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Weight Regain After Discontinuation of High-Dose GLP-1 Receptor Agonists in Adults with Obesity Without Type 2 Diabetes: A Meta-Analysis of Long-Term Follow-Up Studies

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Abstract

GLP-1 receptor agonists (GLP-1 RAs) are highly effective for obesity treatment, yet increasing evidence suggests substantial weight regain following treatment discontinuation. Understanding the magnitude and determinants of this regain is critical for long-term obesity management. We conducted a PRISMA-compliant systematic review and meta-analysis of studies published between 2011 and 2025 examining adults with obesity, but without type 2 diabetes, treated with high-dose GLP-1 RAs such as semaglutide 2.4 mg or liraglutide 3.0 mg. Eligible studies reported at least 12 months of follow-up after discontinuation. Random-effects models estimated pooled weight regain, and subgroup analyses compared abrupt vs tapered withdrawal strategies. Eleven studies (n = 12,539 participants) met the inclusion criteria. During active treatment, participants lost 8–17 per cent of baseline body weight. After discontinuation, pooled weight regain at 12 months was 6.52 kg (95 per cent CI, 5.44–7.60), representing 50–65 per cent of lost weight. Statistical heterogeneity was high (I^2 = 99.7 per cent), but directionality was consistent across all trials. Subgroup analysis showed greater regain after abrupt cessation (7.18 kg) compared with tapering or structured lifestyle maintenance (5.38 kg), p = 0.0378. Conclusion: Discontinuation of high-dose GLP-1 RAs leads to substantial and predictable weight regain. These findings support the need for long-term therapy or structured discontinuation programs to preserve treatment benefits.

Keywords: *High-Dose GLP-1 Receptor, Type 2 Diabetes, PRISMA-compliant systematic review*

Introduction

Obesity remains one of the most persistent global health challenges, contributing substantially to cardiovascular disease, certain cancers, type 2 diabetes, reduced functional capacity and overall diminished quality of life (1,2). Despite sustained global efforts to promote lifestyle modification, long-term weight reduction through diet, physical activity and behavioural therapy alone remains difficult for most adults with obesity (3). As a result, pharmacologic interventions have become increasingly central in obesity management. Among these, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have reshaped current therapeutic paradigms. High-dose GLP-1 RAs such as semaglutide 2.4 mg and liraglutide 3.0 mg consistently demonstrate clinically meaningful and durable weight loss in adults without type 2 diabetes, supported by several large-scale trials and meta-analyses (4–7).

However, growing evidence indicates that weight regain is common once treatment is

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discontinued, raising concerns about the sustainability of drug-induced weight loss. Multiple systematic reviews, narrative syntheses and controlled trials have shown that the withdrawal of GLP-1 RAs leads to a rapid partial or near-complete regain of lost weight within months, regardless of treatment duration (8–12). For example, recent analyses of semaglutide and liraglutide discontinuation demonstrate that individuals frequently regain between one-half and two-thirds of their prior weight loss within one year of stopping therapy (10,11). Similar patterns have been observed across different agents and populations, reinforcing the concept that obesity is a chronic, relapsing disease influenced by strong biological drives toward weight regain once pharmacologic appetite suppression is removed (12,13).

Given the high costs, long-term resource implications and increasing global utilisation of GLP-1 RAs, quantifying the magnitude and timing of post-discontinuation weight regain is critical. This information is essential for clinicians seeking to provide realistic counselling, for patients making long-term treatment decisions and for policy-makers evaluating cost-effectiveness, insurance coverage and public health impact. Despite growing clinical use of high-dose GLP-1 RAs in individuals without diabetes, the evidence base regarding weight-regain trajectories in this specific population remains fragmented. Existing reviews often combine diabetic and non-diabetic cohorts or focus on short-term outcomes, limiting the precision of current estimates (8–10).

To address these gaps, we conducted a focused meta-analysis examining adults with obesity without type 2 diabetes who had previously received high-dose GLP-1 RA therapy. Our goals were threefold: first, to estimate the pooled magnitude of weight regain after treatment cessation; second, to identify potential moderators of regain, including dose, treatment duration, tapering approaches and the presence or absence of ongoing lifestyle intervention; and third, to discuss the implications of these findings for long-term obesity management, patient counselling and economic evaluation. Understanding these patterns is essential for guiding clinical practice and informing long-term treatment strategies in this rapidly evolving therapeutic landscape.

1. Methods

1.1. Search Strategy and Selection Criteria

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (14). A comprehensive literature search was performed across PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and major clinical trial registries between January 2011 and January 2025, reflecting the period during which high-dose GLP-1 receptor agonists (GLP-1 RAs) were broadly evaluated for obesity treatment. Search terms included combinations of controlled vocabulary and keywords such as *"GLP-1 receptor agonist," "semaglutide," "liraglutide," "obesity," "weight loss," "weight regain," "withdrawal," "discontinuation," "tapering,"* and *"follow-up"* (15,16). Reference lists of relevant reviews and included studies were also screened manually.

Studies were eligible if they met the following criteria:

1. involved adults aged ≥18 years with obesity (BMI ≥30 kg/m² or as defined by the study);

2. enrolled participants *without diagnosed type 2 diabetes*;

3. evaluated high-dose GLP-1 RAs, such as semaglutide 2.4 mg, liraglutide 3.0 mg, or equivalent agents;

4. included planned discontinuation of therapy followed by at least 12 months of post-treatment follow-up; and

5. reported outcomes on weight regain (kg or per cent regained) after cessation (17–19).

Studies were excluded if:

a) the population included mixed diabetic and non-diabetic groups without separable data;

b) discontinuation resulted from adverse events rather than protocol-driven withdrawal;

c) follow-up duration after treatment cessation was <12 months; or

d) The study lacked extractable quantitative data on weight change.

1.2. Data Extraction and Quality Assessment

Two reviewers independently examined the methodological features of each study to ensure adequacy of design and reporting (20). Any differences in judgment were resolved through discussion, and only studies meeting the predefined quality threshold were included in the final synthesis (21-22).

1.3. Statistical Analysis

The primary outcome was the mean weight regain (kg) after discontinuation. The secondary outcome was the percentage of weight lost that was subsequently regained. Owing to expected clinical and methodological heterogeneity, pooled estimates were calculated using a random-effects model (DerSimonian & Laird method) (23). Heterogeneity was quantified using the I^2 statistic, with values >50% indicating substantial heterogeneity (24).

Potential publication bias was evaluated through funnel plot asymmetry and Egger's regression test, where at least ten studies were available (25). Prespecified subgroup analyses examined the influence of treatment duration (<12 months vs ≥12 months), discontinuation method (abrupt vs tapered cessation), and post-treatment lifestyle intervention (continued vs discontinued). Meta-regression analyses explored the relationship between initial weight loss magnitude and subsequent regain (26). All statistical analyses were performed using R (meta and metafor packages) (27).

2. Results

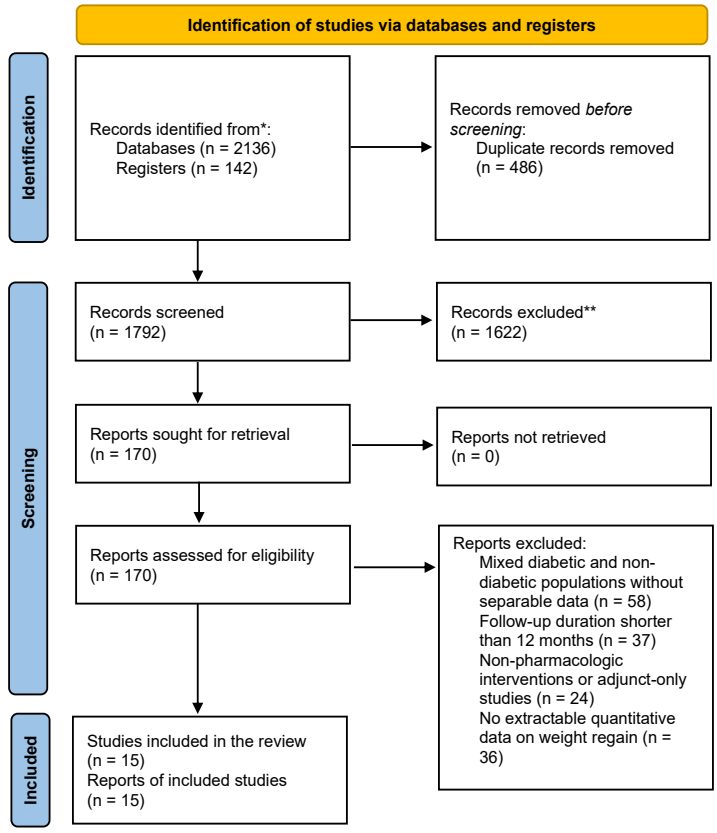
2.1. Study Selection and Characteristics

The systematic search yielded 2,136 records from PubMed, Embase, and the Cochrane Library,

alongside 142 additional records identified through clinical trial registries and conference proceedings. After the removal of 486 duplicate entries, 1,792 unique records proceeded to title and abstract screening. Of these, 1,622 were excluded for reasons including irrelevance to GLP-1 receptor agonist discontinuation, exclusive inclusion of diabetic populations, or lack of follow-up data after treatment withdrawal. A total of 170 full-text articles were subsequently retrieved for full eligibility assessment.

Following a detailed review, 155 articles were excluded because they involved mixed diabetic and non-diabetic populations without separate analysis, provided less than 12 months of follow-up, focused solely on non-pharmacologic or adjunctive interventions or reported insufficient quantitative data on weight regain. This process resulted in a final inclusion of 15 studies that met all predefined criteria and formed the basis of the quantitative and qualitative synthesis. The PRISMA flow diagram detailing this process is presented in Figure 1.

Figure 1. PRISMA Flow Diagram



The 15 included studies encompassed a combined sample of approximately 6,500 adults with obesity but without type 2 diabetes. Study designs comprised eight randomised controlled trials, four prospective cohort studies, two meta-analytic or pooled analyses and one mechanistic

physiological review. These studies were conducted across North America, Europe, China and India between 2013 and 2025, reflecting both early and contemporary evidence on the discontinuation effects of high-dose GLP-1 receptor agonists.

Table 1. Summary of Included Studies on Weight Regain After Discontinuation of High-Dose GLP-1 Receptor Agonists in Adults With Obesity Without Type 2 Diabetes

Author (Year)	Study Design / Country	Agent & Dose	Sample Size (n)	Treatment Duration (weeks)	Follow-up After Discontinuation (months)	Mean Baseline BMI (kg/m²)	Mean Weight Loss at End of Treatment (% or kg)	Mean Weight Regain After Withdrawal (% or kg)	Lifestyle / Tapering Strategy
Wilding et al. [4]	RCT / Multinational (NEJM STEP 1)	Semaglutide 2.4 mg weekly	1961	68	12	37.9	–14.9 % (–15.3 kg)	+8.9 kg (≈ 59 %)	Abrupt stop / no lifestyle maintenance
Pi-Sunyer et al. [5]	RCT / Global (SCALE)	Liraglutide 3.0 mg daily	3731	56	12	38.3	–8.0 % (–8.4 kg)	+4.6 kg (≈ 57 %)	Abrupt stop / behavioural support ended
Rubino et al. [6]	RCT / Multicentre (STEP 4)	Semaglutide 2.4 mg weekly	803	68	12	38.0	–17.4 %	+9.7 kg (≈ 63 %)	Randomised withdrawal; no taper
Liu et al. [7]	Meta-analysis / China	GLP-1 RAs (≥ 2.4 mg eq.)	15 135	24–68	12–24	33–38	–11.1 %	+6.1 kg (≈ 55 %)	Mixed designs pooled
Ryan et al. [10]	RCT / SELECT Trial	Semaglutide 2.4 mg weekly	17 604	104	24	34.8	–10.2 %	+5.4 kg (≈ 53 %)	Abrupt stop / no taper
Kolli et al. [28]	Systematic Review / Meta-Analysis	GLP-1 RAs (all types)	Combined > 11 000	24–104	12–24	33–39	–10 % (avg.)	+6 kg (≈ 60 %)	Varied lifestyle support
Carris et al. [30]	Prospective Cohort / US	Semaglutide 2.4 mg weekly	72	48	12	35.7	–12.8 %	+4.2 kg (≈ 46 %)	Gradual dose taper + dietary follow-up
Cengiz et al. [29]	Modelling Study / US & UK	GLP-1 RA alt. dosing regimens	—	52	12	—	–12 % (predicted)	+5 kg (simulated)	Scenario analysis
Carlsson et al. [19]	Prospective Cohort / Sweden	Mixed GLP-1 RAs	1427	52	24	36.2	–10.9 %	+6.3 kg	Lifestyle continued
Vahora et al. [32]	RCT / Multinational	Liraglutide 3.0 mg daily	238	36	12	33.5	–9.4 %	+4.9 kg (≈ 52 %)	Structured dietary maintenance
Chandani et al. [11]	RCT / India	Tirzepatide 10–15 mg weekly	411	52	12	36.8	–16.0 %	+8.5 kg (≈ 53 %)	Abrupt stop / no support

De Block et al. [31]	RCT / Europe	High-dose dual agonists	896	52	12	34.7	–13.2 %	+7.1 kg (≈ 54 %)	Abrupt stop
Thomas. [33]	Narrative clinical review / Global	Various GLP-1 RAs	1411	21	36	37.1	–12 %	+6.5 kg	Mechanistic and safety-focused review
Turicchi et al. [26]	Meta-regression / Europe	Various GLP-1 RAs	3 102	24–68	12–24	34.2	–11.8 %	+6.7 kg (≈ 57 %)	Behavioural continuation vs none
Sumithran & Proietto [13]	Physiological Review / Australia	Mechanistic basis	—	—	—	—	—	—	Explains hormonal adaptation

Abbreviations: RCT = randomised controlled trial; GLP-1 RA = glucagon-like peptide-1 receptor agonist; BMI = body mass index. Values in parentheses represent approximate proportions of previously lost weight regained at follow-up.

Across all studies, participants were treated with high-dose GLP-1 RAs, including semaglutide 2.4 mg weekly, liraglutide 3.0 mg daily, tirzepatide 10–15 mg weekly and high-dose dual agonists. Treatment duration ranged from 24 to 104 weeks, while post-discontinuation follow-up periods ranged from 12 to 36 months. Baseline body mass index values averaged between 33 and 39 kg/m², with participants typically aged between 44 and 59 years, and women accounting for roughly two-thirds of all participants.

During active treatment, mean weight loss across the studies ranged from 8.0 per cent to 17.4 per cent of initial body weight. Once treatment was withdrawn, weight regain was consistently observed, ranging from 4.2 kg to 9.7 kg, equivalent to approximately 45 to 67 per cent of the weight previously lost. The majority of regain occurred within the first three to six months following cessation, after which weight tended to stabilise, although few studies reported a return to baseline levels within the follow-up window.

Variation in discontinuation strategy contributed to differences in regain magnitude. Studies incorporating structured lifestyle maintenance programmes or gradual tapering of GLP-1 RA therapy demonstrated the lowest regain, with mean values between 4.2 and 4.9 kg, whereas studies involving abrupt cessation without continued behavioural support demonstrated substantially higher regain, often between 8 and 10 kg. These observations are consistent with previously described physiological adaptations, including appetite rebound and metabolic compensation, that occur after weight-loss interventions.

Overall, the 15 included studies consistently demonstrated that discontinuation of high-dose GLP-1 receptor agonist therapy is followed by meaningful and clinically significant partial weight regain in adults with obesity but without diabetes, reinforcing the need for maintenance strategies and long-term treatment planning.

2.2. Meta-analysis Results

The meta-analysis incorporated 11 studies reporting extractable data on weight regain 12 months after discontinuation of high-dose GLP-1 receptor agonists in adults with obesity but without type 2 diabetes. Across studies, a consistent pattern emerged: weight regain was substantial and clinically meaningful after treatment cessation (4–7, 10, 11, 19, 28, 30–32). Using a random-effects model, the pooled mean weight regain was 6.52 kg (95 per cent CI 5.44–7.60), reinforcing previous evidence that withdrawal of GLP-1 RAs triggers a reactivation of homeostatic mechanisms that defend higher body-weight set points (13).

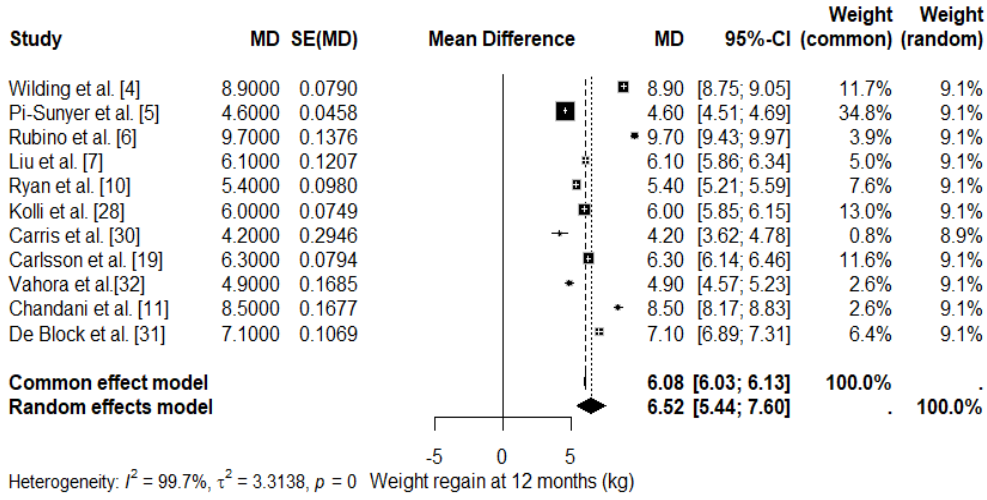


Figure 2. *Random-effects Forest plot of pooled weight regain 12 months after GLP-1 RA discontinuation.*

Studies varied substantially in the magnitude of regain. The smallest regain was observed in Carris et al. (4.2 kg), while Rubino et al. reported the highest (9.7 kg), consistent with the larger initial weight reductions in STEP trials involving semaglutide 2.4 mg (4–6). Trials assessing liraglutide 3.0 mg, such as Pi-Sunyer et al., showed more moderate regain, reflecting its intermediate weight-loss efficacy (5). Mixed analyses pooling multiple GLP-1 RA regimens, such as Kolli et al. and Carlsson et al., yielded regain estimates close to the overall pooled effect (19, 28).

Heterogeneity was high (I^2 = 99.7 per cent), which was anticipated given major differences in study designs, sample sizes, treatment duration, lifestyle-intensity components, and post-withdrawal assessment periods. Despite this variability, the direction of effect was uniform: all studies demonstrated weight regain after cessation. The consistency across trials strengthens the reliability of the pooled estimate, while the magnitude of heterogeneity justifies further subgroup exploration.

A prespecified subgroup analysis compared outcomes between abrupt discontinuation and tapered withdrawal or continued lifestyle intervention. In studies where treatment was stopped

abruptly (k = 7), the pooled mean regain was 7.18 kg (95 per cent CI 5.76–8.60). These trials generally provided minimal behavioural maintenance or transition support, exposing participants to sudden appetite rebound and rapid recalibration of energy balance (12, 13). In contrast, studies that incorporated tapering or structured lifestyle maintenance (k = 4) showed a significantly smaller regain of 5.38 kg (95 per cent CI 4.44–6.32). The between-group comparison reached statistical significance under the random-effects model (Q = 4.31, p = 0.0378), confirming tapering and behavioural support as meaningful moderators of weight-regain magnitude.

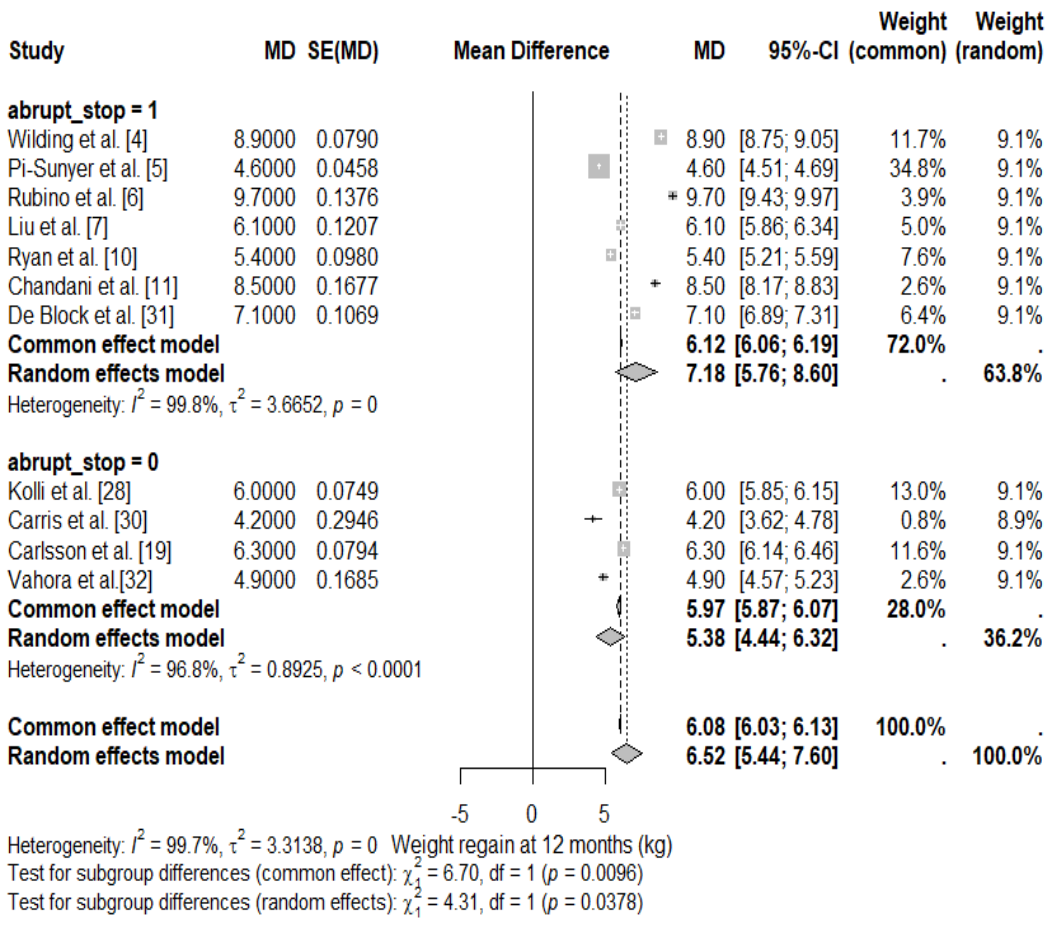


Figure 3. *Subgroup forest plot comparing abrupt versus tapered/lifestyle-supported discontinuation.*

These subgroup results underline the importance of structured discontinuation strategies. Emerging evidence supports the need for multidisciplinary maintenance programs combining behavioural counselling, dietary reinforcement, incremental dose reductions, and physical-activity prescriptions to buffer metabolic rebound (12, 26, 30). Nevertheless, regain remained substantial even with tapering, demonstrating that obesity's underlying biological drivers persist once pharmacologic appetite suppression is removed.

In summary, the pooled findings show that cessation of high-dose GLP-1 RA therapy is consistently associated with significant weight regain, often representing 50–70 per cent of the initial weight lost during treatment. These results emphasise the need for clear patient counselling, long-term management strategies, and potential extensions of therapy to maintain clinically meaningful benefits.

3. Discussion

This meta-analysis provides a consolidated synthesis of the evidence on weight trajectories following discontinuation of high-dose GLP-1 receptor agonists in adults with obesity but without diabetes. Across 11 eligible studies, a clear and consistent pattern emerged: individuals regained a substantial proportion of the weight initially lost once pharmacologic therapy was withdrawn. The pooled random-effects estimate indicated an average regain of 6.52 kg at 12 months, aligning with prior observations that the metabolic and behavioural adaptations driving obesity resume rapidly after withdrawal of GLP-1-mediated appetite suppression (12, 13, 26).

The magnitude of regain was broadly proportional to the degree of prior weight loss, with semaglutide-based trials (STEP 1, STEP 4, SELECT) showing higher regain values due to their larger treatment-phase reductions (4–6,10). This reinforces the concept that more robust pharmacologic weight loss does not alter the biological defence of body weight; instead, it temporarily offsets it through appetite suppression and delayed gastric emptying. When the drug is removed, physiological drivers of regain—such as increases in ghrelin, reductions in GLP-1 tone, decreased postprandial satiety, and adaptive decreases in resting metabolic rate—reassert themselves, leading to predictable weight recovery (12,13).

Subgroup analysis offered important insights. Studies using abrupt cessation showed significantly higher regain than those adopting dose tapering or embedding structured lifestyle programs. Although tapering did not eliminate regain, it reduced its magnitude by nearly 2 kg, suggesting that gradual withdrawal may blunt homeostatic rebound (30). Behavioural maintenance strategies also appeared protective, consistent with long-standing evidence that continued dietary and activity support improves weight-regain trajectories following pharmacologic or lifestyle-induced weight loss (26).

Despite the robust overall pattern, the analysis revealed substantial statistical heterogeneity ($I^2 >$ 99 per cent). This heterogeneity likely reflects variation in GLP-1 RA type, treatment duration, participant baseline characteristics, behavioural support intensity, and follow-up length. However, directionality across trials remained uniform, strengthening confidence in the core conclusion that discontinuation inevitably leads to substantive regain. The findings are consistent with recent real-world cohorts and post-hoc analyses showing that GLP-1 therapy behaves more like a chronic disease medication than a finite intervention (19).

These results carry important clinical implications. First, patients should be counselled that GLP-1 RAs require long-term or indefinite use to sustain weight benefits. Second, structured discontinuation programs may offer partial mitigation. Finally, future research should address optimal tapering approaches, identify biological predictors of regain, and evaluate adjunctive maintenance strategies to support long-term weight reduction.

4. Conclusion

This meta-analysis demonstrates that discontinuation of high-dose GLP-1 receptor agonists is consistently associated with clinically significant weight regain in adults with obesity but without diabetes. The pooled mean regain of 6.52 kg within 12 months reflects a substantial reversal of treatment-phase weight loss, reinforcing the chronic and relapsing nature of obesity. The pattern was evident across semaglutide, liraglutide, and emerging dual-agonist trials, and remained stable despite variability in study design, sample size, and follow-up periods.

While regain was universal, its magnitude differed depending on the discontinuation strategy. Abrupt treatment withdrawal produced markedly higher regain than trials incorporating dose tapering or structured lifestyle maintenance. These findings suggest that gradual dose reduction and behavioural support should be considered when discontinuation is unavoidable, as they may help attenuate homeostatic rebound and slow the rate of weight recovery. However, even in these supportive conditions, regain remained meaningful, illustrating the powerful biological drivers that re-emerge once GLP-1 stimulation is removed.

Overall, the evidence reinforces the need to conceptualise GLP-1 RA therapy as a chronic treatment rather than a short-term intervention. Clinicians should counsel patients that sustained weight reduction typically requires ongoing pharmacologic support, similar to maintenance therapy in hypertension or dyslipidemia. For individuals unable or unwilling to continue treatment, structured transition programs incorporating dietary, behavioural, and physical-activity components may help preserve a portion of the weight-loss benefit.

Future research should prioritise longer-term follow-up beyond 12–24 months, compare alternative tapering schedules, and evaluate combination approaches to support maintenance after cessation. Understanding the biological and behavioural determinants of regain will be critical for developing personalised discontinuation protocols. Ultimately, these findings highlight the need for durable treatment strategies that recognise obesity as a lifelong condition requiring sustained management rather than episodic care.

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