Obesity

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Epidemiology/Genetics

Safety and Efficacy of Glucagon-Like Peptide-1 Receptor Agonists Use in Elderly People With Obesity—A Meta-Analysis

Inês Rego de Figueiredo[1,2,3] | Filipa Sofia Simas[1,4] | Angela Ghiletchi[5] | João Oliveira Torres[1,3,6,7] | José Silva-Nunes[1,3,6]

[1]Multidisciplinary Unit of Bariatric and Metabolic Surgery, Curry Cabral Hospital, Unidade Local de Saúde São José, Centro Clínico Académico de Lisboa, Lisbon, Portugal | [2]Egas Moniz School of Health and Science, Almada, Portugal | [3]NOVA Medical School/Faculdade de Ciencias Medicas, New University of Lisbon, Lisbon, Portugal | [4]Department of Nutrition, Curry Cabral Hospital, Unidade Local de Saúde São José, Centro Clínico Académico de Lisboa, Lisbon, Portugal | [5]Department of Internal Medicine, Hospital Garcia de Orta, Unidade Local de Saúde Almada-Seixal, Almada, Portugal | [6]Department of Endocrinology, Diabetes, and Metabolism, Curry Cabral Hospital, Unidade Local de Saúde São José, Centro Clínico Académico de Lisboa, Lisbon, Portugal | [7]Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal

Correspondence: Inês Rego de Figueiredo (ines.r.figueiredo@ulssjose.min-saude.pt)

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ABSTRACT

Objective: This meta-analysis evaluates the safety and efficacy of glucagon-like peptide-1 receptor agonists (GLP-1 RA) for the treatment of older adults with obesity compared to younger individuals.

Methods: A systematic review was conducted following PRISMA guidelines (PROSPERO CRD420251074381). PubMed, Embase, and Scopus were searched until May 17, 2025, for randomized controlled trials and observational studies assessing GLP-1 RA in adults ≥ 65 years with obesity with or without type 2 diabetes. Random effects meta-analyses calculated the log odds ratios (LOR) for dichotomous outcomes and the mean differences (MD) for continuous outcomes, with equivalence testing via two one-sided tests (TOST) and meta-regression for baseline adjustments.

Results: Five studies involving 1229 participants were included. No significant difference in serious adverse events was found between older and younger adults (pooled LOR: 0.06, $p = 0.9$). Older adults had a trend toward lower frequency of nausea (LOR: −0.44, $p = 0.06$) but higher incidence of constipation (LOR: 0.72, $p = 0.02$) and hypoglycemia (LOR: 0.97, $p < 0.001$). Efficacy in metabolic and weight control was comparable. Additionally, one study suggested that liraglutide could reduce fat mass without worsening sarcopenia.

Conclusions: GLP-1 RA therapy seems to be safe and effective in older adults with obesity, achieving similar effects on weight loss and glycemic control as in younger individuals.

1 | Introduction

The global rise in obesity has translated into a 20% increase in its prevalence among older adults [1]. While people living with obesity, in general, are at greater risk of developing its associated musculoskeletal, cardiometabolic, and mental comorbidities, older people are also at risk of developing sarcopenia. This condition was described by the European Working Group on Sarcopenia in Older People as the presence of low muscle strength, low muscle quantity/quality, and low physical performance. Frequently, both entities are present in the same individual, hence the term sarcopenic obesity [1].

Study Importance

- What is already known?
  - SCALE trials pooled analysis of elderly patients showed similar weight loss rates but greater rates of gastrointestinal disturbance when compared to younger adults.
  - SUSTAIN 1–5 pooled analysis showed similar weight reduction, glycemic control, and safety profiles when comparing older and younger adults.
- What does this review add?
  - GLP-1 RA therapy appears to be safe and effective for managing obesity in older adults, with comparable weight loss and glycemic control to younger individuals.
  - Serious adverse events seem similar, but older adults may experience higher rates of constipation and hypoglycemia.
- How might these results change the direction of research or the focus of clinical practice?
  - Further research is required regarding body composition changes with GLP-1 RA therapy to ensure safety.

Weight loss is associated with improvements in comorbidities, quality of life, and health care costs in younger adults. That shall not be assumed in elderly people with obesity, as there is concern for sarcopenia and reduced bone density with weight loss programs [1]. A meta-analysis of observational studies in older adults found a 59% increase in mortality risk with weight loss [2]. However, the analysis did not account for the intentionality of the weight loss. As a matter of fact, a meta-analysis of randomized controlled trials (RCTs) assessing the impact of intentional weight loss found a 15% decrease in all-cause mortality [3].

The need to improve cardiometabolic outcomes has led to a growing use of glucagon-like peptide-1 receptor agonists (GLP-1 RA) such as liraglutide, semaglutide, and dulaglutide for metabolic improvements, and the first two also for obesity management. These agents mimic the incretin hormone GLP-1, promoting weight loss by enhancing satiety, slowing gastric emptying, and improving glycemic control, making them effective for obesity and related metabolic disorders [4, 5]. However, most trials assessing their efficacy and safety were performed in younger adults, frequently displaying an upper age limit for exclusion criteria. Those that included older adults often failed to clearly specify the number of participants in each age group.

Pooled analysis of older participants in the Satiety and Clinical Adiposity–Liraglutide Evidence (SCALE) trials showed similar weight loss rates but greater rates of gastrointestinal disturbance when compared to younger adults [6]. The Semaglutide Treatment Effect in People with obesity (STEP) studies had no upper limit of age for exclusion criteria. A mean body weight reduction of 14.8% in participants on semaglutide 2.4 mg weekly (vs. 2.4% in the placebo group) was shown [7]. Pooled analysis of Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) 1–5 showed similar weight reduction, glycemic control, and safety profiles when comparing older and younger adults [8]. However, the SUSTAIN program assessed lower doses of semaglutide (0.5 or 1 mg) than the STEP program (2.4 mg).

The SELECT trial assessed the impact on cardiovascular outcomes of semaglutide 2.4 mg weekly versus placebo in patients over 45 years of age, body mass index (BMI) $\geq 27 kg/m^2$, and established cardiovascular disease. There was no upper limit of age for inclusion in the trial, and the mean age of the 17,604 participants was 61.6 years old. A 20% reduction in the primary endpoint (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) in the semaglutide group was shown [9, 10].

This meta-analysis aims to address the remaining evidence gap by synthesizing data from both randomized and nonrandomized study types to assess the safety and efficacy of GLP-1 RA use in older adults aged ≥ 65 years compared to younger adults living with obesity.

2 | Methods

2.1 | Search Strategy and Selection Criteria

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [11]. The review protocol was previously registered in the International Prospective Register of Systematic Reviews (PROSPERO): CRD420251074381 and received no external funding.

The present systematic review addressed the following clinical question: "Are GLP-1 RA safe and efficient in the elderly?"

The Participant-Intervention-Comparison-Outcome (PICO) methodology was conducted:

- Participants (P): older (≥ 65 years old) adults with obesity with or without type 2 diabetes (T2D).
- Intervention (I): GLP-1 RA treatment.
- Comparison (C): older versus younger adults (≥ 65 years old vs. < 65 years old).
- Outcomes (O): safety (serious adverse events, gastrointestinal side effects, hypoglycemia, sarcopenia, low bone density, nutritional deficits) and/or efficacy (hemoglobin A1c [HbA1c], body weight loss, body composition, comorbidities remission).

Studies were included if they reported at least one safety or efficacy outcome as defined earlier. Eligible studies included RCTs and observational studies published in English in peer-reviewed journals. Studies were required to report at least one safety or efficacy outcome in adults aged ≥ 65 years with obesity (either as the overall study population or subgroup of adults ≥ 65 years), with or without T2D. Excluded studies included animal studies, non-peer-reviewed studies, studies exclusively in young adults

or nonobese populations or with no comparison to younger patients, studies with dual agonists, non-peer-reviewed articles, conference abstracts without full data, case reports, reviews (narrative or systematic), editorials, or studies not reporting relevant outcomes.

A literature search was conducted in PubMed, Embase, and Scopus, covering the period until May 17, 2025, and using the following research strategy "GLP-1 RA" OR "glucagon-like peptide 1 receptor agonist" AND "older obese people" OR "elderly obese" OR "people with obesity over 65 years old" AND "safety" OR "outcome" OR "efficacy" OR "results."

No supplementary search strategies, such as hand-searching reference lists of systematic reviews or searching gray literature and trial registries, were conducted due to resource constraints.

Screening was done using the RAYYAN platform. After removing duplicate articles, studies were screened by title and abstract by three independent reviewers (I.R.d.F., F.S.S., and A.G.). To maximize sensitivity and ensure no potentially relevant studies were excluded, articles were selected for full-text review if deemed eligible by at least one reviewer. Full texts were then independently assessed by two reviewers (I.R.d.F. and F.S.S.). Reviewers were not blinded to study authors or institutions due to resource constraints. Inter-rater agreement was not formally assessed; however, disagreements at both screening stages were resolved through discussion among reviewers to reach consensus.

2.2 | Data Analysis

Data were extracted by two reviewers (I.R.d.F. and F.S.S.) using a standardized data extraction form developed in Microsoft Excel. The form was pilot tested with the first two studies to ensure consistency and refine the extraction process. The following relevant information was extracted from each eligible study: study type and design, study site, patient characteristics, type and dose of GLP-1 RA, population characteristics, sample size, safety outcomes (serious adverse events, nausea, diarrhea, vomiting, constipation, decreased appetite, hypoglycemia and nocturnal hypoglycemia, and also changes in fat mass and fat-free mass), and efficacy outcomes (on HbA1c, fasting glucose, body weight, systolic blood pressure, diastolic blood pressure, and heart rate).

Outcome definitions were standardized across studies to ensure consistency. For example, serious adverse events were defined as events leading to hospitalization, disability, or death, as reported by studies, while hypoglycemia was defined based on study-specific thresholds (e.g., blood glucose < 70 mg/dL) or clinical symptoms requiring intervention. Where outcome definitions varied, reviewers discussed and aligned data extraction with the most commonly reported definitions. Discrepancies between reviewers were resolved through discussion to reach consensus, with a third reviewer (A.G.) consulted if agreement could not be reached.

Due to resource constraints, study authors were not contacted for missing or unclear data. Instead, available data were extracted as reported, and missing or unclear data were noted in the analysis with potential impacts addressed in the Discussion section.

Statistical analysis was conducted in IBM SPSS Statistics version 30.0.0.0. Random effects models were used for all pairwise meta-analyses due to clinical heterogeneity of demographic differences, indications for therapy, associated drug variability, differences in type of GLP-1 RA, doses, and intervention timing, as well as outcome measures. Effect estimates are presented as log odds ratio (LOR) for dichotomous variables and mean difference (MD) for continuous variables, both with the corresponding 95% confidence intervals (CI). Considering that the standard error (SE) and standard deviation (SD) of mean changes of continuous variables were frequently not available, SD from baseline data was used as an approximate measure. Therefore, effect size was assessed through unstandardized MD to account for uncertainty with missing data. Baseline differences in HbA1c and body weight were adjusted via weighted linear regression. Equivalence was tested using two one-sided tests (TOST). Meta-regression through linear regression was performed when there was a need to adjust for baseline values. Egger's test was used to assess publication bias.

Results are presented in summary tables and forest plots. When a single study reported an outcome or there was a lack of a comparator, or when data were not reported, this precluded meta-analysis; in that case, studies were instead presented narratively in a descriptive analysis.

2.3 | Quality Assessment

Aligned with PRISMA guidelines, we have performed a quality assessment of the included studies. For observational studies, the Newcastle-Ottawa Scale (NOS) was used. It assigns nine stars across three domains for cohort and case–control studies, with higher scores indicating better quality. For RCTs, the Risk of Bias 2 (RoB 2) tool was used. Two reviewers (I.R.d.F. and F.S.S.) independently assessed quality, with disagreements resolved by consensus or with a third reviewer (A.G.).

3 | Results

A total of 1634 articles were retrieved from PubMed, Embase, and Scopus databases. After removal of 178 duplicates, 1456 articles were screened by title and abstract, followed by 141 articles screened by full text according to the inclusion and exclusion criteria. A total of 5 articles were deemed relevant to be included in the analysis (Figure 1, Table 1).

3.1 | Characteristics and Quality of the Included Studies

We collected data for the meta-analysis from four studies that assessed safety and/or efficacy of GLP-1 RA use in the elderly. They were post hoc analyses of RCTs, performing subgroup analysis on patients with obesity (with or without T2D) over and under 65 years old. One of the studies (Yabe et al.) considered two different RCTs (SUSTAIN Japan Mono and SUSTAIN Japan Oral

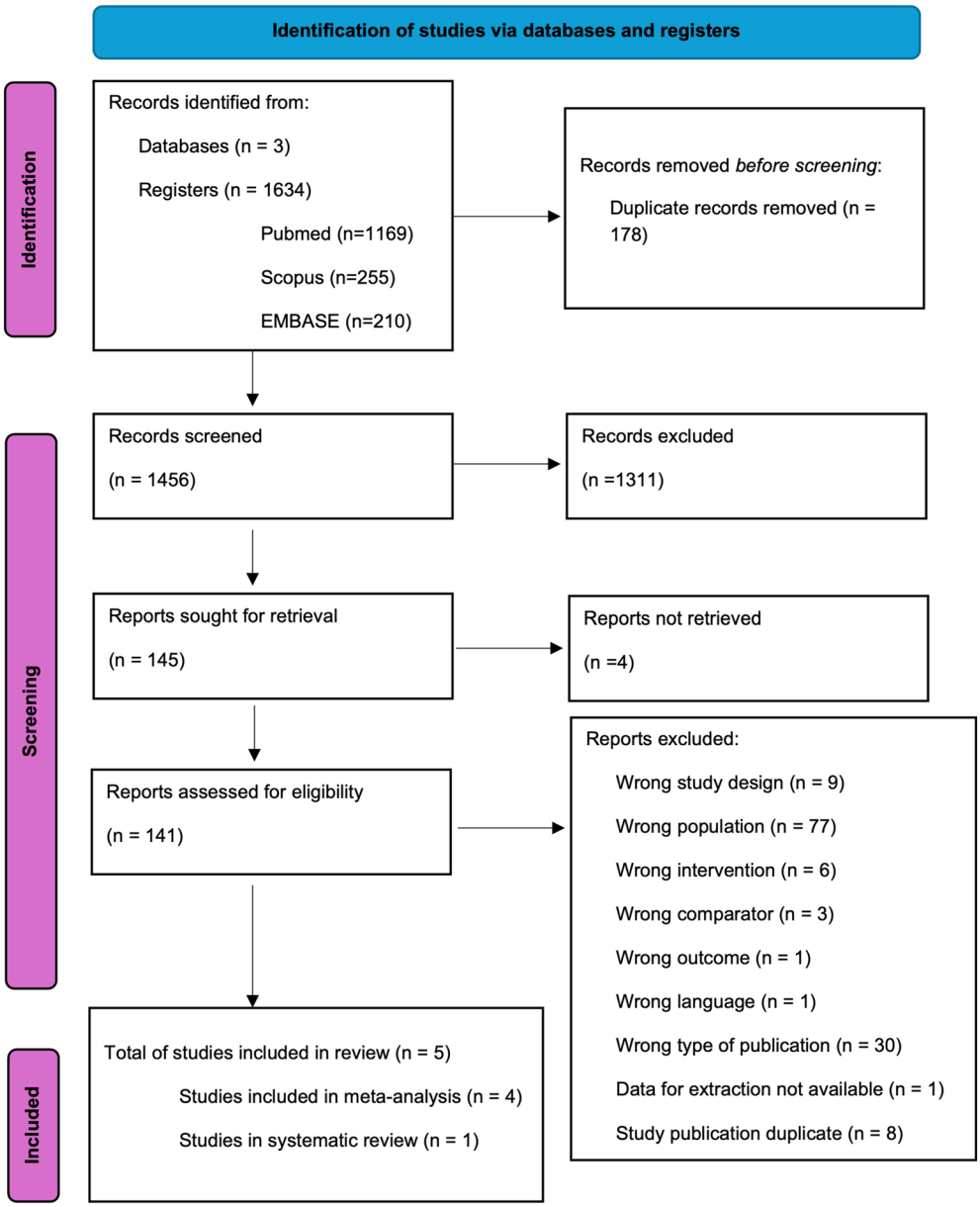

FIGURE 1 | PRISMA diagram for literature search process and total number of studies screened and included at each stage.

Antidiabetes Drug [OAD]) and so they were included in the meta-analysis as two different studies. Most of these studies were performed in Japan; therefore, the cutoff used for obesity was BMI ≥ 25 kg/m^2, instead of the usual 30 kg/m^2.

A prospective observational study was also included in this review, but not in the meta-analysis, due to the lack of a control group (Perna et al.).

The safety of using these medications was assessed by the occurrence of adverse events such as nausea, diarrhea, vomiting, constipation, and hypoglycemia. To assess efficacy, most studies evaluated HbA1c and body weight change; some studies also assessed fasting glucose and blood pressure. One study assessed changes in body composition.

The quality of the four included RCTs was assessed using the RoB 2 tool. Yabe et al. (SUSTAIN Japan post hoc) had low risk in 60% of domains (randomization, missing data, outcome measurement) but some concerns in deviations from intervention (open-label design) and selective reporting (post hoc analysis). Kadowaki et al. (STEP 6 post hoc) and Frias et al. (AWARD-11 post hoc) had low risk in 80% of domains, with some concerns in selective reporting due to post hoc analyses. Hamano et al. (Japanese phase 3 studies post hoc) had low risk in 20% of domains (missing data), some concerns in 40% (randomization, outcome measurement), and high risk in 40% (deviations, selective reporting) due to open-label and nonrandomized designs. Overall, three studies had some concerns, and one had high risk, primarily due to lack of blinding and post hoc analyses, potentially overestimating treatment effects.

Application of the NOS for cohort studies (and an adapted version for case series) resulted in the following: score of 7/9 stars for Yabe et al. (SUSTAIN Japan post hoc, RCT), with minor concerns in comparability due to open-label design in one trial.

TABLE 1 | Studies characteristics and findings.

Author (year)	Hamano et al. (2017) [12]	Frias et al. (2021) [13]	Yabe et al. (2022) [14]	Yabe et al. (2022) [14]	Kadowaki et al. (2024) [15]	Perna et al. (2015) [16]
Title	Efficacy and safety analyses across 4 subgroups combining low and high age and body mass index groups in Japanese phase 3 studies of dulaglutide 0.75 mg after 26 weeks of treatment	Efficacy and safety of dulaglutide 3.0 and 4.5 mg in patients aged younger than 65 and 65 years or older: Post hoc analysis of the AWARD-11 trial	Efficacy and safety of once-weekly semaglutide in Japanese individuals with T2D by baseline age and body mass index	Efficacy and safety of once-weekly semaglutide in Japanese individuals with T2D by baseline age and body mass index	Clinical characteristics affecting weight loss in an East Asian population receiving semaglutide: A STEP 6 subgroup analysis	Liraglutide and obesity in elderly: efficacy in fat loss and safety in order to prevent sarcopenia. A perspective case series study
Study design	Combined data from 3 phase 3 studies: (1) "the monotherapy study," (2) "the combination study," (3) "the safety study"	Post hoc analysis of phase 3 RCT AWARD 11 trial	Post hoc analysis of RCT SUSTAIN Japan mono	Post hoc analysis of RCT SUSTAIN japan OAD	Post hoc analysis of phase 3 RCT STEP 6 trial	Prospective observational (case series)
Site	Japan	Multicenter	Japan	Japan	Japan and South Korea	Italy
Patient characteristics	Adults with T2D, without or with obesity (BMI > 25 kg/m^2)	Adults with HbA1c of 7.5% to 11.0%, BMI ≥ 25 kg/m^2, and simultaneous treatment with metformin	Adults with T2D, without or with obesity (BMI > 25 kg/m^2)	Adults with T2D, without or with obesity (BMI > 25 kg/m^2)	≥ 18 years of age (Korea) or ≥ 20 years of age (Japan), with at least 1 self-reported unsuccessful dietary effort to lose weight and either BMI ≥ 27.0 kg/m^2 with at least 2 weight- related comorbidities or BMI ≥ 35.0 kg/m^2 with at least 1 weight-related comorbidity	Overweight or obesity (BMI > 25 kg/m^2); HbA1c of 7.0%; metformin at maximal dose and stable regime since 3 months (at least); liraglutide treatment initiated at 1.2 mg once daily and titrated to 3 mg once daily after 1 week; duration of diabetes between 3 and 7 years; any restrictive diet regime; all patients followed a normocaloric standardized diet during treatment (from 1800 to 2500 kcal); age > 65 years; baseline lack of physical activity and a sedentary lifestyle
Type and dose of GLP-1 RA	Dulaglutide	Dulaglutide 3 or 4.5 mg	Semaglutide 1 mg	Semaglutide 1 mg	Semaglutide 2.4 mg	Liraglutide 3 mg
Control	Age < 65 years and BMI ≥ 25 kg/m^2	Adults < 65 years old	Age < 65 years and BMI ≥ 25 kg/m^2	Age < 65 years and BMI ≥ 25 kg/m^2	Age < 65 years old	Nonexistent
No follow-up time	26 weeks	58 weeks	30 weeks	56 weeks	75 weeks	24 weeks
Population characteristics	Older group (≥ 65 years): 65% male, mean age 69.5 years, mean HbA1c 8.3%, BW 71.6 kg Younger group (< 65 years): 78% male, mean age 51.4 years, mean HbA1c 8.3%, BW 80.8 kg	Older group (≥ 65 years): 48.4% female, mean age 69.5 years, mean HbA1c 8.4% (68.3 mmol/mol), mean BMI 32.9 kg/m^2 Younger group (< 65 years): 48.9% female, mean age 53.2 years, mean HbA1c 8.7% (71.6 mmol/mol), mean BMI 34.7 kg/m^2	Older group (≥ 65 years): 83% male, mean age 69.9 years, baseline HbA1c 7.5%, BW 75.8 kg Younger group (< 65 years): 70.6% male, mean age 48.1 years, baseline HbA1c 8.2%, BW 85.1 kg	Older group (≥ 65 years): 53% female, mean age 69.4 years, baseline HbA1c 8.1%, BW 71 kg Younger group (< 65 years): 76% male, mean age 52.6 years, baseline HbA1c 8.4%, BW 82.4 kg	Older group (≥ 65 years): 42.4% female, mean age 69 years, baseline BW 75.2 kg Younger group (< 65 years): 42.8% female, mean age 49 years, baseline BW 89.3 kg	Mean age 68.22 (±3.86 years), mean BMI 32.34 (±4.89 kg/m^2); SMI was 6.66 ± 0.73 kg/m^2 in women and 9.41 ± 1.27 kg/m^2 in men
Sample size (older vs. younger)	77 vs. 386	132 vs. 482	12 vs. 34	30 vs. 109	33 vs. 166	9
Outcome data	Efficacy: HbA1c, fasting glucose, body weight, systolic and diastolic blood pressure, pulse rate; Safety: AE, nausea, diarrhea, vomiting, constipation, decreased appetite, (nocturnal) hypoglycemia	Efficacy: HbA1c, BW; Safety: AE, nausea, diarrhea vomiting, hypoglycemia	Efficacy: HbA1c, BW; Safety: AE, nausea, diarrhea, vomiting, constipation, hypoglycemia	Efficacy: HbA1c, BW; Safety: AE; nausea, diarrhea, vomiting, constipation, hypoglycemia	Efficacy: BW; Safety: serious AE	Efficacy: BW, HbA1c, FM, FFM
Risk of Bias 2 (RoB 2)	High risk	Some concerns	Some concerns	Some concerns	Some concerns	NA
Newcastle-Ottawa Scale (NOS)	5/9	8/9	7/9	7/9	8/9	4/9

Abbreviations: AE, adverse events; BW, body weight; FFM, fat-free mass; FM, fat mass; NA, nonapplicable; SMI, skeletal muscle index; T2D, type 2 diabetes.

Score of 8/9 stars for Kadowaki et al. (STEP 6 post hoc, RCT) and Frias et al. (AWARD-11 post hoc, RCT), with deductions for comparability due to post hoc analyses. Score of 5/9 stars for Hamano et al. (Japanese phase 3 studies post hoc, mixed RCT/nonrandomized) with concerns in selection and comparability due to nonrandomized components and open-label designs. Score of 4/6 stars for Perna et al. (liraglutide case series), with strengths in ascertainment (objective DXA outcomes) and reporting (complete follow-up) but weaknesses in selection (small, nonrepresentative sample, unclear criteria). Overall, three of the four studies presented moderate to high quality (RCTs), but the Perna et al. case series design and small sample limit robustness, potentially overestimating treatment effects.

A summary of the studies' characteristics and findings, as well as the quality assessment of each study, can be found in Table 1.

The meta-analysis included 1261 participants from five studies, with 284 older adults (≥65 years, mean age 69.5 years, 43.0% female, mean HbA1c 8.3%, mean body weight 72.6 kg, mean BMI 30.0 kg/m^2) receiving GLP-1 RA treatment and 977 younger adults (<65 years, mean age 51.7 years, 36.8% female, mean HbA1c 8.5%, mean body weight 83.0 kg, mean BMI 31.7 kg/m^2). Ethnicity was not reported but likely predominantly East Asian based on study sites (Japan and South Korea), limiting generalizability. Baseline BMI was unavailable as continuous data for Kadowaki et al. which may impact obesity-related outcome analyses.

3.2 | Safety

3.2.1 | Serious Adverse Events

A total of six of the included studies assessed adverse events of GLP-1 RA use in the elderly, but only five had data on the incidence of adverse events. Definition of the severity of the events was not uniform throughout the papers. They also assessed different GLP-1 RA in different dosages (dulaglutide and semaglutide). However, they were considered homogenous, with I^2 of 0% and Q of 0.6, $p = 0.9$.

Overall, the pooled LOR was 0.06, nonsignificant, showing there was no difference between elderly and young patients concerning the incidence of adverse events (Figure 2).

Egger's test indicated no significant evidence of publication bias (intercept = 0.037, 95% CI: −0.84 to 0.95, $t = 0.135$, $p = 0.9$).

3.2.2 | Nausea

Five studies evaluated nausea as an adverse side effect, but one of them did not have a control group and, therefore, was not included in the meta-analysis. The four studies included in the analysis were on patients treated with dulaglutide or semaglutide.

Individual LORs suggested a lower prevalence of nausea in the elderly, albeit not significant. The pooled LOR (−0.44) confirmed this tendency with a borderline p value ($p = 0.06$).

The studies showed homogeneity: $I^2 = 0\%$, Q 0.6, $p = 0.9$ and no evidence of publication bias: Egger intercept = −0.249, 95% CI: −2.3 to 1.8, $t = -0.5$, $p = 0.6$.

3.2.3 | Vomiting

The same studies also assessed vomiting frequency with GLP-1 RA use. They included patients on dulaglutide or semaglutide. No significant tendency was observed with a pooled LOR of 0.03 and p value of 0.92.

There was no heterogeneity with I^2 of 0%, Q of 0.6, $p = 0.88$. No publication bias was evident through Egger's regression test (intercept = −0.2, 95% CI: −1.97 to 2.4, $t = 0.4$, $p = 0.7$).

3.2.4 | Diarrhea

Hamano et al., Frias et al., and Yabe et al. also compared the incidence of diarrhea in elderly and young patients on GLP-1 RA (namely dulaglutide and semaglutide).

Individual studies and the pooled LOR showed no significant difference between older and younger patients (pooled LOR −0.43, $p = 0.1$) for the incidence of diarrhea as a side effect of GLP-1 RA therapy.

The heterogeneity test showed I^2 of 0% and Q of 0.45, $p = 0.93$. There was no evidence of publication bias according to Egger's test (intercept = −0.8, 95% CI: −3.7 to 2.1, $t = -1.18$, $p = 0.35$).

3.2.5 | Constipation

Regarding constipation, only Hamano et al. and Yabe et al. assessed its incidence with the use of GLP-1 RA in elderly versus young patients.

A significant pooled LOR of 0.72 ($p = 0.02$) indicated there was a significantly higher risk for elderly patients to develop constipation as a side effect of these drugs (Figure 3).

Overall, the studies were homogenous (I^2 0%, Q 3, $p = 0.2$) and showed no significant publication bias (intercept = −0.9, 95% CI: −15.9 to 14, t −0.8, $p = 0.56$).

3.2.6 | Hypoglycemia

Hypoglycemia incidence in the elderly with GLP-1 RA therapy for T2D metabolic control was evaluated in four studies. Together, they showed that the risk for hypoglycemia was significantly higher in the elderly with a pooled LOR of 0.97 and $p < 0.001$ (Figure 4).

There was homogeneity between the studies (I^2 0%, Q 0.09, $p = 0.9$). There was no evidence of publication bias as assessed by Egger's test (intercept 0.9, 95% CI: −0.89 to 2.7, t 2.2, $p = 0.16$).

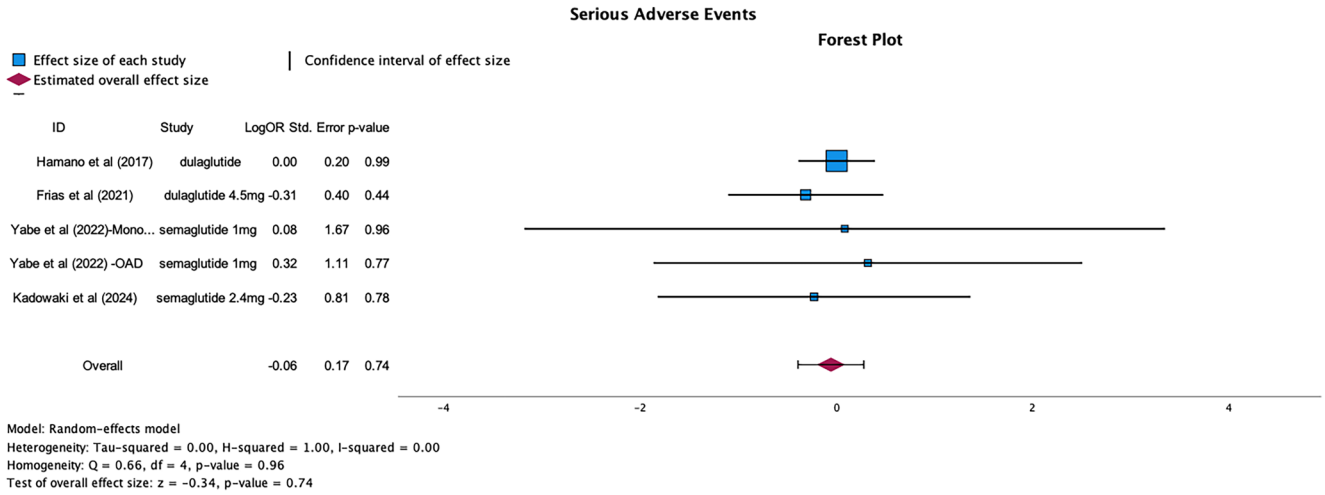

FIGURE 2 | Serious adverse events of GLP-1 RA use in elderly versus young patients.

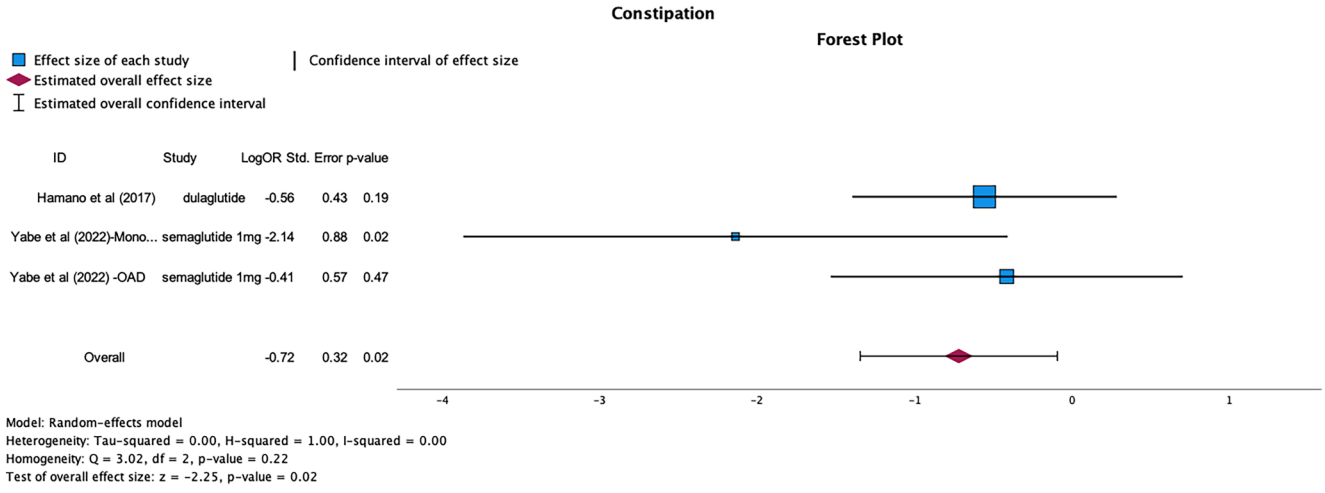

FIGURE 3 | Constipation as a side effect of GLP-1 RA use in elderly versus young patients.

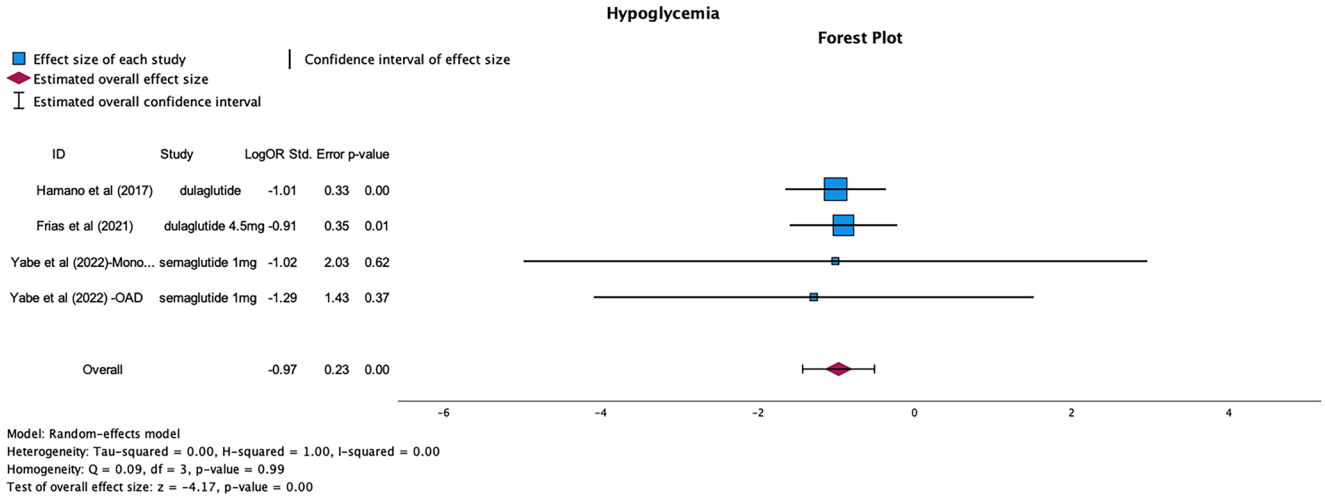

FIGURE 4 | Hypoglycemia as a side effect of GLP-1 RA use in elderly versus young patients.

To summarize the safety outcomes we present Table 2, in which pooled odds ratios (OR) and 95% CI are presented.

3.3 | Efficacy

3.3.1 | Glycated Hemoglobin (HbA1c)

Considering the dual use of GLP-1 RA in diabetes and obesity treatments, some studies were performed in patients with T2D and obesity. Therefore, changes in HbA1c and fasting glucose were frequently assessed as an efficacy endpoint.

The pooled MD was 0.1% (95% CI: −0.22% to 0.42%, $p = 0.53$), indicating no statistically significant difference in HbA1c decrease between elderly and young patients. High heterogeneity was observed (I^2 77%, Q 15, $p = 0.001$), suggesting substantial variability across studies. TOST confirmed equivalence (t_lower = 3.75, t_upper = −2.50, $p < 0.05$). Egger's test showed no evidence of publication bias (intercept = −0.1, $t = -0.2$, $p = 0.80$) (Figure 5).

Meta-regression adjusting for baseline HbA1c differences showed a nonsignificant effect (coefficient = −1.043, 95% CI: −2.364 to 0.277, $p = 0.077$). The adjusted MD was −0.202% (95% CI: −0.742% to 0.339%, $p = 0.250$), indicating a higher decrease, although not significant, in HbA1c among elderly patients when baseline values were similar. Following adjustment, TOST also confirmed equivalence (t_lower = 2.37, t_upper = −5.57, $p < 0.05$).

TABLE 2 | Comparison of safety outcomes for GLP-1 RA between elderly (≥ 65 years) and younger (< 65 years) groups.

Safety outcome	Pooled OR (95%)	*p*
Serious adverse events	−0.057 (−0.393 to 0.278)	0.737
Nausea	0.442 (−0.021 to 0.906)	0.061
Vomiting	−0.029 (−0.585 to 0.526)	0.917
Diarrhea	0.425 (−0.081 to 0.932)	0.100
Constipation	−0.720 (−1.347 to −0.092)	**0.025**
Hypoglycemia	−0.974 (−1.432 to −0.516)	**< 0.001**

Note: Pooled odds ratios (OR) and 95% CI are presented, with significant differences ($p < 0.05$ or CI excluding 1) bolded.

3.3.2 | Body Weight

Body weight change was the primary endpoint in studies assessing efficacy of GLP-1 RA use in obesity regardless of other patient characteristics. In this meta-analysis we assessed whether elderly patients experienced a different response than younger patients. Five studies were included, resulting in a nonsignificant difference in weight loss between the elderly and young (pooled MD 0.07 kg, 95% CI −1.8 to 1.9, $p = 0.9$) (Figure 6).

The studies were overall homogeneous (I^2 0%, Q 0.79, $p = 0.9$). However, TOST failed to confirm equivalence (t_lower = 0.5979 and t_upper = −0.4438, both $<|1.86|$). There is no evidence of publication bias through Egger's test (intercept = −0.37, $t = -0.159$, $p = 0.88$).

Meta-regression for baseline adjustment was not performed, despite the substantial baseline differences in body weight for the two groups, because there is no heterogeneity among them and the unadjusted MD (0.07 kg) is clinically irrelevant. Furthermore, failed equivalence is due to large SE, which would not be addressed by body weight baseline adjustment. This suggests that adjustments will not add further clinical insight.

3.3.3 | Other Efficacy Data

Perna et al. assessed the effect of 24 weeks of treatment with liraglutide on body composition in elderly patients with obesity, with a focus on sarcopenia. The lack of a control group and being the sole study assessing that outcome limited its use in the meta-analysis. However, considering the higher frequency of sarcopenia in elderly people, this prospective observational study is very important when considering the use of GLP-1 RA in this population.

This study confirmed the decrease in HbA1c (−0.8%), body weight (−2 kg), and BMI (−0.78 kg/m^2) with an accompanying

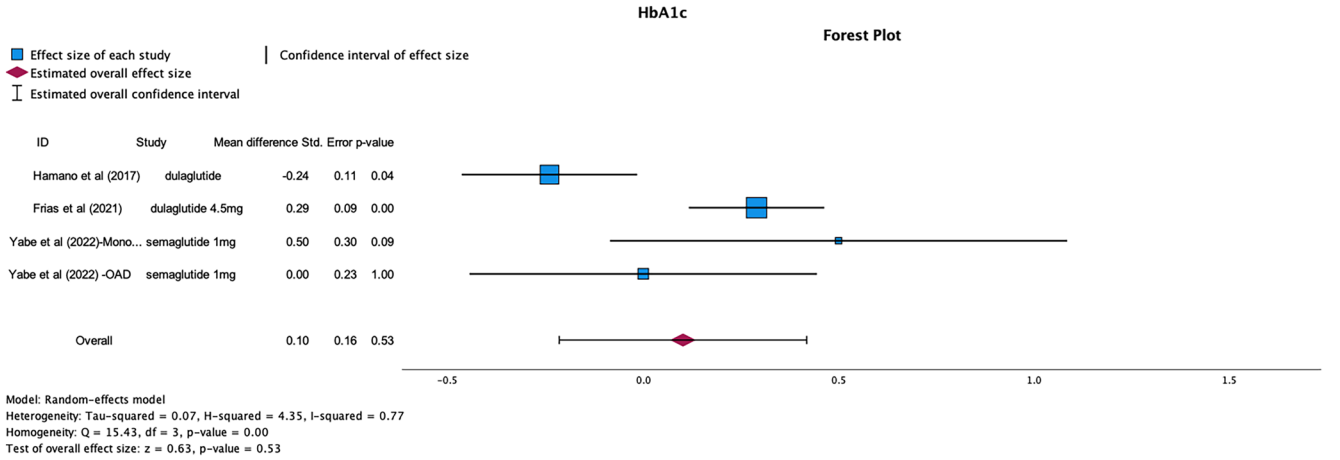

FIGURE 5 | HbA1c difference with GLP-1 RA use in elderly versus young patients.

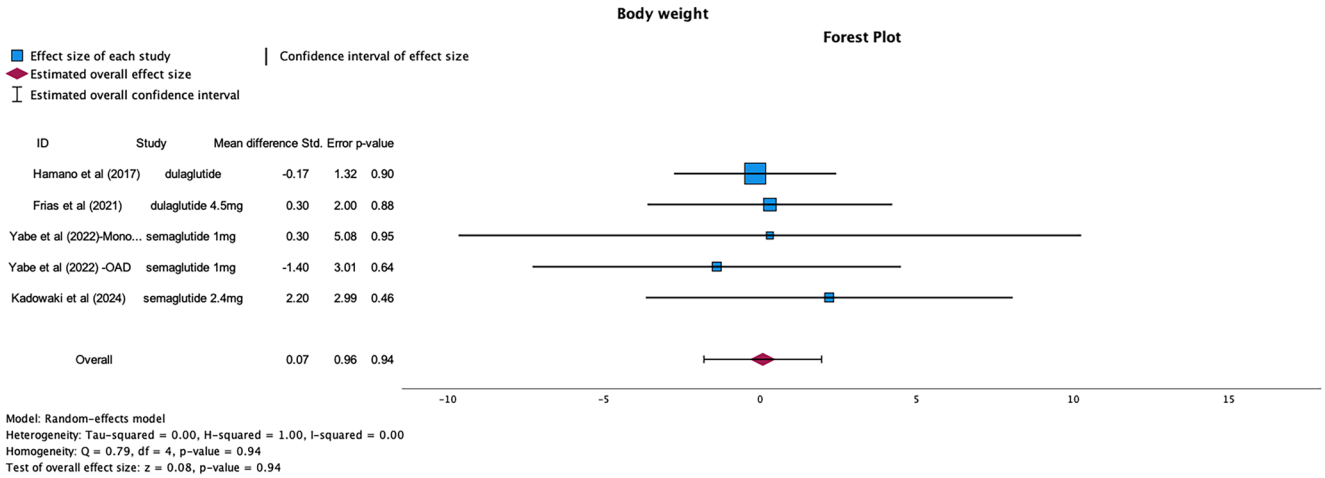

FIGURE 6 | Body weight difference with GLP-1 RA use in elderly versus young patients.

decrease of fat mass (−1498 g) and android fat (−0.9%). There was no increase in fat-free mass at the arms, but an increase of leg fat-free mass of 172 g was reported, which resulted in an increase of the skeletal muscle index (SMI) of 0.03 kg/m^2.

4 | Discussion

This systematic review synthesizes evidence from five papers, including four post hoc analyses of RCTs and one prospective observational study, to evaluate the safety and efficacy of GLP-1 RA in older adults (≥ 65 years) with obesity, with or without T2D, compared to younger adults with obesity. The findings provide valuable insights into the use of GLP-1 RA in this population, addressing concerns about safety and efficacy in the context of age-related conditions such as sarcopenia and increased comorbidity risks.

The safety profile of GLP-1 RA in older adults with obesity appears comparable to that in younger adults for most adverse events, with some notable differences. The lack of significant difference in serious adverse events (pooled LOR: 0.06, $p = 0.9$) suggests that GLP-1 RA do not pose a significantly higher risk of severe outcomes in that population compared to younger participants. This is reassuring, as older adults are often more vulnerable to adverse drug effects due to polypharmacy, reduced physiological reserve, and more frequent comorbidities.

Gastrointestinal side effects, a common concern of GLP-1 RA, showed nuanced results. Although not statistically significant, nausea trended toward lower incidence in older adults (pooled LOR: −0.44, $p = 0.06$). This may reflect age-related differences in gastrointestinal sensitivity or drug metabolism, potentially due to different gastric emptying speeds or altered gut hormone responses in older individuals. Occurrence of vomiting and diarrhea showed no significant difference (pooled LOR: 0.03, $p = 0.92$ for vomiting; LOR: −0.43, $p = 0.1$ for diarrhea), indicating similar tolerability across age groups. Constipation, however, was significantly more frequent in older adults (pooled LOR: 0.72, $p = 0.02$). This could be attributed to age-related reductions in gastrointestinal motility, which may be exacerbated by GLP-1 RA action. Clinicians should monitor for constipation in older patients on GLP-1 RA therapy and consider preventive measures, such as an increase in dietary fiber or hydration strategies.

Regarding hypoglycemia, one of the most feared complications in T2D treatment, this was significantly more frequent in older adults than in younger participants (pooled LOR: 0.97, $p < 0.001$). This may reflect the higher baseline risk of hypoglycemia in older adults due to impaired counter-regulatory mechanisms, polypharmacy, and concurrent use of other glucose-lowering agents. Careful dose titration and monitoring are essential in this population, especially when GLP-1 RA are used alongside therapy with insulin or sulfonylureas.

The homogeneity across studies ($I^2 = 0\%$ for all safety outcomes) strengthens the confidence in these findings, and the lack of publication bias (based on Egger's test) suggests that these results are not skewed by selective reporting.

Considering efficacy, GLP-1 RA therapy was comparable in older and younger adults with obesity. No significant difference was found in HbA1c reduction between older and younger adults (pooled MD: 0.1%, $p = 0.53$). Despite high heterogeneity ($I^2 = 77\%$), equivalence was confirmed via TOST, suggesting that GLP-1 RA are equally effective in improving glycemic control in older and younger adults. Meta-regression adjusting for baseline HbA1c showed no significant HbA1c reduction (adjusted MD: −0.202%, $p = 0.250$). Weight loss was similar between older and younger adults (pooled MD: 0.07 kg, $p = 0.9$), with high homogeneity ($I^2 = 0\%$). However, TOST failed to confirm equivalence, likely due to large SE, indicating that while the MD is clinically negligible, the precision of the estimate is limited. This suggests that GLP-1 RA are similarly effective for weight loss in older adults and it is consistent with the findings from the STEP and SUSTAIN trials.

The observational study by Perna et al. provides additional context, particularly regarding body composition. Liraglutide treatment over 24 weeks resulted in a modest weight loss (−2 kg) and reduced fat mass (−1498 g), but a slight increase in fat-free mass in legs (+172 g) as well as in skeletal muscle index (SMI: +0.03 kg/m^2). These findings suggest that GLP-1 RA-induced

weight loss in older adults primarily reduces fat mass without significantly exacerbating sarcopenia; this is a critical concern given the high prevalence of sarcopenic obesity in this population. However, the lack of a control group limits the strength of these conclusions.

These findings support the use of GLP-1 RA as a safe and effective option for managing obesity in older adults. The comparable efficacy in weight loss and glycemic control, coupled with a generally tolerable safety profile, suggests that age alone should not preclude the use of GLP-1 RA. However, clinicians must consider the increased risk of constipation and hypoglycemia among older patients.

The SELECT trial's findings of a 20% reduction in major cardiovascular events with semaglutide 2.4 mg in a population with obesity and mainly elderly (mean age 61.6 years) further underscore the potential cardiometabolic benefits of GLP-1 RA in the elderly population, particularly for those with established cardiovascular disease.

Several limitations should be considered: (1) Most studies were conducted in Japan, using a lower BMI cutoff for obesity ($\geq 25\,kg/m^2$) than the global standard ($\geq 30\,kg/m^2$), which may limit generalization to other populations. (2) Additionally, most studies included patients with T2D, which may confound outcomes related to obesity alone. (3) The small number of studies ($n = 4$) and relatively small sample sizes for older adults (e.g., $n = 12$ to 132 in individual studies) reduced statistical power. This could be a result of only including studies in English, as well as the research question search in only three databases (PubMed, Embase, and Scopus). (4) The screening process allowed articles to proceed to full-text review if deemed eligible by at least one reviewer, which deviates from standard systematic review methodology that typically requires dual-independent screening with consensus or third-party adjudication. While this approach was chosen to maximize sensitivity, it may have increased the risk of including irrelevant studies at the full-text stage, potentially introducing selection bias. Additionally, reviewers were not blinded to study authors or institutions, which could introduce bias, and inter-rater agreement was not formally assessed, relying instead on discussion to resolve disagreements. (5) There were some missing data regarding SD for continuous outcomes. Due to resource constraints, we were not able to contact the authors and so the sample SDs were used to estimate the missing ones. This may introduce imprecision or bias particularly in heterogeneity assessment and effect size calculations. (6) The observational study by Perna et al. lacked a control group, limiting its inclusion in the meta-analysis and the ability to draw causal inferences about body composition outcomes. (7) Studies assessed different GLP-1 RA (liraglutide, semaglutide, dulaglutide) at varying doses (e.g., semaglutide 0.5 to 2.4 mg), which may introduce variability in outcomes. (8) Only one study addressed body composition, and none directly assessed bone mass density, despite these being critical concerns in older adults undergoing weight loss programs. (9) Most studies had follow-up periods of 24–75 weeks, which may not capture long-term safety or efficacy outcomes, particularly for chronic conditions like sarcopenia or cardiovascular diseases.

Future studies should focus on RCTs specifically designed for older adults with obesity, without upper age limits, and with sufficient sample sizes to assess rare outcomes. They should also have longer follow-up periods to evaluate sustained weight loss, glycemic control, and bone mass density loss, as well as comprehensive assessments of muscle mass, strength, and physical performance, to better understand the impact of GLP-1 RA on sarcopenic obesity. Also, studies in non-Asian populations using standardized obesity criteria (BMI $\geq 30\,kg/m^2$) are necessary to improve generalization of the conclusions. Similarly, head-to-head comparisons of different GLP-1 RA and doses are required to optimize treatment strategies for older adults with obesity, with or without T2D.

5 | Conclusion

GLP-1 RA therapy appears to be safe and effective for managing obesity in older adults, with comparable weight loss and glycemic control to younger participants. While the risk of serious adverse events is similar, older adults may experience higher rates of constipation and hypoglycemia, requiring careful monitoring and individualized treatment plans. Limited evidence on body composition changes suggests that GLP-1 RA therapy primarily reduces fat mass without significantly worsening sarcopenia. However, more research is needed to confirm these findings in body composition and assess long-term outcomes. These results support the cautious use of GLP-1 RA in older adults with obesity with or without T2D, with attention to mitigate specific risks and to preserve muscle health.

Author Contributions

Study design: I.R.d.F. and F.S.S. Data collection: I.R.d.F., F.S.S. and A.G. Data analysis: I.R.d.F. Manuscript writing: I.R.d.F., F.S.S. and J.O.T. Manuscript revision: J.O.T. and J.S.-N.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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