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Efficacy and safety of orforglipron 12 mg versus orforglipron 36 mg maintenance dose among patients with obesity with or without diabetes: a systematic review and comprehensive meta-analysis

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Abstract

Background Obesity is projected to affect about one billion adults by 2030 and is associated with cardiometabolic morbidity. Orforglipron is an oral, non-peptide glucagon-like peptide-1 receptor agonist developed to provide weight and metabolic benefits. Prior meta-analyses have supported its efficacy and safety but were limited by shorter follow-up and a predominance of non-diabetic populations. This meta-analysis aims to provide the most comprehensive head-to-head comparison between the two most commonly studied maintenance doses (12 mg vs. 36 mg), assessing weight, glycemic, cardiometabolic, and safety outcomes.

Methods We searched PubMed, Web of Science, Cochrane, and Scopus until March 1, 2026, for randomized controlled trials (RCTs) comparing orforglipron 12 mg and 36 mg in obese adults. Outcomes of interest included percentage and absolute body weight change, BMI, HbA1c, waist circumference, lipid parameters, blood pressure, and adverse events. Results were pooled using a fixed-effects model, and prespecified subgroup analyses examined differences by diabetes status and treatment duration.

Results Six RCTs (3459 participants) were included. Compared with the 12 mg dose, the 36 mg dose was associated with greater reductions in percentage body weight change ($p < 0.00001$), absolute body weight change ($p < 0.00001$), body mass index ($p < 0.00001$), HbA1c ($p < 0.00001$), waist circumference ($P < 0.00001$), percent change in triglycerides ($P = 0.002$), and systolic blood pressure ($P = 0.002$). Adverse events were comparable between doses. No significant differences were observed in gastrointestinal events or pancreatic functions. A small difference in pulse rate was noted but was not considered clinically significant.

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Conclusion In obese adults, orforglipron 36 mg improved weight and metabolic outcomes compared with 12 mg. No statistically significant differences between doses were detected for the prespecified safety outcomes, although small increases in ALT and AST were observed with the 36 mg dose and the trials included were not powered to detect rare or long-term adverse events. These findings support consideration of the higher maintenance dose when clinically appropriate. Longer-term studies are needed to confirm the benefit and cardiovascular outcomes.

Clinical trial number Not applicable.

Keywords Orforglipron, Obesity, Meta-analysis, Head-to-head, Safety, Efficacy

Introduction

About 2.9 billion adults will have high body mass index (BMI) by 2030, with 1.1 billion adults suffering from obesity (BMI ≥ 30 kg/m2) [1]. Obesity-related complications include type 2 DM, dyslipidemia, cardiovascular diseases, nonalcoholic fatty liver disease, polycystic ovary syndrome, infertility, obstructive sleep apnea, GERD, and depression [2].

The American Diabetes Association (ADA) recommends dietary, exercise, and behavioral regimens to achieve and maintain a body weight loss of ≥ 5% [3]. Patients should use drug therapy when a BMI is ≥ 30 kg/m2, or a BMI of 27 to 29.9 kg/m2 with obesity related complications, when lifestyle modification fails to achieve the target weight loss (5% of total body weight within 3 to 6 months). The American Association of Clinical Endocrinologists (AACE) and ADA recommend a patient-centered approach while choosing the appropriate drug therapy, as cardiovascular, heart failure, and chronic kidney diseases come first before the risk of hypoglycemia, cost, effect on weight, and adverse events [4, 5].

The US Food and Drug Administration (FDA) has approved two GLP-1 agonist drugs: a once-weekly Semaglutide and a once-daily Liraglutide, in addition to a dual GLP-1 and GIP agonist: a once-weekly Tirzepatide, as first-line pharmacotherapy for obesity. However, their gastrointestinal side effects, injectable nature, and high cost can affect the patient's tolerance [6–9]. In the USA, Semaglutide is approved for the treatment of DM either orally or by subcutaneous injection. For weight management, subcutaneous semaglutide (Wegovy) has long been approved, and in December 2025 the FDA additionally approved an oral semaglutide 25 mg tablet (Wegovy tablets) for chronic weight management in adults with obesity or overweight with at least one weight-related comorbidity, so an oral option for weight reduction is now also available [10].

Orforglipron is a novel, oral non-peptide GLP-1 partial agonist that favors the activation of G protein more than β-arrestin, with the potential of a similar physiological outcome to the first-line drugs and offers a high bioavailability without the necessity of food and water restriction, favoring it over other injectable GLP-1 agonists [11, 12]. A recent meta-analysis has demonstrated the use of Orforglipron in weight and glycemic control. However, it is limited by the inadequate reported outcomes, such as liver enzymes, cardiovascular parameters, and lipid profile, also some safety-related outcomes as the incidence of serious adverse events were limited by the non-diabetic predominance, and short treatment duration for most of the included studies [13], so our study aims to provide a comprehensive efficacy and safety analysis with additional outcomes and a recent phase 3 trial to achieve a high quality of evidence [14]. Furthermore, our study is the only meta-analysis that provides a comprehensive head-to-head comparison between 12 mg and 36 mg maintenance doses, which are the most frequently addressed doses in clinical trials.

Materials and methods

This meta-analysis was conducted in accordance to the PRISMA checklists [15]. This study protocol was submitted to and registered on PROSPERO: CRD420251275501.

Search strategy

Our search was conducted across PubMed, Cochrane, Scopus, and Web of Science. We searched the databases from inception until March 1, 2026. To capture all relevant literature, we included a variety of appropriate synonyms and intervention-related terms (Orforglipron, LY3502970, or "oral GLP-1 receptor agonist"), in combination with condition and outcome-related keywords (obesity, type II diabetes mellitus, HbA1c, BMI, body weight, gastrointestinal outcomes, adverse events, and cardiometabolic markers). The full search strategy is provided within the supplementary file.

Eligibility criteria

Studies were included if they matched these criteria: (1) were randomized controlled trials (RCTs); (2) enrolled adult patients (≥ 18 years) with obesity and with or without type 2 diabetes mellitus; (3) evaluated Orforglipron at maintenance doses of 12 mg or 36 mg, (4) provided data of both 12 mg and 36 mg arms; (5) reported at least one of the pre-specified efficacy or safety endpoints of interest. Because several of the included trials were originally designed to evaluate orforglipron in T2D populations, they applied lower BMI eligibility thresholds than

the conventional WHO obesity cutoff (BMI ≥ 30 kg/m²): Frias et al. (2023) and Rosenstock et al. (2025) required BMI ≥ 23 kg/m², Horn et al. (2025) required BMI > 27 kg/m², and Rosenstock et al. (2026) required BMI ≥ 25 kg/m². Only Wharton et al. (2023) and Wharton et al. (2025) restricted enrollment to participants meeting the conventional WHO obesity threshold (BMI ≥ 30 kg/m², or ≥ 27 kg/m² with a weight-related comorbidity). We retained all six trials in the primary analysis because each nonetheless enrolled a predominantly overweight/obese population and reported the pre-specified 12 mg vs. 36 mg efficacy and safety outcomes; however, this difference in BMI eligibility is acknowledged as a source of clinical heterogeneity across the included trials (see Discussion, Limitations). To assess the robustness of the primary efficacy findings to this heterogeneity, a sensitivity analysis restricted to the two trials applying the conventional WHO obesity threshold (Wharton et al. 2023 and Wharton et al. 2025) was performed for the primary weight-related outcomes (Supplementary material).

Studies were excluded if they (1) were not RCTs; (2) did not provide sufficient data regarding 12 mg and 36 mg Orforglipron for at least one of the outcomes of interest; (3) were animal or preclinical studies; (4) were reviews, editorials, or conference abstracts.

Data extraction and outcomes

Both title/Abstract and full text screening were performed independently by two authors. Conflicts were resolved by a third author.

Two independent authors extracted the data. The data extraction mainly focused on data regarding the characteristics of included studies (Study ID, study design, setting, sample sizes, age, sex, race, and duration of treatment) and baseline data, mainly focused on measured effects and outcomes. The data were extracted into Microsoft Excel spreadsheets and then revised by a third author.

Quality assessment

Risk of bias for each included trial was individually assessed using the Cochrane Risk of Bias 2.0 (ROB 2.0) tool [16]. Two independent authors evaluated the studies across five domains that were specified by the tool. The domains are: (1) bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias of missing outcome data, (4) bias of outcome measurement, and (5) bias in the selection of reported results. Each domain was judged as low risk, some concerns, or high risk, and then an overall risk of bias judgment was concluded accordingly. Disagreements between reviewers were resolved through discussion in a group call of the two authors joined by the remaining authors.

Data analysis and outcomes

The outcomes measured included: measures of efficacy (percent change in bodyweight (%), change in BMI (kg/m2), absolute body weight change (kg), percent change in HbA1c (percentage points), absolute change in waist circumference (cm), percent change in serum total cholesterol (%),percent change in LDL cholesterol (%), percent change in HDL cholesterol (%), percent change in triglycerides (%), change in fasting serum glucose (mg/dL), change in systolic blood pressure (mmHg), change in diastolic blood pressure (mmHg), change in pulse rate (bpm)) and measures of safety (any TEAE, serious adverse events, adverse events leading to treatment discontinuation, death, nausea, vomiting, diarrhea, constipation, percent change in total serum lipase (%), percent change in total serum amylase (%), percent change in serum calcitonin (%), percent change in Serum Alanine Aminotransferase ALT (%), percent change in Serum Aspartate Aminotransferase AST (%)).

We analyzed the outcomes by Review Manager Version 5.4 [17]. Dichotomous outcomes were reported as risk ratio (RR) and 95% confidence interval (CI), while continuous outcomes were reported as mean difference and 95% confidence interval. When not reported, standard deviations were calculated using the equations listed in the supplementary file. I-squared (I^2), and Chi-square (chi^2) tests were used to assess heterogeneity. Heterogeneity across studies was assessed using the p-value of chi^2 test and the I^2 statistic. Rather than applying a fixed P-value/I2 threshold to declare heterogeneity "significant," I2 and tau-squared are reported for every outcome and interpreted alongside the underlying clinical and methodological differences between studies (e.g., diabetes status, treatment duration, phase 2 vs. phase 3 design). Where heterogeneity was appreciable, it was explored through sensitivity analysis (including the random-effects model described below) or subgroup analysis. A prespecified subgroup analysis was conducted based on diabetic status (diabetics vs. non-diabetics) and treatment duration (≤ 40 weeks vs. ˃ 40 weeks) for all assessed outcomes. fixed-effect model was used as the primary analysis for all outcomes because the included studies enrolled broadly similar populations (adults with obesity, with or without T2D) and used a consistent intervention (orforglipron 12 mg vs. 36 mg) under comparable trial designs. I^2 and τ^2 are reported for every outcome, and heterogeneity was interpreted in light of both statistical indices and clinical/methodological differences between studies (e.g., diabetes status, treatment duration, phase 2 vs. phase 3 design), rather than a single I^2/P threshold. To test the robustness of the fixed-effect estimates, a random-effects (DerSimonian-Laird) model was applied as a sensitivity analysis for all outcomes with at least moderate heterogeneity or clinical relevance; results are reported in the

Supplementary material and, where the conclusion differed from the fixed-effect analysis, this is noted explicitly in the Results. For continuous outcomes, analyses used the change-from-baseline mean and standard deviation reported by each trial; where standard deviations were not directly reported, they were imputed using the formulas detailed in the supplementary file, and outcomes affected by such imputation were re-examined in sensitivity analyses excluding the affected study. Subgroup analyses by diabetes status and treatment duration were prespecified but are considered exploratory given the limited number of trials contributing to each stratum; between-subgroup differences were evaluated using the chi-square test for subgroup differences implemented in Review Manager (a formal test of interaction), and findings should not be interpreted as confirmatory.

Results

Study selection

This systematic review included six RCTs with a total of 3459 patients [14, 18–22], filtered through an initial pool starting with 326 records. After duplicate removal, 200 records were eligible for the Title and abstract screening, which resulted in the exclusion of 184 records. The remaining 16 reports were assessed for eligibility. After excluding conference abstracts and secondary analyses without additional data of interest to our study, we landed on 9 reports and excluded three reports that did not address the target doses of 12 mg and 36 mg [23–25]. The detailed identification process is addressed in Fig. 1.

Baseline characteristics and patient demographics

This study included two phase 2 trials (Frias et al., 2023; Wharton et al., 2023) and four phase 3 trials (Horn et al., 2025; Rosenstock et al., 2025; Rosenstock et al.,

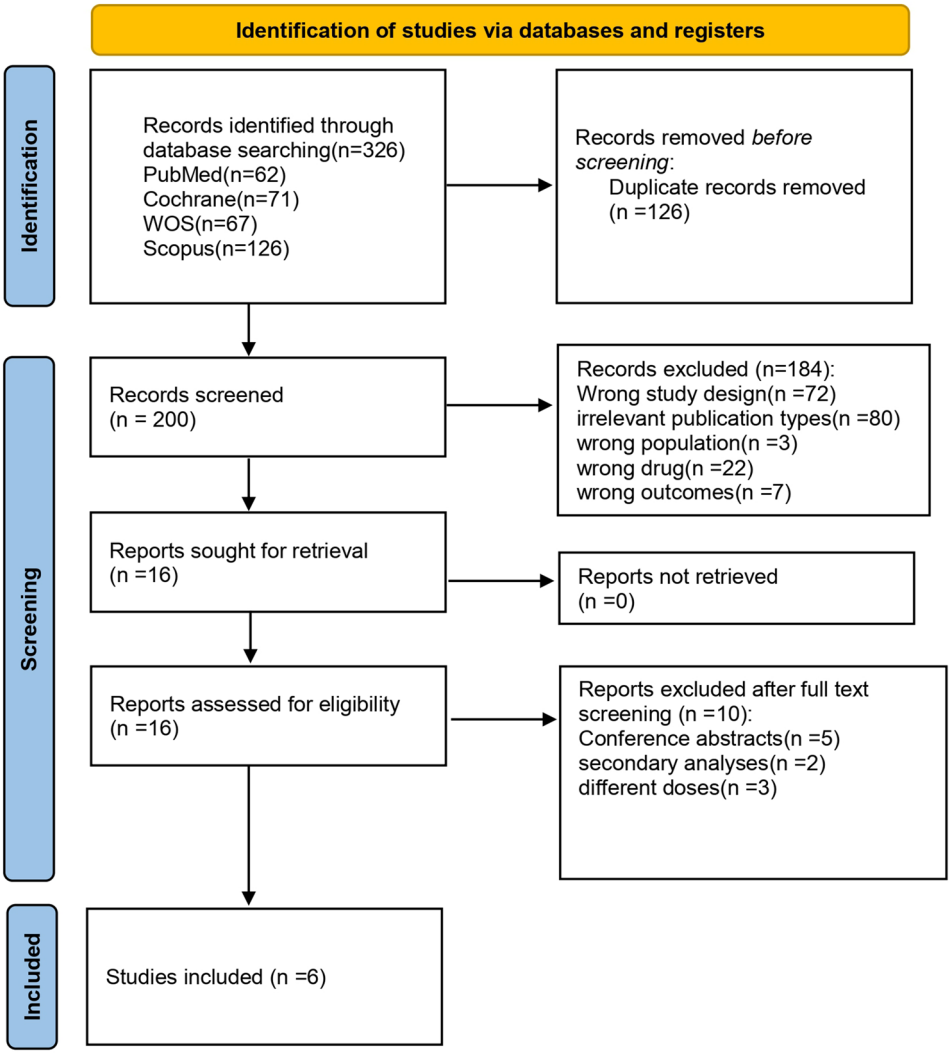


Fig. 1 PRISMA flow diagram of the included studies

2026; Wharton et al., 2025) with a total of 3459 patients, divided into two arms based on the dose of Orforglipron, a 12 mg arm and a 36 mg arm, consisting of 1724 and 1735 patients, respectively. The samples were fairly balanced gender-wise, with a slight female predominance of 1909 patients (55%), and race-wise has shown a white race predominance of 2045 patients (59%). The treatment duration varied from 26 to 72 weeks. Characteristics and baseline values of included studies are demonstrated in Tables 1 and 2, respectively (Tables 1 and 2).

Risk of bias assessment

The risk of bias of included double-arm parallel clinical trials was assessed using the ROB 2 tool, considering five main domains. The evaluation of bias for the included clinical trials revealed that three studies were at low risk for bias in all domains. At the same time, one (Frias et al., 2023) exhibited a high risk in the third domain. Another two (Rosenstock et al., 2026) and (Wharton et al., 2023) exhibited unclear risk in the second and third domains, respectively. The main source of bias was due to missing outcome data and Deviations from Intended Interventions. The detailed quality evaluation of the selected studies is shown in Fig. 2.

Efficacy outcome

Percentage change in body weight

The 36-mg dose of Orforglipron was associated with a significantly greater reduction in percentage body weight compared with the 12-mg dose (MD: 2.62%; CI: 2.07 to 3.17; $p < 0.00001$; $I^2 = 0\%$) (Fig. 3A). In a sensitivity analysis restricted to the two trials applying the conventional WHO obesity threshold (BMI ≥ 30 kg/m²; Wharton et al. 2023 and Wharton et al. 2025), the effect was slightly larger and remained highly statistically significant (MD: 2.97%; 95% CI: 1.98 to 3.96; $P < 0.00001$), indicating that the primary weight-loss finding is not driven by the trials with lower BMI eligibility thresholds.

Subgroup analysis based on diabetic status and treatment duration consistently favored the 36-mg dose. Within the non-diabetic subgroup, the pooled 36-mg-vs-12-mg difference in percentage body weight change was (MD: 2.97%; CI: 1.98 to 3.96; $p < 0.00001$; $I^2 = 0\%$). Within the >40-week subgroup, the corresponding pooled difference was (MD: 2.63%; CI: 2.00 to 3.26; $p < 0.00001$; $I^2 = 0\%$) (Figure S1A, S1B).

Absolute change in bodyweight (kg)

The 36-mg dose of Orforglipron was associated with a significantly greater reduction in absolute body weight compared with the 12-mg dose (MD: 2.31 kg; CI: 1.89 to 2.72; $p < 0.00001$; $I^2 = 0\%$) (Fig. 3B).

Subgroup analysis based on diabetic status and treatment duration consistently favored the 36-mg dose. Within the diabetic subgroup, the pooled 36-mg-vs-12-mg difference in absolute body weight change was (MD: 2.35 kg; CI: 1.68 to 3.02; $p < 0.00001$; $I^2 = 0\%$). Within the ≤40-week subgroup, the corresponding pooled difference was (MD: 2.68 kg; CI: 1.53 to 3.83; $p < 0.0001$; $I^2 = 8\%$) (Figure S2A, S2B).

Change in BMI (kg/m2)

The 36-mg dose of Orforglipron was associated with a significantly greater reduction in BMI compared with the 12-mg dose (MD: 0.92 kg/m²; CI: 0.77 to 1.07; $p < 0.00001$; $I^2 = 0\%$) (Fig. 3C).

Subgroup analysis based on diabetic status and treatment duration consistently favored the 36-mg dose. Within the non-diabetic subgroup, the pooled 36-mg-vs-12-mg difference in BMI change was (MD: 1.27 kg/m²; CI: 0.81 to 1.73; $p < 0.00001$; $I^2 = 0\%$). Within the ≤40-week subgroup, the corresponding pooled difference was (MD: 0.95 kg/m²; CI: 0.54 to 1.35; $p < 0.0001$; $I^2 = 17\%$) (Figure S3A, S3B).

Change in HbA1c (percentage points)

The 36-mg dose of Orforglipron was associated with a significantly greater reduction in HbA1c (in percentage points) compared with the 12-mg dose (MD: 0.08% points; CI: 0.05 to 0.10; $p < 0.00001$; $I^2 = 39\%$). Initial heterogeneity was detected and was resolved through sensitivity analysis by excluding Wharton et al., 2023 (Fig. 4A). This finding remained statistically significant in the random-effects sensitivity analysis (MD: 0.12% points; 95% CI: 0.04 to 0.20; $P < 0.05$), although the confidence interval was wider than under the fixed-effect model, indicating somewhat greater uncertainty around the effect estimate (Supplementary material).

Subgroup analysis based on diabetic status and treatment duration consistently favored the 36-mg dose. Within the diabetic subgroup, the pooled 36-mg-vs-12-mg difference in HbA1c change was (MD: 0.18% points; CI: 0.08 to 0.27; $p = 0.0005$; $I^2 = 0\%$). Substantial heterogeneity was initially observed within the non-diabetic subgroup, largely driven by the zero mean difference reported in Wharton et al., 2023, attributable to imputed standard deviation values due to insufficient reported data (Figure S4A). Accordingly, the subgroup analysis was repeated after exclusion of this study, resulting in resolution of heterogeneity (Figure S4B). Within the >40-week subgroup, the corresponding pooled 36-mg-vs-12-mg difference in HbA1c change was (MD: 0.08% points; CI: 0.05 to 0.11; $P < 0.00001$; $I^2 = 68\%$) (Figures S4C).

Change in waist circumference (cm)

The 36-mg dose of Orforglipron was associated with a significantly greater reduction in waist circumference

Table 1 Characteristics of the included studies

Study ID	study design	countries	sample size (*n*)		Age (mean ± SD) in years		Sex *n*(%)		Race *n*(%)		Duration of treatment
			12 mg	36 mg	12 mg	36 mg	12 mg	36 mg	12 mg	36 mg	
Frias et al. 2023 [19]	Phase 2, double-blind, randomized, multicenter study	USA, Hungary, Poland, and Slovakia	56	61	57·4 ± 9·2	59·7 ± 9·2	Female 20 (36%) Male 36 (64%)	Female 25 (41%) Male 36 (59%)	Asian: 1(2%) white: 49(88%) black: 5(9%)	Asian: 1(2%) white: 58 (95%) black: 0(0%)	26 weeks
Horn et al. 2025 [18]	Phase 3, double-blind, placebo-controlled trial	Argentina, Australia, Brazil, China, Czech, Germany, Greece, India, South Korea, and USA	332	322	56·2 ± 10·5	58·1 ± 10·8	Female 155 (46·7%) Male 177 (53·3%)	Female 154 (47·8%) Male 168 (52·2%)	Asian: 55(16·6%) white: 235(70·8%) black: 19(5·7%)	Asian: 54(16·8%) white: 228(70·8%) black: 28(8·7%)	72 weeks
Rosenstock et al. 2025 [20]	Phase 3, double-blind, placebo-controlled trial,	United States, Japan, India, China, and Mexico	137	141	54.1 ± 11.8	52.8 ± 11.8	Female 71 (51.8%) Male 66 (48.2%)	Female 72 (51.1%) Male 69 (48.9%)	Asian: 59(43.1%) white: 30(21.9%) black: 9(6.6%)	Asian: 62(44.0%) white: 40(28.4%) black: 4(2.8%)	40 weeks
Rosenstock et al. 2026 [14]	multinational, multicenter, open-label, randomized, phase 3 trial	Argentina, China, Japan, Mexico, and the USA	424	423	54 ± 11·3	53.4 ± 11.4	Female: 195 (46%) Male: 229 (54%)	Female: 218 (52%) Male: 205 (48%)	Asian: 50/418(12%) white: 250/418(60%) black: 17/418 (4%)	Asian: 51/415(12%) white: 259/415(62%) black: 16/415 (4%)	52 weeks
Wharton et al. 2023 [21]	Phase 2, randomized, double-blind trial	Canada, the United States, and Hungary	50	58	49.8 ± 10.5	55.8 ± 11.28	Female 31 (62%) Male 19 (38%)	Female 36 (62%) Male 22 (38%)	Asian: 0(0%) white: 47(94%) black: 3(6%)	Asian: 0(0%) white: 50(86%) black: 8(14%)	36 weeks
Wharton et al. 2025 [22]	Phase 3, multinational, randomized, double-blind trial	Brazil, China, India, Japan, South Korea, Slovakia, Spain, Taiwan, and USA	725	730	45.4 ± 12.6	44.9 ± 11.9	Female 467 (64.4%) Male 258 (35.6%)	Female 465 (63.7%) Male 265 (36.3%)	Asian: 201(28.1%) white: 405(56.6%) black: 60(8.4%)	Asian: 214 (29.6%) white: 394(54.4%) black: 67(9.3%)	72 weeks

Table 2 Baseline values of the included studies

	Study ID											
	Frias et al. 2023 [19]		Horn et al. 2025 [18]		Rosenstock et al. 2025 [20]		Wharton et al. 2023 [21]		Wharton et al. 2025 [22]		Rosenstock et al. 2026 [14]	
	12 mg	36 mg	12 mg	36 mg	12 mg	36 mg	12 mg	36 mg	12 mg	36 mg	12 mg	36 mg
Duration of obesity years (mean ± SD)	NA	NA	15.47 ± 11.9	16.1 ± 11.6	NA	NA	NA	NA	13.7 ± 10.6	13.4 ± 11.1	NA	NA
Duration of diabetes years (mean ± SD)	7.8 ± 6.77	6.1 ± 4.7	6.67 ± 4.9	8 ± 6.78	5.1 ± 6.0	4.2 ± 5.1	NA	NA	NA	NA	9 ± 7.1	8.2 ± 5.8
Body weight kg (mean ± SD)	99·3 ± 18·1	98·9 ± 17·5	102·7 ± 21·3	99·8 ± 23·0	90.6 ± 23.1	90.1 ± 22.9	107.5 ± 25.3	108.3 ± 25.45	102.2 ± 21.6	103.1 ± 23.2	96.1 ± 22.2	96.5 ± 21.9
BMI kg/m2 (mean ± SD)	34·8 ± 6·3	34·4 ± 5·4	36·1 ± 6·3	35·1 ± 6·5	33.3 ± 7.8	33.1 ± 7.3	37.7 ± 7.7	38 ± 6.29	36.7 ± 6.5	36.9 ± 6.7	34.5 ± 7.1	35.3 ± 7.2
Hb A1C % (mean ± SD)	8·2 ± 0·9	8 ± 0·7	8·08 ± 0·76	8·05 ± 0·73	7.98 ± 0.91	8.07 ± 0.9	5.5 ± 0.4	5.65 ± 0.4	5.6 ± 0.3	5.6 ± 0.3	8.3 ± 1	8.3 ± 1.1
Fasting serum glucose mg/dL (mean ± SD)	172·1 ± 42·8	157·9 ± 28·7	155·1 ± 43·0	154·7 ± 40·1	155.3 ± 55.1	148.8 ± 40	94.4 ± 9.8	96.85 ± 13.28	92.1 ± 10	93 ± 10.5	169 ± 54	167 ± 52
Waist circumference Cm(mean ± SD)	113.7 ± 11.8	112.1 ± 12.7	116·2 ± 13·4	114·7 ± 15·1	107.7 ± 16.9	107.6 ± 17	114.4 ± 16.5	117.3 ± 15.37	112 ± 14.2	112.4 ± 15.3	111.4 ± 14.9	112.3 ± 15.2
Systolic blood pressure mmHG (mean ± SD)	134·9 ± 12·6	132·9 ± 12·7	132·1 ± 15	132·5 ± 13·7	127.5 ± 14.5	128.3 ± 14.3	129.4 ± 12.1	131.4 ± 11.9	125.1 ± 13.7	125.8 ± 15.9	129.6 ± 13.8	129.1 ± 13.1
Diastolic blood pressure mmHG (mean ± SD)	80·2 ± 8·5	80·5 ± 7·3	82·1 ± 10·0	81·8 ± 10·1	80.5 ± 9.3	80.8 ± 9.1	82.9 ± 6.8	81.35 ± 7.786	81.2 ± 9.4	80.9 ± 10.1	80 ± 9.2	79.9 ± 8.3
Pulse beats/min (mean ± SD)	72.4 ± 10.27	75.6 ± 10.36	73·7 ± 10·7	74·6 ± 10·5	75.9 ± 9.3	76.6 ± 9.6	73.9 ± 9.1	69.35 ± 9.22	73 ± 9.9	73.5 ± 10.8	74.7 ± 10	75.1 ± 10.1
Total cholesterol mg/dL (mean ± SD)	166.28 ± 40.5	181.75 ± 42.3	167·1 ± 26	167·6 ± 27·4	179.6 ± 42.3	178.7 ± 42.1	187 ± 6	189 ± 8.7	195 ± 39	196.3 ± 39.5	169.3 ± 40.98	171 ± 41.13
Total LDL mg/dL (mean ± SD)	85 ± 37.6	96.67 ± 42.3	83·8 ± 45·3	85·5 ± 50	102.7 ± 38.9	96.6 ± 37.5	112.3 ± 5.4	108 ± 7.34	118.3 ± 34.1	119.4 ± 33.6	88.7 ± 37.48	92.5 ± 38.25
Total HDL mg/dL (mean ± SD)	42.5 ± 11.6	42.5 ± 12	42·8 ± 23·8	43·1 ± 25·1	41 ± 12.6	41.2 ± 11.7	49.3 ± 2	50.15 ± 3.08	50.1 ± 12.4	48.5 ± 12.6	40.6 ± 11.33	41.5 ± 11.52
Total triglycerides mg/dL (mean ± SD)	159.4 ± 79.5	177.14 ± 83	164·4 ± 53·3	157·2 ± 52·1	168.9 ± 103.2	192.9 ± 187.1	106.1 ± 7.2	120.5 ± 10.45	133.5 ± 75.8	142.8 ± 89.1	161 ± 82.37	155.5 ± 79.18
Lipase, U/L (mean ± SD)	38 ± 21.85	36·4 ± 21	35.7 ± 17.47	37.2 ± 18.27	32.5 ± 15.2	34.2 ± 15.4	30.8 ± 14.85	33.35 ± 16.13	29.9 ± 10.7	28.7 ± 10.8	NA	NA
Pancreatic-amylase, U/L (mean ± SD)	24.7 ± 12.8	23.4 ± 12.4	23 ± 10.92	23.1 ± 10.93	22.5 ± 10.5	22.5 ± 9.5	23.9 ± 12.73	24.45 ± 12.285	23.4 ± 8.07	23.2 ± 8.09	NA	NA
Alanine aminotransferase U/L (mean ± SD)	28.5 ± 15.7	26 ± 14.3	26.9 ± 14.19	25.1 ± 13.26	23 ± 12.88	25 ± 14.25	24.3 ± 12.73	23.2 ± 11.82	22.7 ± 13.4	22.8 ± 13.5	25.3 ± 14.8	25.8 ± 15
Aspartate aminotransferase, U/L (mean ± SD)	22.2 ± 9.35	21.3 ± 9	22.2 ± 9.28	21.6 ± 9.14	20.7 ± 9.36	22.2 ± 9.5	19.9 ± 7.07	20.75 ± 7.3	20.3 ± 8.07	20.1 ± 8.09	20.7 ± 9.68	21.1 ± 9.87
Calcitonin, ng/L (mean ± SD)	1.9 ± 2.17	1.9 ± 2.19	1.7 ± 1.82	1.5 ± 1.79	1.4 ± 1.17	1.4 ± 1.19	1.2 ± 1.4	1.05 ± 1.078	1.1 ± 1.07	1.2 ± 1.08	NA	NA

Table 2 (continued)

	Study ID											
	Frias et al. 2023 [19]		Horn et al. 2025 [18]		Rosenstock et al. 2025 [20]		Wharton et al. 2023 [21]		Wharton et al. 2025 [22]		Rosenstock et al. 2026 [14]	
	12 mg	36 mg	12 mg	36 mg	12 mg	36 mg	12 mg	36 mg	12 mg	36 mg	12 mg	36 mg
Estimated glomerular filtration rate, mL per min per 1·73 m2 (mean ± SD)	91·3 ± 17	90·2 ± 16·7	83·9 ± 21·0	82·2 ± 22·5	NA	NA	86.4 ± 18.3	83 ± 12.7	92.5 ± 18.7	92.8 ± 18.4	90.4 ± 20.3	92.4 ± 19.2
Anti-hyperglycemic drugs n(%)	Metformin: 52 (93%)	Metformin: 54 (89%)	Biguanide: 275 (82·8%) sulfonylurea:51 (15·4%) SGLT2 inhibitor: 97 (29·2%)	Biguanide: 270 (83·9%) Sulfonylurea:50 (15·5%) SGLT2 inhibitor: 109 (33·9%)	previous treatment with metformin: 53 (38.7%)	previous treatment with metformin: 52 (36.9%)	NA	NA	NA	NA	metformin (100%)	metformin (100%)

NA: not available

compared with the 12-mg dose (MD: 1.84 cm; CI: 1.30 to 2.38; $P < 0.00001$; $I^2 = 0\%$) (Fig. 4B).

Subgroup analysis based on diabetic status and treatment duration consistently favored the 36-mg dose. Within the diabetic subgroup, the pooled 36-mg-vs-12-mg difference in waist circumference change was (MD: 1.90 cm; CI: 1.24 to 2.65; $p < 0.00001$; $I^2 = 0\%$). Within the ≤ 40-week subgroup, the corresponding pooled difference was (MD: 2.19 cm; CI: 0.86 to 3.51; $p = 0.001$; $I^2 = 0\%$) (Figure S5A, S5B).

Percentage change in serum total cholesterol

The reduction in serum total cholesterol was not favored by any of the compared doses (MD: 0.07%; CI: -1.01 to 1.23; $P = 0.91$; $I^2 = 19\%$) (Figure S6A).

Similarly, subgroup analysis based on diabetic status and treatment duration was not favored by any of the compared doses (Figure S6B, S6C).

Percentage change in serum LDL cholesterol

The reduction in serum LDL cholesterol was not favored by any of the compared doses (MD: -0.89%; CI: -2.72 to 0.94; $P = 0.34$; $I^2 = 0\%$) (Figure S7A).

Similarly, subgroup analysis based on diabetic status and treatment duration was not favored by any of the compared doses (Figure S7B, S7C).

Percentage change in serum HDL cholesterol

The reduction in serum HDL cholesterol was not favored by any of the compared doses (MD: -0.91%; CI: -2.11 to 0.29; $P = 0.14$; $I^2 = 50\%$) (Figure S8A).

Similarly, subgroup analysis based on diabetic status and treatment duration was not favored by any of the compared doses (Figure S8B, S8C).

Percentage change in serum triglycerides

Under the fixed-effect model, the 36-mg dose of Orforglipron was associated with a significantly greater reduction in serum triglycerides compared with the 12-mg dose (MD: 3.64%; CI: 1.38 to 5.90; $P = 0.002$; $I^2 = 39\%$) (Fig. 4C). In the pre-specified random-effects sensitivity analysis, this finding was attenuated and did not remain statistically significant (MD: 3.10%; 95% CI: -0.15 to 6.36; $P = 0.06$), indicating that the triglyceride result is not robust to the choice of meta-analytic model and should be interpreted with caution (Supplementary material).

Subgroup analysis based on diabetic status and treatment duration consistently favored the 36-mg dose. Within the non-diabetic subgroup, the pooled 36-mg-vs-12-mg difference in serum triglycerides change was (MD: 5.90%; CI: 2.56 to 9.24; $p = 0.0005$; $I^2 = 2\%$). Within the > 40-week subgroup, the corresponding pooled difference was (MD: 4.13%; CI: 1.68 to 6.59; $P = 0.001$; $I^2 = 68\%$) (Figure S9A, S9B).

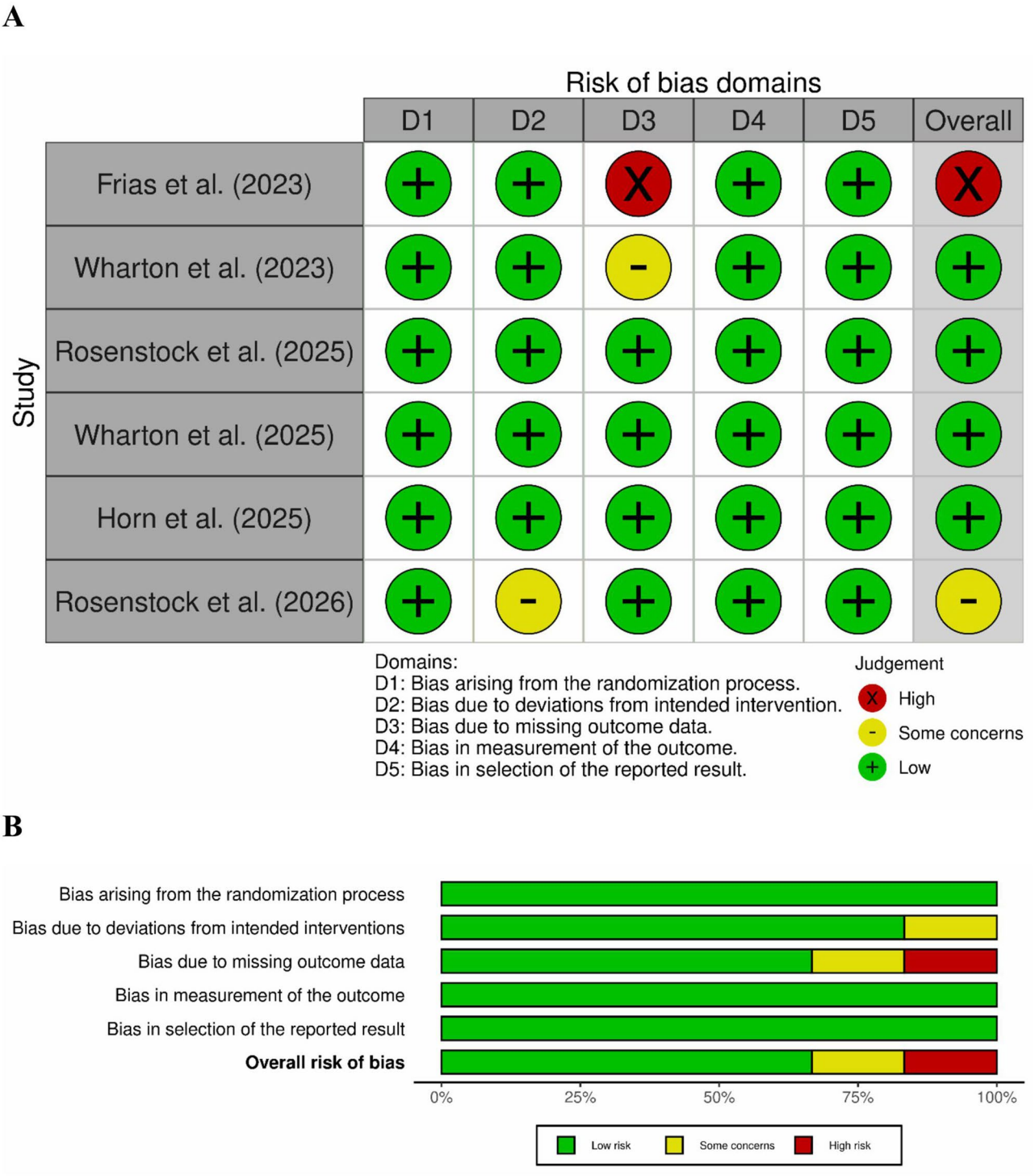


Fig. 2 Overview of the risk of bias assessment according to the Cochrane Risk of Bias 2.0 (ROB 2.0) tool **(A)** presents the domain of level judgment of the included studies, **(B)** presents the five domains of bias with overall risk of bias among the included studies

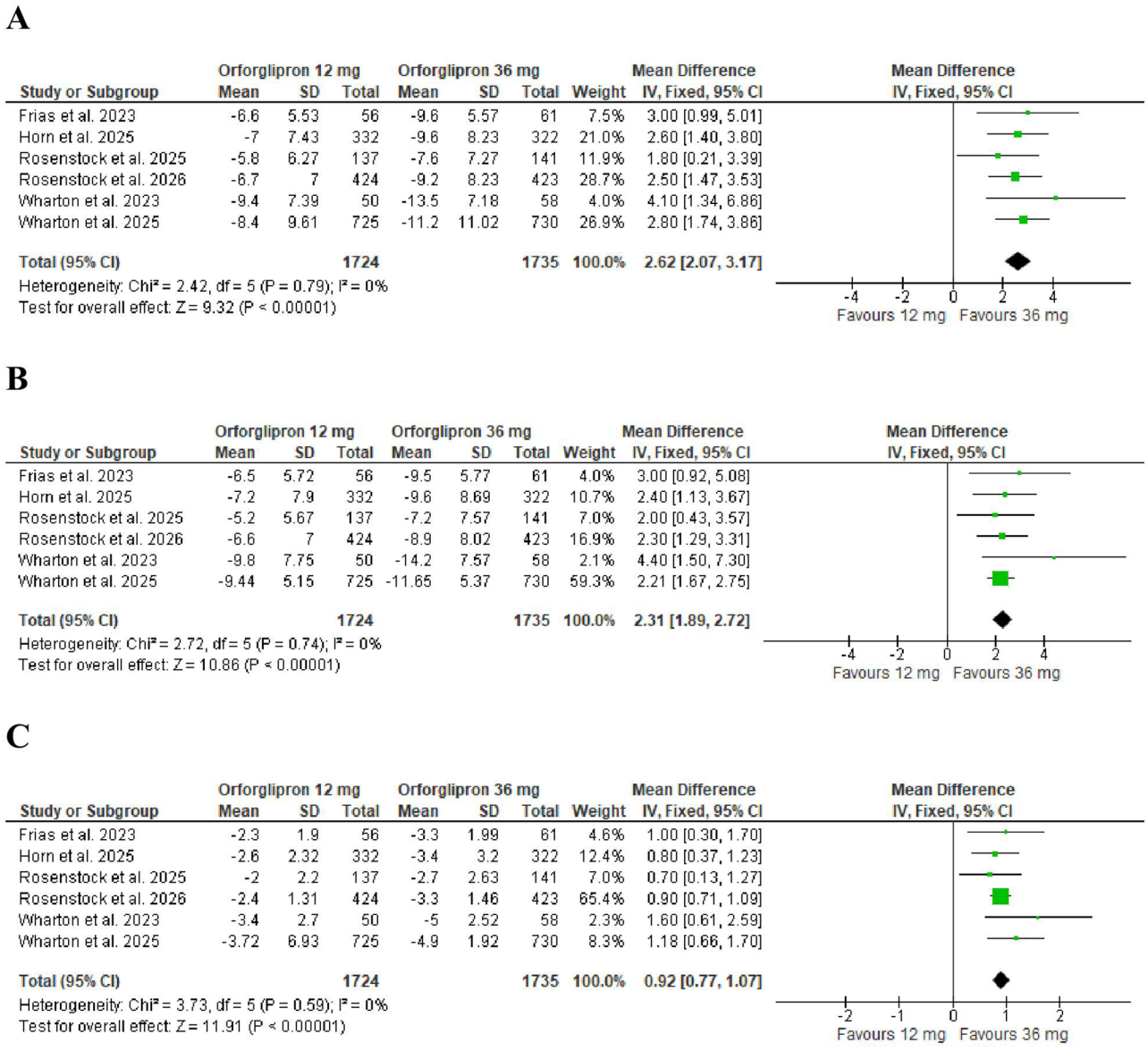


Fig. 3 Forest plots for the meta-analysis of **(3A)** percent change in bodyweight (%), **(3B)** absolute change in body weight(kg), **(3C)** change in BMI (kg/m^2)

Change in fasting serum glucose (mg/dL)

The reduction in fasting serum glucose was not favored by any of the compared doses (MD: 0.73 mg/dL; CI: -0.26 to 1.71; $P = 0.15$; I2 = 0%) (Figure S10A).

Similarly, subgroup analysis based on diabetic status and treatment duration was not favored by any of the compared doses (Figure S10B, S10C).

Change in systolic blood pressure (mmHg)

The 36-mg dose of Orforglipron was associated with a significantly greater reduction in systolic blood pressure compared with the 12-mg dose (MD: 0.94 mmHg; CI: 0.35 to 1.53; $P = 0.002$; $I^2 = 0\%$) (Fig. 4D).

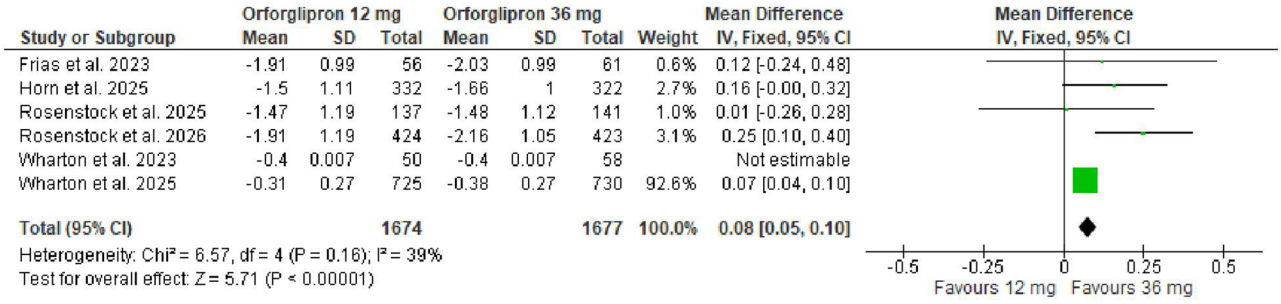
Subgroup analysis based on diabetic status and treatment duration consistently favored the 36-mg dose. Within the non-diabetic subgroup, the pooled 36-mg-vs-12-mg difference in systolic blood pressure did not reach statistical significance (MD: 0.97 mmHg; CI: −0.32 to 2.26; $p = 0.14$; $I^2 = 0\%$). Within the >40-week subgroup, the corresponding pooled difference was (MD: 0.96 mmHg; CI: 0.34 to 1.58; $p = 0.002$; $I^2 = 0\%$) (Figure S11A, S11B)

Change in diastolic blood pressure (mmHg)

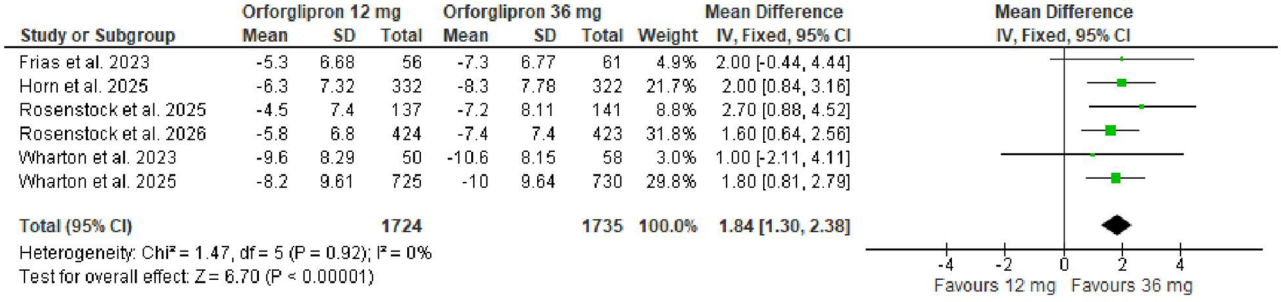
The reduction in diastolic blood pressure was not favored by any of the compared doses (MD: -0.20 mmHg; CI: -0.58 to 0.19; $P = 0.32$; $I^2 = 0\%$) (Figure S12A).

Similarly, subgroup analysis based on diabetic status and treatment duration was not favored by any of the compared doses (Fig. 12B, S12C).

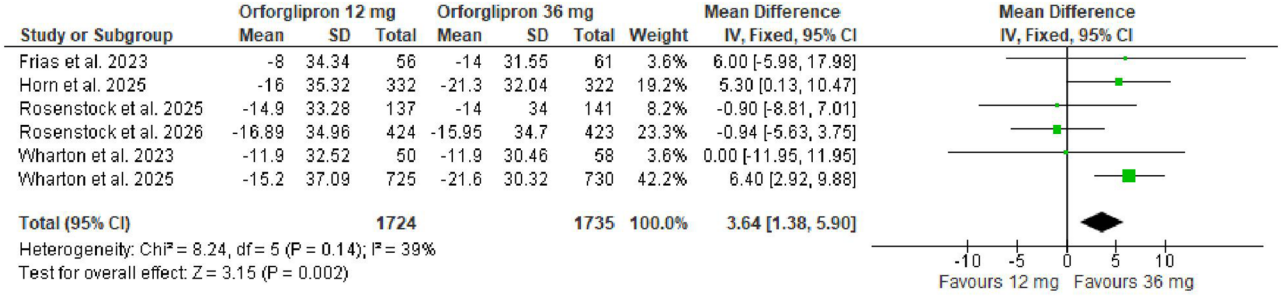
A



B



C



D

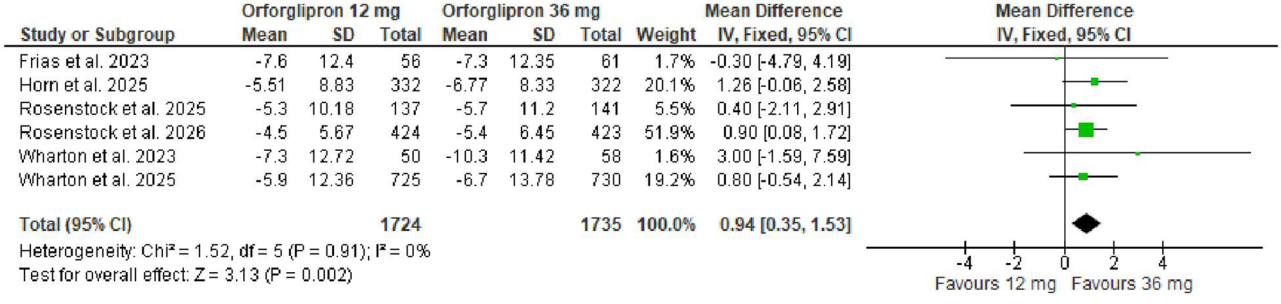


Fig. 4 Forest plots for the meta-analysis of **(4 A)** percent change in HBA1c, **(4B)** change in waist circumference (cm), **(4 C)** percent Change in triglycerides (%), **(4D)** Change in systolic blood pressure (mmHg)

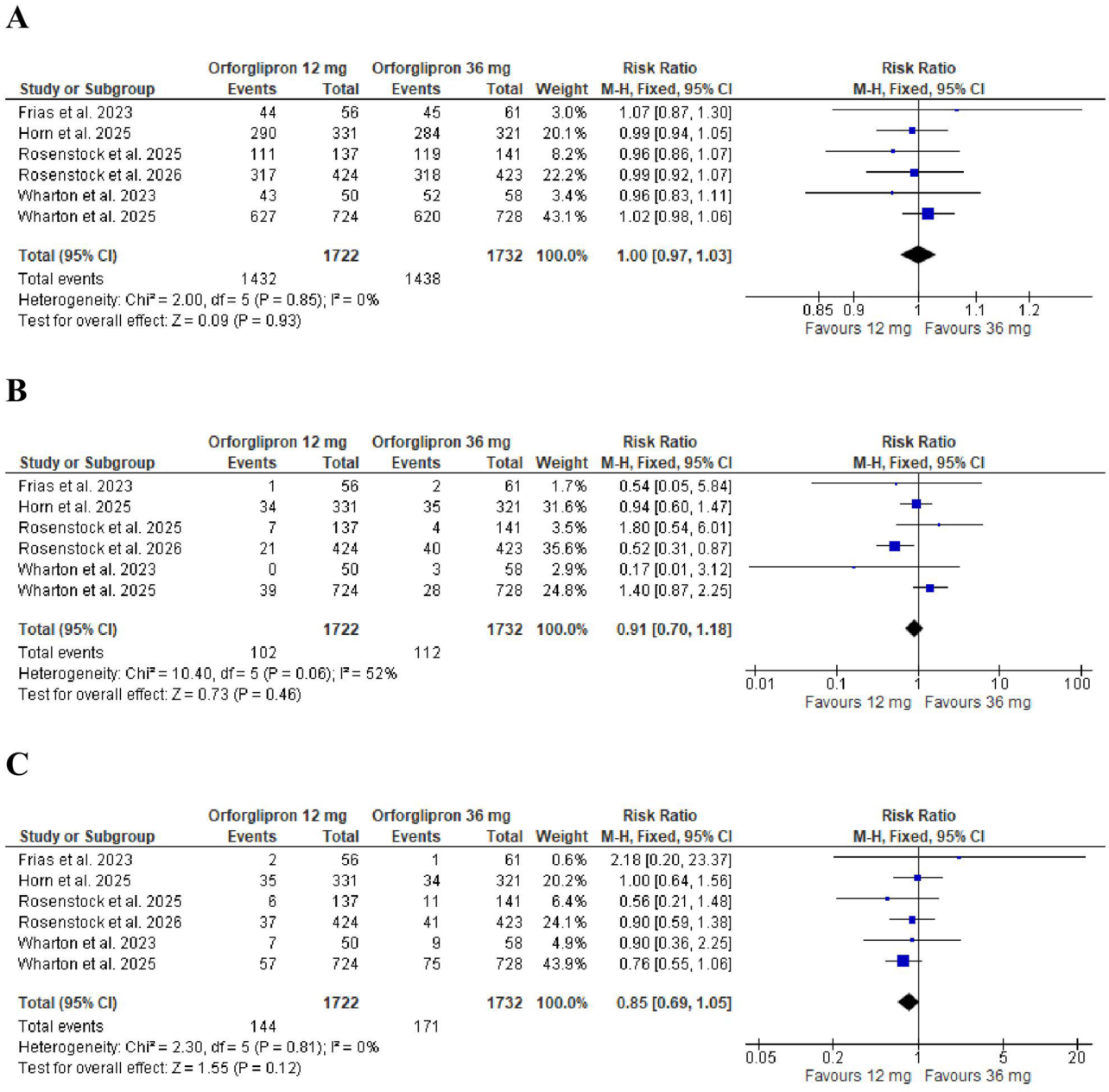


Fig. 5 Forest plots for the meta-analysis of **(5 A)** any TEAE, **(5B)** serious adverse events, **(5 C)** adverse events leading to treatment discontinuation

Safety

Change in pulse rate (bpm)

The 12-mg dose of Orforglipron was associated with a significantly lower rate of pulse change compared with the 36-mg dose (MD: -0.86 bpm; CI: -1.28 to -0.44; $P < 0.0001$; $I^2 = 0\%$) (Figure S13A).

Subgroup analysis based on diabetic status and treatment duration consistently favored the 12-mg dose. Similarly, treatment duration > 40 weeks showed a statistically significant lower pulse rate change with the 12 mg dose (MD: -0.81 bpm; CI: -1.25 to -0.38; $p = 0.0002$; $I^2 = 28\%$) (Figure S13B, S13C).

Any treatment-emergent adverse events (TEAEs)

The incidence of treatment-emergent adverse events was not favored by any of the compared doses. (RR: 1.00; CI: 0.97 to 1.03; $P = 0.93$; $I^2 = 0\%$). (Fig. 5A).

Across diabetic status and treatment duration subgroups, the incidence of treatment-emergent adverse events was not favored by any of the compared doses (Figure S14A, Figure S14B).

Serious adverse events

The incidence of Serious Adverse Events was not favored by any of the compared doses. (RR: 0.91; CI: 0.70 to 1.18; $P = 0.46$; $I^2 = 52\%$) (Fig. 5B).

Across diabetic status and treatment duration subgroups, the incidence of Serious Adverse Events was not favored by any of the compared doses (Figure S15A, Figure S15B).

Adverse events leading to treatment discontinuation

The incidence of Adverse events leading to treatment discontinuation was not favored by any of the compared doses. (RR: 0.85; CI: 0.69 to 1.05; $P = 0.12$; $I^2 = 0\%$) (Fig. 5C).

Across diabetic status and treatment duration subgroups, the incidence of Adverse events leading to treatment discontinuation was not favored by any of the compared doses (Figure S16A, Figure S16B).

Nausea

The incidence of Nausea was not favored by any of the compared doses. (RR: 1.01; CI: 0.92 to 1.11; $P = 0.86$; $I^2 = 0\%$) (Figure S17A).

Across diabetic status and treatment duration subgroups, the incidence of Nausea was not favored by any of the compared doses (Figure S17B, Figure S17C).

Vomiting

The incidence of Vomiting was not favored by any of the compared doses. (RR: 0.90; CI: 0.79 to 1.03; $P = 0.12$; $I^2 = 0\%$) (Figure S18A).

Across diabetic status and treatment duration subgroups, the incidence of Vomiting was not favored by any of the compared doses (Figure S18B, Figure S18C).

Diarrhea

The incidence of Diarrhea was not favored by any of the compared doses. (RR: 0.97; CI: 0.85 to 1.09; $P = 0.57$; $I^2 = 9\%$) (Figure S19A).

Across diabetic status and treatment duration subgroups, the incidence of Diarrhea was not favored by any of the compared doses (Figure S19B, Figure S19C).

Constipation

The incidence of Constipation was not favored by any of the compared doses. (RR: 1.11; CI: 0.97 to 1.26; $P = 0.12$; $I^2 = 0\%$) (Figure S20A).

Across diabetic status and treatment duration subgroups, the incidence of Constipation was not favored by any of the compared doses (Figure S20B, Figure S20C).

Percentage change in serum lipase (%)

The reduction in Percentage serum Lipase was not favored by any of the compared doses (MD: 2.75%; CI: -1.45 to 6.95; $P = 0.20$; $I^2 = 0\%$) (Figure S21A).

Similarly, subgroup analysis based on diabetic status and treatment duration was not favored by any of the compared doses (Figure S21B, Figure S21C).

Percentage change in total serum amylase (%)

The reduction in Percentage total serum amylase was not favored by any of the compared doses (MD: 0.48%; CI: −2.36 to 3.33; $p = 0.74$; $I^2 = 0\%$) (Figure S22A).

Similarly, subgroup analysis based on diabetic status and treatment duration was not favored by any of the compared doses (Figure S22B, Figure S22C).

Percentage change in serum calcitonin (%)

The reduction in Percentage of serum calcitonin was not favored by any of the compared doses (MD: 0.13%; CI: −3.15 to 3.41; $P = 0.94$; $I^2 = 23\%$) (Figure S23A).

Similarly, subgroup analysis based on diabetic status and treatment duration was not favored by any of the compared doses (Figure S23B, Figure S23C).

Percentage change in ALT (%)

The 36 mg dose led to a statistically significantly greater percentage increase in ALT compared to the 12 mg dose (MD: 2.66%; CI: 0.14 to 5.19; $P = 0.04$; $I^2 = 0\%$) (Figure S24A). No between-study heterogeneity was observed.

Subgroup analysis based on diabetic status and treatment duration consistently favored the 36-mg dose. Within the diabetic subgroup, the pooled 36-mg-vs-12-mg difference in percentage ALT change was not statistically significant (MD: 2.86%; CI: -0.45 to 6.17; $P = 0.09$; $I^2 = 4\%$) (Figure S24B). Within the >40-week subgroup, the corresponding pooled difference was (MD: 2.78%; CI: 0.00 to 5.56; $p = 0.05$; $I^2 = 26\%$) (Figure S24C).

Percentage change in AST (%)

The 36-mg dose of Orforglipron was associated with a greater reduction in AST Percentage compared with the 12-mg dose (MD: 2.43%; CI: 0.46 to 4.39; $P = 0.02$; $I^2 = 0\%$) (Figure S25A). No between-study heterogeneity was observed.

Subgroup analysis based on diabetic status and treatment duration consistently favored the 36-mg dose. Within the diabetic subgroup, the pooled 36-mg-vs-12-mg difference in percentage AST change was (MD: 3.09%; CI: 0.44 to 5.74; $P = 0.02$; $I^2 = 18\%$) (Figure S25B). Within the >40-week subgroup, the corresponding pooled difference was (MD: 2.80%; CI: 0.65 to 4.95; $p = 0.01$; $I^2 = 35\%$) (Figure S25C).

Death

Overall, mortality events were rare and comparable between the orforglipron 12 mg and 36 mg dose arms. No statistically significant difference in all-cause mortality was observed between the two doses (RR: 1.32; CI: 0.46 to 3.81; $P = 0.61$); given the small number of events, this analysis is underpowered to detect a true difference in mortality risk (Figure S26).

Discussion

This meta-analysis of six randomized controlled trials, encompassing 3459 patients, provides a comprehensive comparative evaluation of two maintenance doses (12 mg vs. 36 mg) of the novel oral GLP-1 receptor agonist orforglipron, in adults with obesity with or without type 2 diabetes (T2D). The principal finding is that the 36 mg dose confers statistically superior efficacy across a broad spectrum of cardiometabolic parameters, including body weight, BMI, HbA1c, waist circumference, and systolic blood pressure, compared to the 12 mg dose (the triglyceride benefit was significant under the fixed-effect model but attenuated in a random-effects sensitivity analysis), with no statistically significant between-dose differences detected for the prespecified safety outcomes other than small increases in ALT and AST.

The dose-dependent efficacy of orforglipron for weight reduction aligns with the established pharmacodynamics of the GLP-1 receptor agonist class [26]. The mean difference in percentage body weight loss (2.62%) and absolute weight loss (2.31 kg), favoring the 36 mg dose, is clinically meaningful, as weight reductions of ≥ 5% are associated with significant improvements in obesity-related comorbidities [27, 28]. Notably, in the 72-week ATTAIN-1 trial, orforglipron 36 mg led to a mean weight loss of 11.2% of baseline body weight, with over one-third of patients achieving ≥ 15% weight loss; a threshold linked to remission of comorbidities like obstructive sleep apnea and non-alcoholic fatty liver disease (NAFLD) [22]. This finding is consistent with the dose-response relationship seen with other GLP-1 RAs, such as subcutaneous semaglutide in the STEP trials and liraglutide in the SCALE program [6, 29]. The significant reductions in waist circumference, a marker of visceral adiposity, further underscore the potent metabolic action of the higher dose, as central obesity is a key driver of insulin resistance and cardiovascular risk [30, 31]. The results affirm the principle, observed with incretin-based therapies like tirzepatide, that robust receptor agonism translates into superior metabolic outcomes [32].

In glycemic control, the 36 mg dose produced a significantly greater reduction in HbA1c (MD: 0.08% points), with a more pronounced effect in studies of longer duration (> 40 weeks). This incremental benefit, though modest, is relevant in the context of T2D management where stringent glycemic targets are pursued [33]. It mirrors the dose-response relationship seen with oral semaglutide in the PIONEER program and positions orforglipron as a potent oral alternative [34]. The greater HbA1c reduction in longer trials suggests sustained efficacy, a critical attribute for chronic disease management, as highlighted in guidelines from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [35].

The impact on cardiovascular risk markers was notably heterogeneous. While systolic blood pressure improved significantly with the higher dose, consistent with the vasodilatory effects of GLP-1 [36], other lipid parameters (total cholesterol, LDL-C) did not show statistically significant between-dose differences. However, the robust reduction in triglycerides (3.64%) is a salient finding. Hypertriglyceridemia is a key component of atherogenic dyslipidemia, and its reduction is a recognized benefit of GLP-1 RAs, as demonstrated in meta-analyses by Kristensen et al. and Sun et al. [37, 38]. The neutral effect on LDL-C aligns with some previous analyses of GLP-1 therapies, which show more variable effects on this parameter compared to dedicated lipid-lowering agents [39].

The safety and tolerability profile is a paramount consideration for any chronic weight management therapy. Reassuringly, our analysis found no statistically significant increase in the risk of overall treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), or adverse events leading to discontinuation with the 36 mg dose compared to the 12 mg dose. Gastrointestinal events: nausea, vomiting, diarrhea, and constipation were numerically more frequent with the higher dose but without statistical significance, contrasting with the clear dose-dependent increase often seen with other GLP-1 RAs like liraglutide [40]. This may reflect the unique pharmacokinetic profile of orforglipron. The absence of any new safety signal for the prespecified outcomes at the higher dose is reassuring, although the six included trials (maximum follow-up 72 weeks) are underpowered to detect rare or long-term adverse events, and this finding aligns with the safety profile established in the cardiovascular outcome trials (CVOTs) of other GLP-1 Ras [41, 42]. The only statistically significant safety signal was a small between-dose difference in pulse rate, with a numerically smaller reduction (i.e., a relatively greater increase) in pulse rate with the 36 mg dose compared with the 12 mg dose (MD: 0.86 bpm), a finding of questionable clinical relevance given its small magnitude, though directionally consistent with the small tachycardia sometimes associated with other agents [43].

Of particular importance, no significant between-dose differences were observed in markers of pancreatic safety (lipase, amylase). For hepatic markers, small but statistically significant increases with the 36 mg dose were

detected for both ALT (MD 2.66%; $P = 0.04$) and AST (MD 2.43%; $P = 0.02$); although these differences are of uncertain clinical relevance given their modest magnitude and the short-to-moderate follow-up of the included trials, they should not be characterized as equivalent between doses, and longer-term hepatic monitoring data would be valuable. Pancreatitis risk has been a historical concern with GLP-1-based therapies, prompting extensive evaluation by regulators [44]. Large cardiovascular outcome trials (CVOTs) like REWIND (Dulaglutide) and SUSTAIN-6 (semaglutide) have not confirmed an increased risk [41, 42]. Our data, though from shorter-term trials, contribute to the reassuring safety profile regarding pancreatic enzymes. The small, statistically significant ALT/AST increases with the 36 mg dose noted above should be weighed against findings from the LIRA-NAFLD study and other analyses suggesting GLP-1 RAs may benefit, not harm, hepatic steatosis [45, 46].

The subgroup analyses should be regarded as exploratory: although formal tests for subgroup differences were performed (Methods, Section "Data analysis and outcomes"), the number of trials contributing to each stratum was small, limiting the power of these interaction tests to detect true between-subgroup differences. With this caveat, the numerically greater efficacy observed in non-diabetic patients for weight loss and in diabetic patients for waist circumference reduction may hint at differing phenotypic responses, but this hypothesis warrants investigation in dedicated studies [47]. The influence of treatment duration was evident for HbA1c, underscoring the importance of long-term adherence, a known challenge in obesity pharmacotherapy, highlighted by systematic reviews such as that by Khera et al. [48] The minimal heterogeneity in weight outcomes across the six RCTs, despite differences in populations and durations, attests to the reproducibility of the dose effect.

These findings must be interpreted within the context of the evolving therapeutic landscape for obesity and T2D. Orforglipron's oral administration offers a distinct advantage over injectable GLP-1 RAs, potentially improving accessibility and adherence [49]. Its efficacy profile appears competitive, with weight loss approaching that of some injectable GLP-1 RAs and surpassing older oral agents like naltrexone-bupropion [50, 51]. Furthermore, the results provide a basis for comparative effectiveness research against other oral incretin therapies, such as the recently approved oral semaglutide [34].

The clinical implications are significant. Our analysis supports the clinical strategy of titrating to the 36 mg maintenance dose to maximize therapeutic gains, a principle reflected in recent guidelines from the American Association of Clinical Endocrinology (AACE) and the 2023 ADA standards, which recommend GLP-1 RAs for weight management in patients with obesity and T2D [2, 52]. For patients requiring substantial weight loss and metabolic improvement, initiating or titrating to the 36 mg maintenance dose of orforglipron may offer superior benefits without a clinically concerning increase in adverse events. This aligns with a treat-to-target approach. The 2025 World Health Organization (WHO) guideline for obesity pharmacotherapy, giving a conditional recommendation for long-term GLP-1 RA use, further supports this treatment paradigm [53]. Standard clinical monitoring practices used for GLP-1 receptor agonists have not revealed any new safety concern with the 36 mg dose in the available short-to-moderate-term trial data, but given the modest but statistically significant ALT/AST increases observed, the limited follow-up (maximum 72 weeks), and the small number of included trials, we are cautious about concluding that standard monitoring alone is sufficient. Given the limited ability of the current evidence base to detect rare or delayed events, dedicated longer-term hepatic and safety surveillance of the higher dose is warranted rather than assumed unnecessary.

Limitations

This meta-analysis has several limitations. First, the number of included studies is modest ($n = 6$), though the total patient population is substantial. Second, the maximum follow-up duration was 72 weeks; longer-term data on sustained efficacy, safety, and durability of weight loss are needed, as weight regain is a common challenge [54]. Third, all trials were industry-sponsored, underscoring the need for independent confirmation of these findings. Fourth, the included trials had varying proportions of patients with T2D, and while subgroup analyses were performed, patient-level data were not available for more granular exploration of effect modifiers. Relatedly, four of the six included trials (Frias et al. 2023, Rosenstock et al. 2025, Horn et al. 2025, and Rosenstock et al. 2026) applied BMI eligibility thresholds below the conventional WHO obesity cutoff of 30 kg/m² (as low as BMI ≥ 23 kg/m²), reflecting their original design as T2D-focused trials; only Wharton et al. (2023) and Wharton et al. (2025) restricted enrollment to participants meeting the conventional obesity threshold. This is a source of clinical heterogeneity in the population studied. A sensitivity analysis restricted to these two strictly obesity-defined trials showed a body-weight effect of similar or slightly larger magnitude than the full analysis (Results, Sect. "Percentage change in body weight"), suggesting the primary finding is not an artifact of including trials with broader BMI eligibility, though this sensitivity analysis was based on only two trials and should be interpreted cautiously. Fifth, as with all meta-analyses, the results are constrained by the quality and reporting of the original

trials; one study was judged to have a high risk of bias due to missing outcome data. Sixth, although a fixed-effect model was prespecified because the included trials shared a broadly similar design and population, this assumption may not hold for all outcomes; a random-effects sensitivity analysis was therefore performed for the primary outcomes (Supplementary material), and while most effect estimates were robust to model choice, the triglyceride result was attenuated to non-significance under random effects and the HbA1c estimate showed a wider confidence interval, so these two findings should be interpreted cautiously. Seventh, our search was completed on March 1, 2026, and did not include Embase; given the rapidly evolving evidence base for oral GLP-1 receptor agonists, an updated search closer to publication, including Embase and trial registries, is recommended before the findings are considered definitive. Eighth, given the large number of outcomes and subgroup analyses examined, some statistically significant findings may reflect multiplicity rather than true effects; the weight, BMI, waist circumference, HbA1c, and systolic blood pressure findings should be regarded as the primary results, with subgroup and secondary lipid/hepatic findings considered exploratory and hypothesis-generating. Finally, we compared only two fixed doses; a network meta-analysis including placebo and active comparators would provide a broader context for orforglipron's relative efficacy and safety [55].

Conclusions and future directions

In conclusion, this meta-analysis indicates that orforglipron 36 mg is significantly more effective than the 12 mg dose in reducing body weight, improving glycemic control, and reducing systolic blood pressure in patients with obesity with or without T2D; the effect on triglycerides was significant under the fixed-effect model but was attenuated and no longer statistically significant in a random-effects sensitivity analysis, and should therefore be interpreted with caution. No statistically significant between-dose differences were detected for the prespecified safety outcomes, with the exception of small increases in ALT and AST with the 36 mg dose; this should not be read as evidence that the two doses are equally safe, given the limited number of trials, modest overall sample size, and follow-up of up to 72 weeks, which constrain the ability to detect rare or long-term adverse events. The oral administration and favorable efficacy profile position orforglipron as a promising therapeutic option, to be confirmed by further evidence.

Future research should prioritize long-term extension studies to assess the durability of weight loss and long-term safety [56]. Dedicated cardiovascular outcome trials (CVOTs), now a standard for new antidiabetic and anti-obesity medications, are essential to definitively establish the cardiovascular safety and potential benefits of orforglipron [57]. Furthermore, pragmatic real-world evidence studies and head-to-head trials against other potent therapies, including injectable semaglutide and dual agonists like tirzepatide, are needed to clarify its position in the treatment hierarchy [58, 59]. Ultimately, the availability of an effective oral GLP-1 RA may help bridge the significant gap between the high prevalence of obesity and the historical underutilization of pharmacotherapy, enabling more personalized and effective treatment strategies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-026-02538-x.

Supplementary Material 1

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Author contributions

M.G.H. designed the study, screened and extracted data, prepared the figures and tables, managed references and wrote, revised and edited the manuscript. M.Y.A.A. was involved in study conceptualization, screening, data extraction, data analysis, and manuscript writing, review, and editing. A.I.I.K. contributed to the writing of the original draft and the risk of bias assessment. The first draft was written with the help of M.A.N. The first draft was written by O.G.E. A.Z.S. wrote, reviewed and edited the manuscript and supervised the project. All authors have read and approved the final manuscript.

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Data availability

All data generated or analysed during this study are derived from previously published randomized controlled trials, which are cited in the reference list. The data extraction spreadsheets and forest plot datasets generated for this meta-analysis are available from the corresponding author on reasonable request.

Declarations

Ethical approval

No humans participate in this study, and informed consent is not required.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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