 2025 [cited 2025 June 7]. Available from: https://papers.ssrn.com/abstract=5207768.
23 McKenzie AL, Athinarayanan SJ. Impact of glucagon-like peptide 1 agonist deprescription in type 2 diabetes in a real-world setting: a propensity score matched cohort study. *Diabetes Ther*. 2024;15(4):843–853.
24 Bartelt K, Mast C, Deckert J, Gracianette M, Joyce B. Many patients maintain weight loss a year after stopping semaglutide and liraglutide [cited 2025 June 7]; Available from: https://epicresearch.org/articles/many-patients-maintain-weight-loss-a-year-after-stopping-semaglutide-and-liraglutide; 2024.
25 Bunck MC, Cornér A, Eliasson B, et al. Effects of exenatide on measures of β-Cell function after 3 years in metformin-treated patients with type 2 diabetes. *Diabetes Care*. 2011;34(9):2041–2047.
26 *Semaglutide for Managing Overweight and Obesity*. London: National Institute for Health and Care Excellence; 2023. Available from: https://www.nice.org.uk/guidance/ta875.
27 *Tirzepatide for Managing Overweight and Obesity*. London: National Institute for Health and Care Excellence; 2024. Available from: https://www.nice.org.uk/guidance/ta1026.
28 Zheng Z, Zong Y, Ma Y, et al. Glucagon-like peptide-1 receptor: mechanisms and advances in therapy. *Signal Transduct Target Ther*. 2024;9(1):1–29.
29 Hollis-Hansen K. *Identifying Strategies to Curtail Weight Regain After GLP-1 receptor Agonist Treatment Cessation*. Clinicaltrials.gov; 2025 [cited 2025 June 7]. Report No.: NCT06273163. Available from: https://clinicaltrials.gov/study/NCT06273163.
30 Neeland IJ, Linge J, Birkenfeld AL. Changes in lean body mass with glucagon-like peptide-1-based therapies and mitigation strategies. *Diabetes Obes Metab*. 2024;26(S4):16–27.
31 Karakasis P, Patoulias D, Fragakis N, Mantzoros CS. Effect of glucagon-like peptide-1 receptor agonists and co-agonists on body composition: systematic review and network meta-analysis. *Metabolism*. 2025;164:156113.
32 Coskun T, Sloop KW, Loghin C, et al. LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: from discovery to clinical proof of concept. *Mol Metab*. 2018;18:3–14.
33 Jastreboff AM, Kaplan LM, Frías JP, et al. Triple–Hormone-Receptor agonist retatrutide for obesity — a phase 2 trial. *N Engl J Med*. 2023;389(6):514–526.