Diabetes Care
American Diabetes Association

Efficacy of GLP-1 Receptor Agonists on Weight Loss, BMI, and Waist Circumference for Patients With Obesity or Overweight: A Systematic Review, Meta-analysis, and Meta-regression of 47 Randomized Controlled Trials

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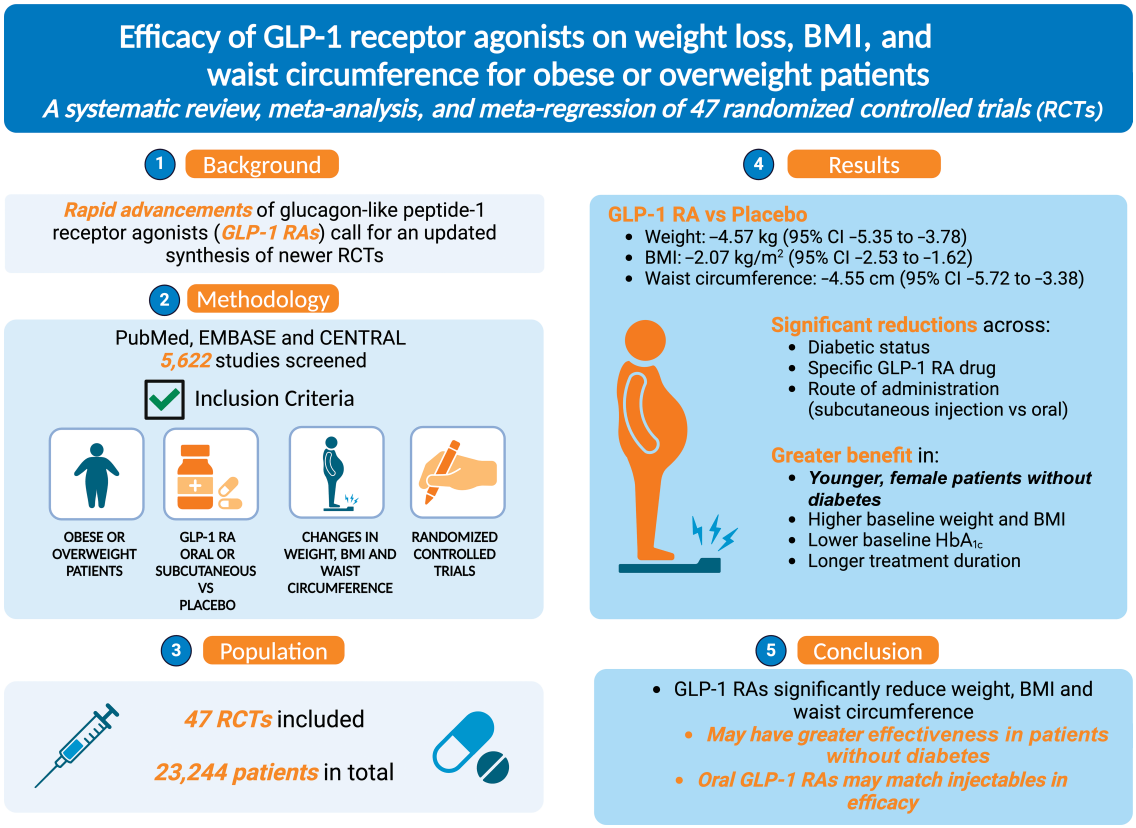
Diabetes Care 2025;48(2):292–300 | https://doi.org/10.2337/dc24-1678



ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Given rapid advancement of GLP-1 RA development, an updated synthesis incorporating randomized controlled trials describing impacts of novel GLP-1 RAs on weight, BMI, and waist circumference is timely.
- **What question did we want to answer?**
  We examined the weight loss efficacy of GLP-1 RAs in populations with diabetes and overweight or obesity versus populations without diabetes but with overweight or obesity and whether there are differences in weight loss efficacy of oral versus injected GLP-1 RAs.
- **What did we find?**
  Oral GLP-1 RAs may be as effective as injected GLP-1 RAs; GLP-1 RAs could be more effective in younger female patients without diabetes but with higher baseline weight/BMI but lower baseline HbA_{1c}.
- **What are the implications?**
  Our findings lend support to usage of GLP-1 RAs in patients with overweight or obesity but without diabetes. This study may provide greater evidence for the use of oral GLP-1 RAs over injected GLP-1 RAs where available.

Efficacy of GLP-1 Receptor Agonists on Weight Loss, BMI, and Waist Circumference for Patients With Obesity or Overweight: A Systematic Review, Meta-analysis, and Meta-regression of 47 Randomized Controlled Trials

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SYSTEMATIC REVIEW

OBJECTIVE

To provide an updated synthesis on effects of glucagon-like peptide 1 receptor agonists (GLP-1 RAs) on weight, BMI, and waist circumference incorporating newer randomized controlled trials (RCTs), particularly in individuals with overweight or obesity.

RESEARCH DESIGN AND METHODS

We systematically searched PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) for RCTs published from inception to 4 October 2024. The search was limited to RCTs evaluating the use of GLP-1 RAs for mean differences from baseline in weight, BMI, and waist circumference in adults with obesity or overweight with or without diabetes. Two independent reviewers performed the literature search and data extraction, resolving disagreements via consensus or third-reviewer consultation.

RESULTS

Forty-seven RCTs were included, with a combined cohort of 23,244 patients. GLP-1 RAs demonstrated a mean weight reduction of −4.57 kg (95% CI −5.35 to −3.78), mean BMI reduction of −2.07 kg/m^2 (95% CI −2.53 to −1.62), and mean waist circumference reduction of −4.55 cm (95% CI −5.72 to −3.38) compared with placebo. This effect was consistent across diabetes status, GLP-1 RA used, and route of administration. The greatest treatment benefit appeared to favor patients who were younger, female, without diabetes, with higher baseline weight and BMI but lower baseline HbA_{1c}, and treated over a longer duration. Limitations include substantial statistical heterogeneity, in part due to broad inclusion criteria. However, this heterogeneity may improve generalizability by reflecting a wide range of study designs and patient populations.

CONCLUSIONS

GLP-1 RAs demonstrated significant weight, BMI, and waist circumference reduction benefits in this meta-analysis.

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Received 12 August 2024 and accepted 22 November 2024

This article contains supplementary material online at https://doi.org/10.2337/figshare.27890331.

H.J.W., B.S., and Y.H.T. are co–first authors.

M.D. and C.-H.S. cosupervised the manuscript.

The rising prevalence of overweight and obesity elicits a significant strain on global public health systems, contributing toward 5 million deaths and 160 million disability-adjusted life years in 2019 (1). Glucagon-like peptide 1 receptor agonists (GLP-1 RAs), initially developed for the management of type 2 diabetes, are increasingly being used as weight loss medications (2). GLP-1 RAs augment glucose-stimulated insulin secretion during states of hyperglycemia (3), and attenuate postprandial glucose excursions (4). Additionally, GLP-1 RAs act on the hypothalamus to increase satiety (5) and reduce appetite drive (6). Weight, or its surrogate measure—BMI, serves as a risk stratification tool and prognostic indicator that guides treatment strategies (7–9). Waist circumference, a measure of visceral adipose tissue (10) and component of metabolic syndrome (11), is associated with obesity-related risks (12). This includes the development of type 2 diabetes and cardiovascular disease (8,9,13). Hence, the impact of GLP-1 RAs on these commonly used parameters is of key clinical significance.

GLP-1 RA development has advanced rapidly. The once subcutaneous injection–only GLP-1 RAs are now available for oral administration. Novel oral GLP-1 RAs include semaglutide (14) and orforglipron (15). An updated evidence synthesis incorporating newer large-scale randomized controlled trials (RCTs) evaluating not only pooled and individual efficacies of old and new GLP-1 RAs but also relative effectiveness of subcutaneous injection versus oral GLP-1 RAs in the population of individuals with overweight or obesity is hence timely. Furthermore, most existing reviews evaluate the weight loss efficacy of GLP-1 RAs in patients with diabetes. However, GLP-1 RAs are also of relevance in the population without diabetes but with overweight or obesity (16). The comparative effect of GLP-1 RAs in individuals with diabetes versus patients without diabetes but with overweight or obesity is also not known (17).

Hence, we performed this systematic review and meta-analysis to address the aforementioned queries. We included all available GLP-1 RAs regardless of Food and Drug Administration approval status. The varying efficacies with GLP-1 RA dose and baseline characteristics were also explored via meta-regression. We sought to summarize current insights into the utilization of GLP-1 RAs for weight management in patients with or without diabetes, which can aid drug selection, administration protocols, target populations, and guideline development.

RESEARCH DESIGN AND METHODS

Search Strategy and Selection Criteria

This meta-analysis was done in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (18). The protocol was registered in International Prospective Register of Systematic Reviews (PROSPERO) (CRD42023448443). We searched PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) without language restrictions for RCTs published from inception to 4 October 2024. The search terms are available in Supplementary Material. Hand search was conducted by reviewing the bibliographies of included studies. We restricted the search to RCTs evaluating the use of GLP-1 RAs currently available in the market, regardless of Food and Drug Administration approval, in adult patients with overweight or obesity (≥18 years old) with or without diabetes, for the outcomes of mean differences in weight, BMI, and waist circumference. We included studies that made use of the standard criteria for overweight (25.0 kg/m^2 ≤ BMI < 30 kg/m^2, Asians 23.0 kg/m^2 ≤ BMI) and obesity (BMI ≥ 30 kg/m^2, Asians BMI ≥ 25 kg/m^2) (19,20). Studies that did not specify whether patients had obesity or overweight were included if the mean BMI, minus 1 SD, still fell within the standard criteria for overweight. Excluded from the meta-analysis were studies that included patients with separate conditions that interfere with the assessment of the primary outcome such as pregnancy, or patients undergoing or with a history of weight reduction procedures such as metabolic/bariatric surgery. The Patient, Intervention, Comparison, Outcome, Study Design (PICOS) (20) inclusion and exclusion criteria are summarized in Supplementary Table 1. With regard to publications that comprise reanalyses of similar or overlapping participant populations, we selected the publication that we assessed to provide the most recent and detailed information. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist can be found in Supplementary Table 5.

Risk of Bias Assessment

Two reviewers independently assessed the quality of included studies using the Cochrane Risk of Bias Tool for RCTs (21). It assesses bias arising from the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective outcome reporting. Studies judged to have a severe risk of bias were excluded to ascertain the reliability of our findings.

Data Extraction

Two reviewers independently performed the literature search and data extraction, with all disagreements resolved via mutual consensus; if unsuccessful, a third reviewer was consulted. Baseline information for age, sex, race, body weight, BMI, waist circumference, and type of diabetes was collected. The drug name, dosage, frequency of administration, and route of administration were also collected.

Grading of the Evidence

The quality of pooled evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (22). Included RCTs were considered high-quality evidence by default and were downgraded based on preset criteria (statistical heterogeneity). $I^2 > 60\%$ indicated substantial statistical heterogeneity, 30–60% indicated moderate heterogeneity, and <30% indicated low heterogeneity.

Statistical Analysis

R (v4.3.1; R Core Team 2023) was used to pool and analyze the results, using general approaches laid out by the *Cochrane Handbook* (23). In studies that did not report SDs, CIs were converted to SEs. A simple unit conversion was performed if study-reported outcomes were in a different unit. The inverse variance method and random-effects model were used to derive the pooled outcomes. I^2 and τ^2 statistics were used to present interstudy heterogeneity. In studies that reported mean differences for multiple dosages, a mini fixed-effect meta-analysis was performed to calculate a pooled mean difference, and the average dose was

taken. Statistical significance was indicated by nominal *P* values of <0.05.

We performed subgroup analysis for diabetes status, GLP-1 RA drug, duration of follow-up, and route of administration (subcutaneous injection versus oral). Further analysis was conducted via subgroup comparisons based on diabetes status with individual GLP-1 RAs, and comparing peptide and nonpeptide GLP-1 RAs, given their differing pharmacology and mechanisms of action (24). Sensitivity analyses were also conducted. Meta-regression was performed to identify any dose-dependent, age-dependent, sex-dependent, baseline weight-dependent, baseline BMI-dependent, baseline HbA_{1c}-dependent, and follow-up or treatment duration–dependent effects on study outcomes. Meta-regression was performed using STATA v16.0 (StataCorp LLC, College Station, TX).

RESULTS

A literature search of the three databases—PubMed, Embase, and CENTRAL—yielded 8,342 results, of which 2,720 duplicates were removed. Title and abstract screening excluded another 5,400 articles. Full-text review excluded 175 articles. A total of 47 articles were included in the final analysis. The PRISMA flowchart is illustrated in Fig. 1. The majority of included RCTs were judged to be of overall low risk of bias, with the exception of 11 studies that were judged to be of moderate risk (Supplementary Table 4).

The 47 studies comprised a combined cohort of 23,244 patients. The participant baseline data as well as the characteristics of the included studies are summarized in Supplementary Table 2.

The intervention characteristics of included studies, including location, main trial name, overall sample size, GLP-1 RA drug name, dosage, frequency of dosing, route of administration, concomitant drug use, and mean follow-up duration are described in Supplementary Table 3. Forty-seven studies reported mean differences in weight, 23 studies reported mean differences in BMI, and 24 studies reported mean differences in waist circumference. Liraglutide was reported in 15 studies, exenatide in 4 studies, semaglutide in 18 studies, dulaglutide in 4 studies, danuglipron in 3 studies, orforglipron in 1 study, and efpeglenatide in 2 studies. Twenty-one regimens were given once daily, 5 regimens twice daily, 20 regimens once weekly, and 1 regimen once monthly. The duration of follow-up ranged from 4 weeks to 104 weeks. The route of administration was subcutaneous injection in 41 studies and oral administration in 6 studies. The results of the GRADE assessment per outcome are presented in Tables 1, 2, and 3.

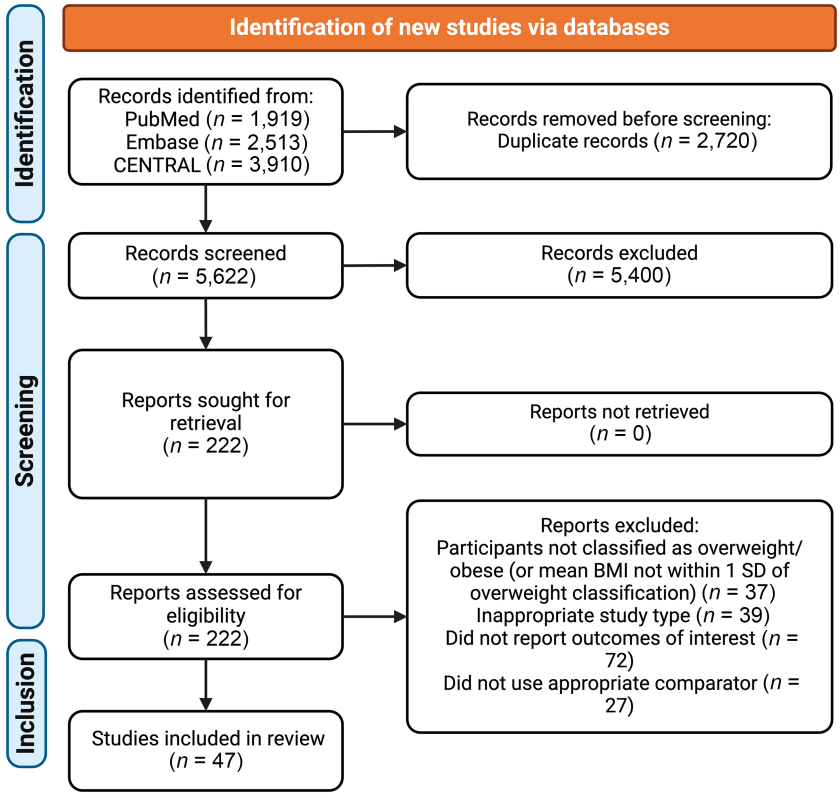

Figure 1—PRISMA flowchart.

Overall

The random-effects meta-analysis demonstrated that patients receiving GLP-1 RAs had a mean weight change of −4.57 kg (95% CI −5.35 to −3.78), a mean BMI change of −2.07 kg/m^2 (95% CI −2.53 to −1.62), and a mean waist circumference change of −4.55 cm (95% CI −5.72 to −3.38). These results are summarized in Tables 1, 2, and 3, respectively, with forest plots presented in Supplementary Fig. 1. These estimates were downgraded by two levels based on the GRADE system, because of severe statistical heterogeneity.

Subgroup Analysis

Diabetes Status

Patients without diabetes experienced greater weight, BMI, and waist circumference reduction with GLP-1 RAs than patients with diabetes. GLP-1 RAs were significantly associated with a greater decrease in weight in patients without diabetes compared with patients with diabetes (Table 1). The subgroup of patients without diabetes had a greater mean reduction in BMI than patients with diabetes (−2.96 kg/m^2 vs. −1.22 kg/m^2) (Table 2). Patients without diabetes also had a larger waist circumference change compared with patients with diabetes (−6.23 cm vs. −2.45 cm) (Table 3). The test for subgroup differences was significant ($P < 0.01$) for all three outcomes (Supplementary Fig. 2).

GLP-1 RA Administered

Weight and BMI reduction was significant for all GLP-1 RAs (Supplementary Fig. 2), and the results are summarized in Tables 1 and 2, respectively. Semaglutide was associated with the greatest mean reduction in weight (−7.18 kg), while dulaglutide was associated with the smallest degree of weight reduction (−1.23 kg). Semaglutide similarly offered the greatest reduction in BMI from baseline (−2.86 kg/m^2). Exenatide (−1.45 kg/m^2) and liraglutide (−1.45 kg/m^2) were both associated with the lowest mean difference in BMI. Waist circumference reduction was significant for all included GLP-1 RAs with

Table 1—Summary results for weight: kilogram outcome and GRADE assessment

Subgroup	Mean difference, kg (95% CI)	No. of patients (no. of included studies)	Statistical heterogeneity	Quality of evidence (GRADE)
Overall cohort	−4.57 (−5.35 to −3.78)	23,244 (47 studies)	I^2 = 97% ($P < 0.01$)	++−−[a]
Diabetes status				
Diabetes	−2.69 (−3.21 to −2.17)	13,438 (31 studies)	I^2 = 92% ($P < 0.01$)	++−−[a]
No diabetes	−9.19 (−11.52 to −6.85)	8,603 (11 studies)	I^2 = 97% ($P < 0.01$)	++−−[a]
Drug administered				
Exenatide	−2.13 (−3.05 to −1.20)	1,213 (4 studies)	I^2 = 69% ($P = 0.02$)	++−−[a]
Liraglutide	−3.80 (−4.95 to −2.65)	6,645 (15 studies)	I^2 = 94% ($P < 0.01$)	++−−[a]
Dulaglutide	−1.23 (−2.08 to −0.38)	1,340 (4 studies)	I^2 = 77% ($P < 0.01$)	++−−[a]
Semaglutide	−7.18 (−8.85 to −5.51)	12,504 (18 studies)	I^2 = 98% ($P < 0.01$)	++−−[a]
Orforglipron	−5.80 (−6.73 to −4.87)	383 (1 study)	NA	NA
Efpeglenatide	−2.09 (−2.70 to −1.49)	613 (2 studies)	I^2 = 0% ($P = 0.72$)	++++
Danuglipron	−2.12 (−3.55 to −0.70)	546 (3 studies)	I^2 = 89% ($P < 0.01$)	++−−[a]
Route of administration				
Subcutaneous injection	−4.67 (−5.54 to −3.80)	20,621 (40 studies)	I^2 = 97% ($P < 0.01$)	++−−[a]
Oral	−4.04 (−5.94 to −2.14)	2,623 (7 studies)	I^2 = 98% ($P < 0.01$)	++−−[a]
Duration				
≤1 year	−3.20 (−3.81 to −2.59)	9,480 (34 studies)	I^2 = 93% ($P < 0.01$)	++−−[a]
>1 year	−8.00 (−9.89 to −6.12)	13,764 (13 studies)	I^2 = 98% ($P < 0.01$)	++−−[a]
Type of GLP-1 RA				
Peptide	−4.72 (−5.57 to −3.87)	22,315 (43 studies)	I^2 = 97% ($P < 0.01$)	++−−[a]
Nonpeptide	−3.08 (−5.30 to −0.86)	929 (4 studies)	I^2 = 97% ($P < 0.001$)	++−−[a]
Liraglutide: diabetes status				
Diabetes	−2.69 (−3.73 to −1.65)	2,004 (8 studies)	I^2 = 87% ($P < 0.01$)	++−−[a]
Nondiabetes	−5.58 (−5.94 to −5.21)	4,534 (5 studies)	I^2 = 0% ($P = 0.82$)	++++
Semaglutide: diabetes status				
Diabetes	−3.50 (−4.57 to −2.43)	7,339 (9 studies)	I^2 = 95% ($P < 0.01$)	++−−[a]
Nondiabetes	−12.51 (−13.21 to −11.80)	4,069 (6 studies)	I^2 = 3% ($P = 0.40$)	++++

NA, not available. [a]Downgraded by two levels for severe statistical heterogeneity.

the exception of exenatide (Table 3 and Supplementary Fig. 2). Semaglutide offered the greatest reduction in waist circumference from baseline (−6.39 cm). Liraglutide was associated with the smallest decrease in waist circumference of (−3.13 cm).

Sufficient studies were present to enable subgroup analysis via diabetes status for liraglutide and semaglutide individually (Supplementary Fig. 2). Liraglutide demonstrated significantly greater reduction ($P < 0.01$) in weight (−5.58 kg vs. −2.69 kg) (Table 1) and BMI (−2.07 kg/m^2 vs. −0.71 kg/m^2) (Table 2) for patients without diabetes as compared with patients with diabetes. However, there was no evidence of subgroup difference for waist circumference reduction ($P = 0.08$). Semaglutide was associated with a significantly greater decrease ($P < 0.01$) in weight (−12.51 kg vs. −3.50 kg) (Table 1), BMI (−4.35 kg/m^2 vs. −1.41 kg/m^2) (Table 2), and waist circumference (−9.29 cm vs. −2.98 cm) (Table 3) reduction in patients without diabetes compared with patients with diabetes.

Duration of Follow-up

Studies with a mean follow-up period of >1 year were associated with a greater mean weight (−8.00 kg vs. −3.20 kg) (Table 1), BMI (−3.10 kg/m^2 vs. −1.41 kg/m^2) (Table 2), and waist circumference (−6.50 cm vs. −3.24 cm) (Table 3) reduction compared with studies with a mean follow-up period of ≤1 year. The difference between subgroups (Supplementary Fig. 2) was statistically significant for all three outcomes ($P < 0.01$).

Subcutaneous Injection Versus Oral

Studies evaluating the efficacy of parentally administered GLP-1 RAs did not demonstrate significant differences ($P > 0.05$) when compared with oral GLP-1 RAs in terms of weight (−4.67 kg vs. −4.04 kg) (Table 1), BMI (−2.03 kg/m^2 vs. −2.39 kg/m^2) (Table 2), or waist circumference reduction (−4.45 cm vs. −5.18 cm) (Table 3).

Type of GLP-1 RA

There was no significant difference ($P > 0.05$) in mean differences for weight (−4.72 kg vs. −3.08 kg) (Table 1), BMI (−2.08 kg/m^2 vs. −1.93 kg/m^2) (Table 2), and waist circumference (−4.60 cm vs. −3.40 cm) (Table 3) between peptide and nonpeptide GLP-1 RAs.

Sensitivity Analyses

As part of our sensitivity analysis, included studies were categorized according to their assessed risk of bias (Supplementary Table 3): low versus moderate to severe risk of bias. The direction of effect remained consistent in the subgroup of studies with moderate to severe risk of bias. There was also no evidence of subgroup differences ($P > 0.05$) for all three outcomes (Supplementary Fig. 2), suggesting that our findings are robust to varying levels of bias.

We also divided the included studies into two groups: *1*) those that explicitly included only overweight or obese patients and *2*) those that did not specify this criterion but were included if the mean BMI, minus 1 SD, fell within the standard criteria for overweight. The

Table 2—Summary results for BMI: kg/m^2 outcome and GRADE assessment

Subgroup	Mean difference, kg/m^2 (95% CI)	No. of patients (no. of included studies)	Statistical heterogeneity	Quality of evidence (GRADE)
Overall cohort	−2.07 (−2.53 to −1.62)	12,310 (23 studies)	I^2 = 97% ($P < 0.01$)	++−−[a]
Diabetes status				
Diabetes	−1.22 (−1.65 to −0.79)	3,350 (10 studies)	I^2 = 93% ($P < 0.01$)	++−−[a]
Nondiabetes	−2.96 (−3.70 to −2.23)	8,077 (9 studies)	I^2 = 96% ($P < 0.01$)	++−−[a]
Drug administered				
Exenatide	−1.45 (−2.22 to −0.68)	46 (1 study)	NA	NA
Liraglutide	−1.45 (−1.98 to −0.91)	5,339 (11 studies)	I^2 = 94% ($P < 0.01$)	++−−[a]
Semaglutide	−2.86 (−3.75 to −1.97)	6,542 (10 studies)	I^2 = 98% ($P < 0.01$)	++−−[a]
Orforglipron	−1.93 (−2.25 to −1.61)	383 (1 study)	NA	NA
Route of administration				
Subcutaneous injection	−2.03 (−2.53 to −1.53)	10,936 (20 studies)	I^2 = 97% ($P < 0.01$)	++−−[a]
Oral	−2.39 (−3.74 to −1.05)	1,374 (3 studies)	I^2 = 97% ($P < 0.001$)	++−−[a]
Duration				
≤1 year	−1.41 (−1.84 to −0.98)	2,957 (14 studies)	I^2 = 93% ($P < 0.01$)	++−−[a]
>1 year	−3.10 (−3.85 to −2.35)	9,353 (9 studies)	I^2 = 96% ($P < 0.01$)	++−−[a]
Type of GLP-1 RA				
Peptide	−2.08 (−2.57 to −1.60)	11,927 (22 studies)	I^2 = 97% ($P < 0.01$)	++−−[a]
Nonpeptide	−1.93 (−2.25 to −1.61)	383 (1 study)	NA	NA
Liraglutide: diabetes status				
Diabetes	−0.71 (−1.13 to −0.30)	698 (4 studies)	I^2 = 71% (P = 0.01)	++−−[a]
No diabetes	−2.07 (−2.37 to −1.78)	4,534 (5 studies)	I^2 = 68% (P = 0.01)	++−−[a]
Semaglutide: diabetes status				
Diabetes	−1.41 (−2.02 to −0.80)	2,223 (4 studies)	I^2 = 94% ($P < 0.01$)	++−−[a]
No diabetes	−4.35 (−4.83 to −3.87)	3,543 (4 studies)	I^2 = 46% (P = 0.13)	+++−[b]

NA, not available. [a]Downgraded by two levels for severe statistical heterogeneity. [b]Downgraded by one level for moderate statistical heterogeneity.

latter subgroup (Supplementary Fig. 2) was significantly associated ($P < 0.01$) with lower weight (−2.26 kg vs. −7.17 kg), BMI (−1.01 kg/m^2 vs. −2.59 kg/m^2), and waist circumference (−1.98 cm vs. −5.83 cm) reduction efficacy compared with the subgroup of studies that explicitly included only overweight or obese patients.

Meta-Regression

GLP-1 RA Administered

Random-effects meta-regression was performed to ascertain the effect of changes in drug dosages, stratified by GLP-1 RA drug type, on mean reductions in weight, BMI, and waist circumference. The criteria for inclusion was a similar route and frequency of administration. A minimum number of six studies is recommended for random-effects meta-regression (25). Hence, the drugs eligible for meta-regression were semaglutide (subcutaneous injection, once weekly) and liraglutide (subcutaneous injection, once daily), which both showed a dose-dependent treatment effect in terms of weight and BMI. Every 1-mg increase in dose of semaglutide led to a mean weight change of −4.33 kg ($P < 0.01$); for liraglutide, every 1-mg increase in dose led to a mean weight change of −1.99 kg (P = 0.02). Every 1-mg increase in dose of semaglutide led to a greater mean BMI change of −1.51 kg/m^2 (P = 0.01); for liraglutide, every 1-mg increase in dose led to a greater mean BMI change of −0.87 kg/m^2 (P = 0.01). For the outcome of change in waist circumference, semaglutide showed a dose-dependent treatment effect, but liraglutide did not. Every 1-mg increase in dose of semaglutide led to a greater mean waist circumference change of −3.46 cm ($P < 0.01$); for liraglutide, every 1-mg increase in dose led to a greater mean waist circumference change of −0.83 cm (P = 0.35).

Baseline Characteristics

In addition, random-effects meta-regression was used to evaluate whether the effects of GLP-1 RAs on decreasing weight, BMI, and waist circumference were influenced by baseline parameters. The meta-regression bubble plots are presented in Supplementary Fig. 4.

Age. A more advanced age at baseline is significantly associated ($P < 0.02$) with reduced weight, BMI, and waist circumference loss from GLP-1 RAs. For every increase in age by 1 year at baseline, degree of weight loss decreases by 0.25 kg, BMI reduction decreases by 0.09 kg/m^2, and waist circumference reduction decreases by 0.22 cm.

Sex Assigned at Birth. Males may experience reduced weight and BMI loss from GLP-1 RAs when compared with females. For every increase in the percentage of males by 1%, extent of weight loss decreases by 0.09 kg ($P < 0.01$), and BMI reduction decreases by 0.03 kg/m^2 (P = 0.04). However, corresponding decreases in waist circumference reduction efficacy were not significant (P = 0.25).

Baseline Weight. A higher weight at baseline is significantly associated ($P < 0.01$) with greater weight loss, and larger decreases in waist circumference from GLP-1 RAs. For each increase in baseline weight by 1 kg, the degree of weight loss increases by −0.28 kg, and waist circumference reduction increases by −0.20 cm.

Table 3—Summary results for waist circumference: centimeter outcome and GRADE assessment

Subgroup	Mean difference, cm (95% CI)	No. of patients (no. of included studies)	Statistical heterogeneity	Quality of evidence (GRADE)
Overall cohort	−4.55 (−5.72 to −3.38)	13,137 (24 studies)	I^2 = 94% ($P < 0.01$)	++−−[a]
Diabetes status				
Diabetes	−2.45 (−3.43 to −1.47)	4,039 (10 studies)	I^2 = 79% ($P < 0.01$)	++−−[a]
Nondiabetes	−6.23 (−8.16 to −4.30)	8,215 (10 studies)	I^2 = 95% ($P < 0.01$)	++−−[a]
Drug administered				
Exenatide	−0.27 (−3.42 to 2.87)	507 (2 studies)	I^2 = 59% ($P = 0.12$)	+++−[b]
Liraglutide	−3.13 (−4.32 to −1.94)	5,567 (9 studies)	I^2 = 80% ($P < 0.01$)	++−−[a]
Semaglutide	−6.39 (−8.31 to −4.48)	6,680 (10 studies)	I^2 = 96% ($P < 0.01$)	++−−[a]
Orforglipron	−3.40 (−4.52 to −2.28)	383 (1 study)	NA	NA
Route of administration				
Subcutaneous injection	−4.45 (−5.69 to −3.21)	11,673 (19 studies)	I^2 = 94% ($P < 0.01$)	++−−[a]
Oral	−5.18 (−9.49 to −0.86)	1,374 (3 studies)	I^2 = 98% ($P < 0.01$)	++−−[a]
Duration				
≤1 year	−3.24 (−4.34 to −2.13)	3,784 (13 studies)	I^2 = 84% ($P < 0.01$)	++−−[a]
>1 year	−6.50 (−8.32 to −4.68)	9,353 (9 studies)	I^2 = 96% ($P < 0.01$)	++−−[a]
Type of GLP-1 RA				
Peptide	−4.60 (−5.83 to −3.37)	12,754 (21 studies)	I^2 = 94% ($P < 0.01$)	++−−[a]
Nonpeptide	−3.40 (−4.52 to −2.28)	383 (1 study)	NA	NA
Liraglutide: diabetes status				
Diabetes	−2.19 (−4.17 to −0.20)	926 (3 studies)	I^2 = 72% ($P = 0.03$)	++−−[a]
No diabetes	−4.01 (−4.45 to −3.57)	4,534 (5 studies)	I^2 = 0% ($P = 0.43$)	++++
Semaglutide: diabetes status				
Diabetes	−2.98 (−4.30 to −1.66)	2,223 (4 studies)	I^2 = 82% ($P < 0.01$)	++−−[a]
No diabetes	−9.29 (−9.93 to −8.65)	3,681 (5 studies)	I^2 = 0% ($P = 0.54$)	++++

NA, not available. [a]Downgraded by two levels for severe statistical heterogeneity. [b]Downgraded by one level for moderate statistical heterogeneity.

However, an increase in the extent of BMI reduction was not conclusively shown ($P = 0.12$).

Baseline BMI. A higher baseline BMI is significantly associated ($P < 0.01$) with greater weight and waist circumference reduction from GLP-1 RAs. For every increase in baseline BMI by 1 kg/m^2, extent of weight loss increases by −0.78 kg, and waist circumference reduction increases by −0.58 cm; however, there was no significant increase in the degree of BMI reduction ($P = 0.06$).

Baseline HbA$_{1c}$. A higher baseline HbA$_{1c}$ level is significantly associated ($P < 0.01$) with reduced weight loss, BMI reduction, and waist circumference reduction. For each 1% increase in baseline HbA$_{1c}$, extent of weight loss decreases by 2.40 kg, BMI reduction decreases by 0.62 kg/m^2, and waist circumference reduction decreases by 1.72 cm.

Duration of Follow-up. A longer duration of treatment is significantly associated ($P < 0.01$) with larger decreases in weight, BMI, and waist circumference. For every increase in duration of follow-up by 1 week, degree of weight loss increases by −0.10 kg, BMI reduction increases by −0.04 kg/m^2, and waist circumference reduction increases by −0.09 cm.

Discussion

In this meta-analysis of 47 RCTs of 23,244 patients, GLP-1 RAs were associated with a significant reduction in weight (−4.57 kg, 95% CI −5.35 to −3.78) compared with placebo, regardless of diabetes status. Treatment effects were consistent regardless of the GLP-1 RA used and route of administration. From the subgroup analysis and meta-regression, the greatest treatment benefit appeared to favor patients who were younger, female, did not have diabetes, and had higher baseline weight and BMI but lower HbA$_{1c}$ at baseline over a longer duration of treatment. The effect is likely greatest with semaglutide. These findings were largely consistent over the other outcomes of change in BMI and waist circumference from baseline.

The results demonstrated a sustained improvement in the degree of weight, BMI, and waist circumference reduction by GLP-1 RAs. Firstly, greater efficacy was observed in studies with >1 year of follow-up as compared with ≤1 year in the subgroup analysis. Secondly, the meta-regression demonstrated increasing weight, BMI, and waist circumference loss the longer the follow-up duration, even beyond 1 year. These findings indicate that GLP-1 RAs may facilitate continued weight loss beyond the commonly observed plateau at approximately 1 year, as previously reported in literature (26). However, these results should be interpreted cautiously, as they were obtained within controlled settings such as RCTs and may not reflect real-world usage. Patient compliance and concurrent exercise are possible factors influencing outcomes. A study has shown that combining GLP-1 RA treatment with exercise supports weight loss maintenance post-treatment, whereas using GLP-1 RAs alone without exercise leads to weight regain after discontinuation (27). Given that overweight/obesity occurs in association with chronic comorbidities such as type 2 diabetes, chronic kidney disease (28), cardiovascular disease (29), osteoarthritis, and asthma (30), GLP-1 RAs may indirectly contribute toward the management of such chronic diseases, given their sustained antiobesity effect. Of note, GLP-1 RAs are associated with a reduction in the risk for cardiovascular

and all-cause mortality (31). In addition, given their aforementioned effects, GLP-1 RAs may help delay progression to diabetes and its associated complications. Further research is needed to ascertain GLP-1 RAs as an agent against the development of type 2 diabetes in obese patients.

Of note, the results of the subgroup analysis demonstrate a significantly greater extent of weight, BMI, and waist circumference reduction in patients without diabetes as compared with patients with diabetes ($P < 0.001$). Similar efficacy profiles were noted in sensitivity analyses conducted via subgroup analysis stratified by diabetes status for liraglutide and semaglutide individually. In addition, the meta-regression demonstrated that individuals with higher HbA_{1c} are less likely to experience benefit, as the magnitude of reduction in weight, BMI, and waist circumference is reduced. These findings enhance the robustness of the observed association, and GLP-1 RAs may be more effective in patients without diabetes. This may stem from disrupted gastric and small-intestinal motility observed in some patients with diabetes (32), which could attenuate the ability of GLP-1 RA to modulate gastrointestinal motility (33) and thus impair its weight loss effect. Our findings are, at this juncture, entirely exploratory, and further studies to ascertain the superiority of GLP-1 RA in patients without diabetes and elucidate its underlying physiological mechanisms are clearly indicated.

Recent developments present new GLP-1 RAs that are administered orally as compared with traditional subcutaneous injections. Considering the novelty of these GLP-1 RAs, analyses comparing their effects to traditional GLP-1 RAs is timely. In our meta-analysis, we showed that oral administration exerted comparable effects on weight control, BMI, and waist circumference as compared with subcutaneous injection. Oral GLP-1 RAs may improve patient compliance by being more convenient, less painful, and less stressful to take. Hence, oral GLP-1 RAs should be considered where possible, if overall safety is at least comparable to the conventional injected GLP-1 RAs (34). This is further supported by comparative cost effectiveness between oral GLP-1 RAs such as semaglutide and subcutaneous injection-based GLP-1 RAs demonstrated by Feng et al. (35).

The meta-regression results on GLP-1 RA suggested a dose-dependent weight reduction in patients taking either daily liraglutide (subcutaneous injection) or once-weekly semaglutide (subcutaneous injection). The remaining individual GLP-1 RAs were not eligible for meta-regression, because of differing administration frequencies, route of administration, and/or insufficient studies. This could indicate greater weight/BMI lowering through increasing GLP-1 RA dose, in particular for patients for whom extensive weight/BMI loss is indicated, although dose-dependent adverse effects must be considered.

The meta-regression results also suggest that the lower the baseline weight, BMI, or waist circumference, the lower the extent of weight/BMI/waist circumference reduction. These findings support existing guidelines on obesity management that only recommend pharmacological management for adults with a BMI >30 kg/m^2. Hence, this serves as a caution against the use of GLP-1 RAs in non-overweight/nonobese or normal BMI individuals who seek an "easy" method to lose weight. The risks of GLP-1 RAs relating to adverse effects may outweigh the benefits in this regard (36). Further research is required to evaluate the use of GLP-1 RAs in non-obese/overweight or normal BMI patients.

Our meta-regression also suggests that an advanced age might correlate to reduced efficacy of GLP-1 RAs to reduce weight, BMI, and waist circumference. There is a need to balance the possible diminished effect of GLP-1 RAs in lowering these parameters alongside other potential benefits against increased susceptibility to adverse drug reactions in the elderly (37). Notable benefits include significant reductions in all-cause mortality, major adverse cardiovascular outcomes, and major adverse kidney outcomes (38), although these benefits have not been specifically explored in an elderly-only population. Further studies are ultimately required to better elucidate the benefits and risks of GLP-1 RAs in the very elderly.

In our sensitivity analysis, we evaluated subgroup differences between studies that exclusively included overweight/obese patients and those that did not explicitly define overweight/obese status but were included if their mean BMI was within 1 SD of the standard criteria for overweight. We observed that reductions in weight, BMI, and waist circumference were significantly greater in the subgroup of studies focusing on overweight/obese individuals, which helps underscore the excellent efficacy of GLP-1 RAs in this particular patient population. However, it suggests that the effect of GLP-1 RAs on these outcomes may be greater than indicated in the primary analysis. Nonetheless, the primary results remain valuable, representing conservative estimates that might enhance generalizability of our findings to a broader population, perhaps even beyond those with high BMI.

The weight-reducing effects of GLP-1 RAs, as highlighted in this study and existing literature (39), emphasize GLP-1 RAs as important pharmacological therapies in the management of overweight and obesity. Nevertheless, it is important to emphasize that proper diet and regular physical exercise remain key components of any weight loss regimen (40), and should not be overlooked.

Our study should be interpreted in due consideration of its limitations. First, there was substantial statistical heterogeneity across the overall and subgroup mean differences in weight, BMI, and waist circumference, as shown by the GRADE assessment, where the majority of estimates were downgraded by two levels. This heterogeneity likely, in part, because of the inclusion of patients from different countries and populations. However, it serves to enhance the generalizability of our findings. Nonetheless, potential differences in trial design, prescription practices, patient response and tolerance, and more nuanced factors like lifestyle habits should be taken into account when interpreting the results in one's own context. We attempted to account for these factors through various subgroup analyses and meta-regression. Furthermore, sensitivity analysis by risk of bias showed no change in the direction of results. Second, GLP-1 RAs such as exenatide and efpleglenatide had very few studies, which may reduce reliability on pooled effect estimates. It also limited our ability to perform subgroup comparisons within each GLP-1 RA with regards to diabetes status. Third, a small number of studies per subgroup diminishes statistical power, increases the risk of type II errors, and amplifies susceptibility to biases inherent in individual studies. Fourth, the disproportionately small number of studies on oral GLP-1 RAs may bias the assessment of comparative efficacy against subcutaneously injected GLP-1 RAs. Fifth, the follow-up

durations of included studies ranged widely, from 4 to 104 weeks. Our present analysis indicated enhanced efficacies with longer follow-up. Therefore, the potential skewing of treatment benefit toward studies/GLP-1 RAs with longer follow-up should be acknowledged when interpreting the pooled results. Sixth, danuglipron and orforglipron are nonpeptide GLP-1 RAs, whereas the others are peptide-based. Their differences in mechanism of action (24) should be considered when interpreting pooled results. To address this concern, we performed sensitivity analysis via subgroup comparisons of peptide and nonpeptide GLP-1 RAs, and found no significant difference in efficacy ($P > 0.05$). However, this finding is exploratory, particularly considering the limited number of studies on nonpeptide GLP-1 RAs, and further studies are warranted to establish their relative efficacies.

CONCLUSIONS

We performed a meta-analysis and meta-regression on the older and latest GLP-1 RAs. GLP-1 RAs showed significant decreases in weight, BMI, and waist circumference, and the magnitude of effect may be greater in individuals without diabetes compared with individuals with diabetes. Furthermore, oral GLP-1 RAs have comparable efficacies and could offer better patient compliance.

Acknowledgments. N.S. is an editor of *Diabetes Care* but was not involved in any of the decisions regarding review of the manuscript or its acceptance.

Funding. C.-H.S. has received writing support from Novartis.

Duality of Interest. C.-H.S. has received writing support from Novartis; speaker fees from Amgen, Novartis, and Bristol Myers Squibb; consulting fees from Boehringer Ingelheim; and travel grants from Amgen.

Author Contributions. H.J.W., Y.H.T., Y.N.T., and C.-H.S. were responsible for the conceptualization and design of the study. H.J.W., B.S., and Y.H.T. conducted the search and performed data collection. H.J.W., B.S., and Y.H.T. analyzed data and drafted the first manuscript. H.J.W., B.S., Y.H.T., Y.N.T., M.Y.C., L.L.L.Y., P.C.E., B.Y.Q.T., N.S., M.D., and C.-H.S. critically reviewed and edited the manuscript. Y.H.T., Y.N.T., M.Y.C., L.L.L.Y., P.C.E., B.Y.Q.T., N.S., M.D., and C.-H.S. supervised the study. All authors contributed to the article, and read and approved the final manuscript. C.-H.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Handling Editors. The journal editor responsible for overseeing the review of the manuscript was Frank Hu.

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