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SYSTEMATIC REVIEW

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GLP-1 receptor agonists for the treatment of obesity in children and adolescents: a meta-analysis of randomized controlled trials

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BACKGROUND: Glucagon-like peptide-1 (GLP-1) receptor agonists were recently approved for obesity treatment in children 12–17 years by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). However, their effectiveness in younger pediatric patients remains uncertain.
METHODS: We systematically searched PubMed, Embase and Cochrane for randomized controlled trials (RCTs) comparing GLP-1 receptor agonists versus. placebo in children and adolescents. Continuous outcomes were computed with mean differences (MD) and 95% confidence intervals (CI) with random-effect models.
RESULTS: This meta-analysis included 11 RCTs with 1024 patients with obesity, aged from 6 to 19 years old. Compared with placebo, GLP-1 agonists significantly decreased body weight (MD −4.32 kg; 95% CI −7.02 to −1.63 kg; $p < 0.01$), BMI z-score (MD −0.28; 95% CI −0.45 to −0.1; $p < 0.01$) and waist circumference (MD −3.84 cm; 95% CI −6.97 to −0.70 cm; $p = 0.02$) in this population. An analysis of patients <12 years old showed that GLP-1 receptor agonists significantly decreased BMI z-score (MD −0.33; 95% CI −0.47 to −0.20; $p < 0.01$). Gastrointestinal symptoms were the most frequent adverse event (RR 1.52; 95% CI 1.09 to 2.12; $p < 0.01$).
CONCLUSIONS: In conclusion, in children and adolescents with obesity, GLP-1 receptor agonists significantly reduced BMI z-score, waist circumference and body weight.

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IMPACT:

- The importance of this article is based on the limited treatment options for childhood obesity, particularly in children under the age of 12.
- No meta-analysis with a sample size of children under the age of 12 comparable to this one has been conducted thus far.
- For now, GLP-1 analogs are only approved for children over the age of 12; however, the study suggests that children under 12 may also benefit from their use.

BACKGROUND

Obesity in childhood and adolescence has increased substantially in the last decades. The USA has one of the highest prevalences in the world.[1] The etiologies of obesity in this younger population are complex and varied,[2] which represents a challenge when it comes to managing this condition.

Lifestyle intervention is the first step of treatment in pediatric patients with obesity.[3] Pharmacotherapy and bariatric surgery may be considered for children older than 12 years who fail to achieve weight loss goals with lifestyle modification therapy alone.[4] However, options are limited.

Glucagon-like peptide-1 (GLP-1) receptor agonists are a class of medications for type 2 diabetes mellitus (T2DM) and obesity.[5] Liraglutide was recently approved for obesity treatment in children aged 12–17 years by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA),[4] albeit its effects in pediatric patients younger than this age are still unclear.

Several randomized controlled trials (RCTs) showed promising results in weight reduction following GLP-1 receptor agonist therapy in young individuals.[6–16] However, previous meta-analyses[17,18] have shown conflicting results, with a restricted number of patients, including mainly children over 12 years of age. Therefore, we performed a systematic review and meta-analysis of RCTs assessing the efficacy and safety of GLP-1 receptor agonists in pediatric patients with obesity.

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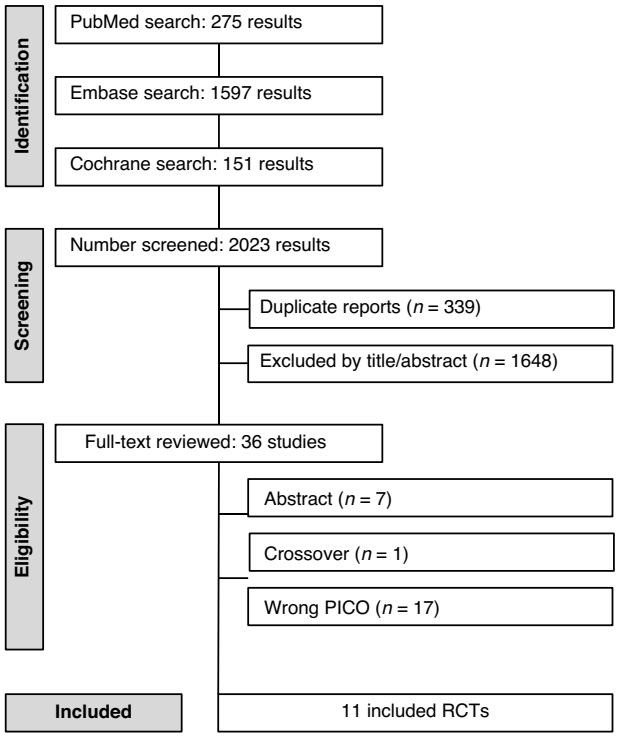


Fig. 1 PRISMA flow diagram of study screening and selection. Flowchart illustrating the process of identification, screening, eligibility assessment, and inclusion of studies in the systematic review and meta-analysis.

METHODS

This systematic review and meta-analysis was performed and reported following the Cochrane Collaboration Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines (Supplemental Methods 1, 2).[19,20] The prospective meta-analysis protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO; CRD42024607369) on November 10, 2024.

Eligibility criteria

We included studies published in English that met all the following eligibility criteria: (1) RCTs; (2) comparing GLP-1 receptor agonists versus placebo; (3) in patients aged 6–19 years old with obesity; (4) reported any of the clinical outcomes of interest. We excluded studies that (1) had an ineligible design (e.g. case reports, cross-sectional studies, reviews, abstracts, or observational); (2) only included adult individuals; (3) did not report any outcomes of interest.

Data extraction

We systematically searched PubMed, Embase and Cochrane Central Register of Controlled Trials from inception until October 20, 2024. Previous systematic reviews and meta-analyses were also screened to recognise significant data. Moreover, we used backward snowballing (i.e. review of references) to identify additional relevant texts from articles found in the original search.

Search strategy

The Patient/Population/Problem, Intervention, Comparison and Outcome Framework (PICO) was utilized to develop the review question and search strategy (Supplemental Methods 3). Electronic databases were searched using the following terms: 'obesity', 'overweight', 'children', 'adolescents'. Details of the search strategy can be found in Supplemental Methods 4.

Selection process and data collection

Two authors (R.L. and C.A.) independently extracted the data for each study using a standardized study form to determine: authors, study publication year, main exclusion criteria (Supplemental Methods 5), sample size, follow-up period, endpoint definition and baseline patient characteristics (Supplemental Methods 6). Uncertainties were resolved by consensus, and R.L. made the final decision for study inclusion or exclusion. The respective authors of studies were contacted when insufficient data were reported.

Endpoints

Our primary efficacy endpoints were the change in BMI z-score from baseline and weight reduction. Prespecified secondary efficacy endpoints included (1) change in waist circumference; (2) glycated haemoglobin (HbA1c); (3) LDL-cholesterol reduction; (4) gastrointestinal adverse events. We also performed an analysis of patients aged <12 years to assess BMI z-score changes and gastrointestinal adverse events.

Risk of bias assessment

Two independent authors (R.L. and F.E.) assessed the risk of bias in the included RCTs using Cochrane's Collaboration tool for assessing the risk of bias in randomized trials (RoB-2).[21] Any disagreements were resolved through consensus between the authors. We explored the potential for publication bias by visual inspection of the comparison-adjusted funnel plots and Egger's regression test.[22] We also performed leave-one-out sensitivity to ensure the results were not dependent on a single study.

Statistical analysis

We used a statistical method that accounts for differences between studies (Mantel-Haenszel random-effects model) to analyze all outcomes. Mean differences (MD) or standardised mean differences with 95% confidence intervals (CI) were computed to assess treatment effects for continuous outcomes, and risk ratios (RR) with 95% CI for binary endpoints. We checked how consistent the results were across studies using standard measures of variation (Cochrane's Q and I^2 statistics), with $p \leq 0.10$ indicating statistical significance.[23] We interpreted I^2 values as follows: 0% = no variation, 1–25% = low, 26–50% = moderate and over 50% = substantial variation. A p value of <0.05 was considered statistically significant. RevMan version 5.4.1 was used for statistical analyses.

RESULTS

Study selection

Figure 1 shows our systematic search and selection flow chart. We identified 2023 potential articles. After removing duplicates, 1684 articles were retrieved and reviewed in full for possible inclusion. Of these, 11 RCTs met all inclusion criteria and were included in the primary analysis.[6–16]

Study characteristics

Study details are described in Table 1. Six studies used liraglutide, three studies used exenatide, one study used semaglutide, and one study used dulaglutide. Follow-up time ranged from 5 to 56 weeks. Six studies included patients with T2DM. The mean age was 13.9 years old, the mean waist circumference was 109.7 cm, and the mean body weight was 98.5 kg.

Results of syntheses

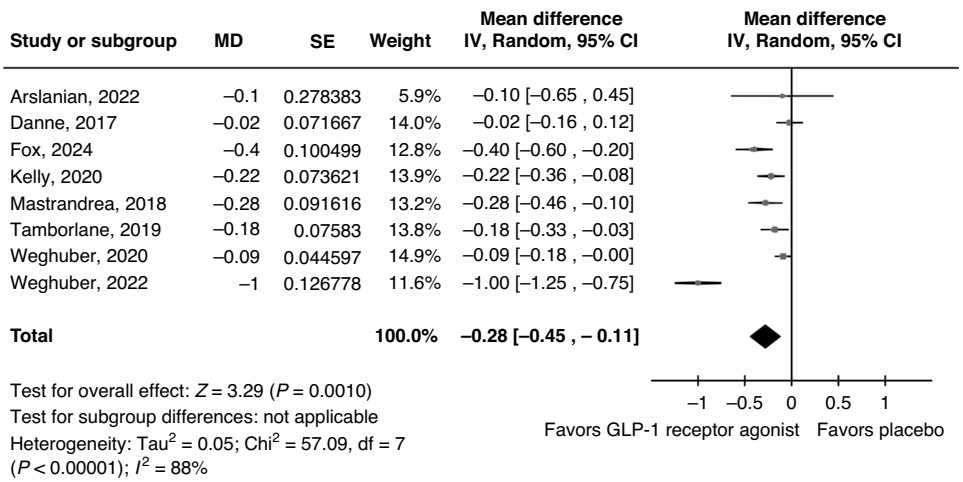
In the overall population, GLP-1 receptor agonists significantly decreased BMI z-score (MD −0.28; 95% CI −0.45 to −0.1; $p < 0.01$; $I^2 = 88\%$; Fig. 2a), body weight (MD −4.32 kg; 95% CI −7.02 to −1.63; $p < 0.01$; $I^2 = 90\%$; Fig. 2b), and waist circumference (MD −3.84 cm; 95% CI −6.97 to −0.70 cm; $p < 0.05$; $I^2 = 85\%$; Fig. 2c). Among children younger than 12

Table 1. Baseline Characteristics of Included Studies.[6–16]

Study, year	Country	Duration (weeks)	Study arms	Route of administration and frequency	No. of patients	Age (years)	Female	Weight (kg)	BMI (kg/m2)	Waist circumference (cm)	HbA1c (%)
Arslanian[14]	Multinational	26	Placebo Dulaglutide 0.75 mg Dulaglutide 1.5 mg	Subcutaneous injections once-weekly	51 51 52	14.2 14.7 14.7	41 35 34	88.9 90.0 92.6	34.3 33.6 34.3	106 105.6 106.3	8.1 7.9 8.2
Danne[8]	Germany	5	Placebo Liraglutide	Subcutaneous injections once-daily	7 14	14.4 15.1	3 11	109.6 103.5	35.7 36.5	-	5.5 5.4
Fox[13]	USA	52	Placebo Exenatide XR	Subcutaneous injections once-weekly	33 33	16.1 15.9	13 18	111.4 105.6	37.3 36.5	-	5.2 5.2
Fox[16]	Multinational	56 treatment and 26 follow-up	Placebo Liraglutide	Subcutaneous injections once-daily	26 56	10 10	12 26	71.0 69.8	31.3 30.9	97.4 94.4	5.4 5.4
Kelly[12]	Multinational	56-week treatment and 26-week follow-up	Placebo Liraglutide	Subcutaneous injections once-daily	126 125	14.5 14.6	78 71	102.2 99.3	35.8 35.3	106.99 104.87	5.3 5.3
Klein[7]	Multinational	5	Placebo Liraglutide	Subcutaneous injections once-daily	7 14	15.6 14.4	5 9	114.2 112.7	39.9 40.0	-	7.8 8.3
Mastrandrea[9]	USA	7 weeks with the allowance of up to six treatment weeks, up to a maximum of 13 weeks	Placebo Liraglutide	Subcutaneous injections once-daily	8 16	10.4 9.7	1 8	81.4 66.6	-	-	5.4 5.5
Kelly[6]	USA	12	Placebo Exenatide	Subcutaneous injections twice-daily	13 13	15.5 14.9	8 8	126 123	42.7 42.3	129 130	5.29 5.23
Tamborlane[10]	Multinational	26	Placebo Liraglutide	Subcutaneous injections once-daily	68 66	14.6 14.6	42 41	89.8 93.3	33.27 34.55	-	7.69 7.87
Weghuber[11]	Multinational	24 treatment and 2 weeks follow-up	Placebo Exenatide	Subcutaneous injections once-weekly	22 22	13.5 14.5	9 13	102.5 106.2	36.2 36.0	112.6 115.1	-
Weghuber[15]	Multinational	68	Placebo Semaglutide	Subcutaneous injections once-weekly	67 134	15.3 15.5	41 84	102.6 109.9	35.7 37.7	107.3 111.9	5.5 5.5

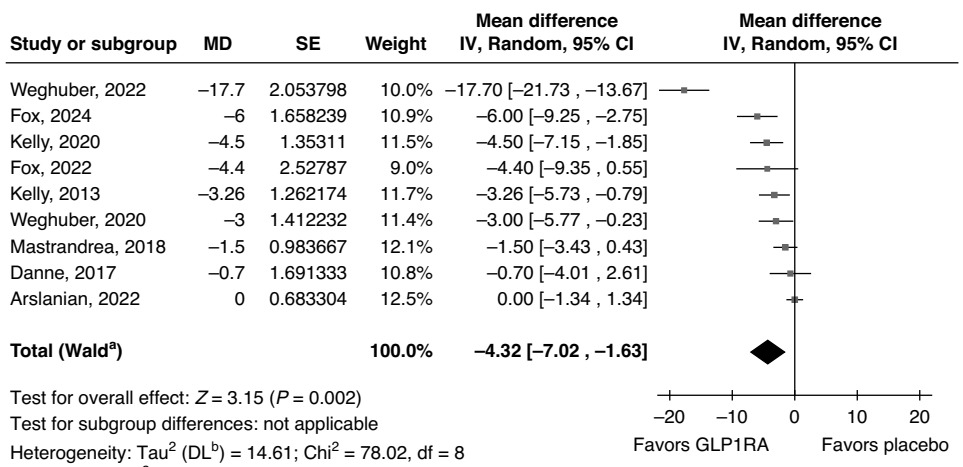
SD Standard Deviation, *RCT* Randomized Controlled Trial, *USA* United States of America, *BMI* Body Mass Index, *HbA1c* Glycated haemoglobin, *FPG* fasting plasma glucose, *T2D* type 2 diabetes.

a



Test for overall effect: $Z = 3.29$ ($P = 0.0010$)
Test for subgroup differences: not applicable
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 57.09$, df = 7 ($P < 0.00001$); $I^2 = 88\%$

b



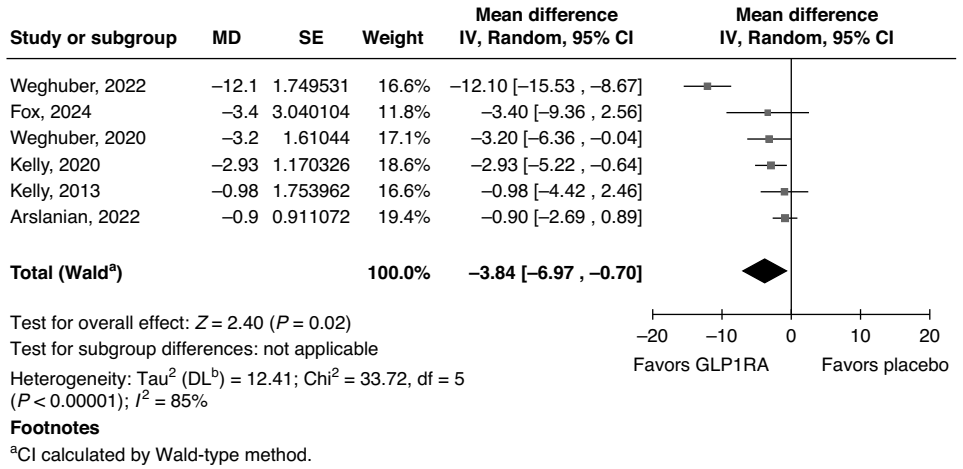
Test for overall effect: $Z = 3.15$ ($P = 0.002$)
Test for subgroup differences: not applicable
Heterogeneity: Tau^2 (DL^b) = 14.61; $Chi^2 = 78.02$, df = 8 ($P < 0.00001$); $I^2 = 90\%$

Footnotes

[a]CI calculated by Wald-type method.

[b]Tau^2 calculated by DerSimonian and Laird method.

c



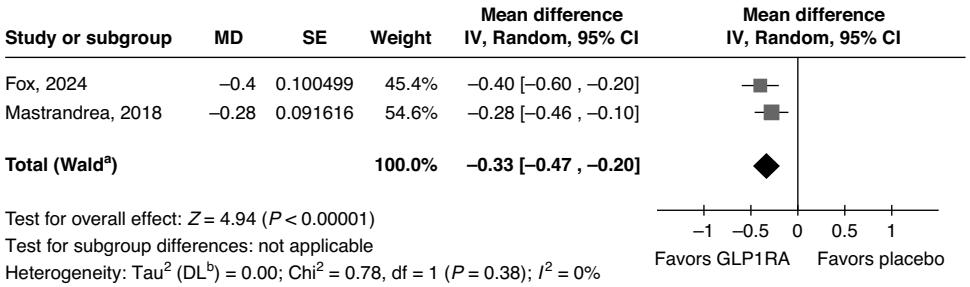
Test for overall effect: $Z = 2.40$ ($P = 0.02$)
Test for subgroup differences: not applicable
Heterogeneity: Tau^2 (DL^b) = 12.41; $Chi^2 = 33.72$, df = 5 ($P < 0.00001$); $I^2 = 85\%$

Footnotes

[a]CI calculated by Wald-type method.

[b]Tau^2 calculated by DerSimonian and Laird method.

Fig. 2 Effects of GLP-1 receptor agonists on anthropometric outcomes in pediatric patients with obesity. a Forest plot presenting the mean difference (MD) and 95% confidence interval (CI) for change in BMI z-score from baseline. **b** Forest plot presenting the mean difference (MD) and 95% confidence interval (CI) for change in body weight (kg) from baseline. **c** Forest plot presenting the mean difference (MD) and 95% confidence interval (CI) for change in waist circumference from baseline. Abbreviations: CI confidence interval, MD mean difference, GLP1RA glucagon-like peptide 1 receptor agonist.

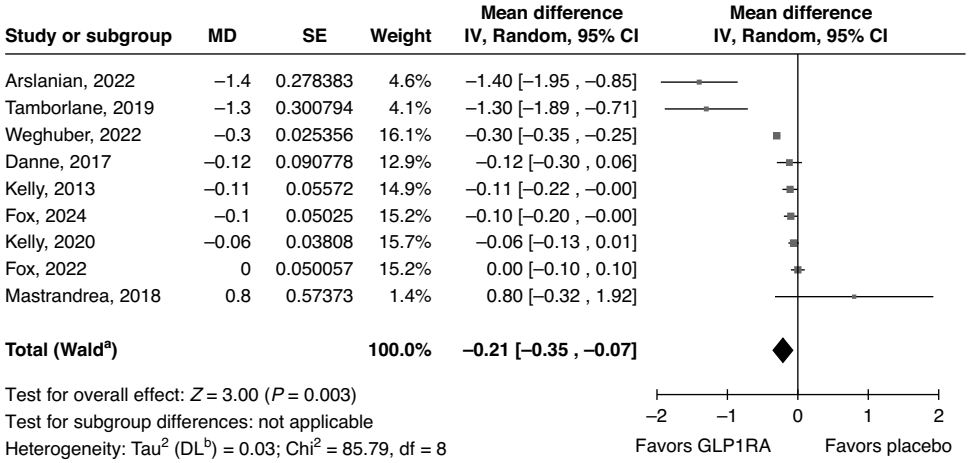


Test for overall effect: $Z = 4.94$ ($P < 0.00001$)
Test for subgroup differences: not applicable
Heterogeneity: Tau^2 (DL^b) = 0.00; $Chi^2 = 0.78$, df = 1 ($P = 0.38$); $I^2 = 0\%$

Footnotes

[a]CI calculated by Wald-type method.
[b]Tau^2 calculated by DerSimonian and Laird method.

Fig. 3 Effects of GLP-1 receptor agonists on BMI z-score in patients <12 years. Forest plot presenting the mean difference (MD) and 95% confidence interval (CI) for change in BMI z-score from baseline. Abbreviations: CI confidence interval, MD mean difference, GLP1RA glucagon-like peptide 1 receptor agonist.

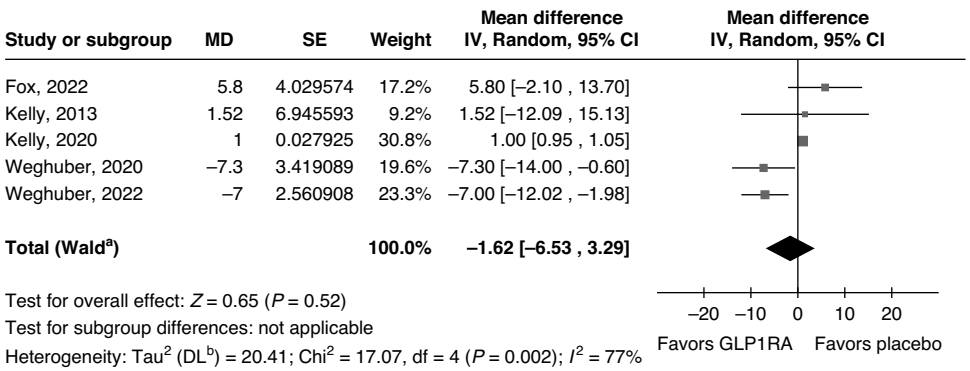


Test for overall effect: $Z = 3.00$ ($P = 0.003$)
Test for subgroup differences: not applicable
Heterogeneity: Tau^2 (DL^b) = 0.03; $Chi^2 = 85.79$, df = 8 ($P < 0.00001$); $I^2 = 91\%$

Footnotes

[a]CI calculated by Wald-type method.
[b]Tau^2 calculated by DerSimonian and Laird method.

Fig. 4 Effects of GLP-1 receptor agonists on HbA1c in pediatric patients with obesity. Forest plot presenting the mean difference (MD) and 95% confidence interval (CI) for change in HbA1c from baseline. Abbreviations: CI confidence interval, MD mean difference, GLP1RA glucagon-like peptide 1 receptor agonist.



Test for overall effect: $Z = 0.65$ ($P = 0.52$)
Test for subgroup differences: not applicable
Heterogeneity: Tau^2 (DL^b) = 20.41; $Chi^2 = 17.07$, df = 4 ($P = 0.002$); $I^2 = 77\%$

Footnotes

[a]CI calculated by Wald-type method.
[b]Tau^2 calculated by DerSimonian and Laird method.

Fig. 5 Effects of GLP-1 receptor agonists on LDL-c levels in pediatric patients with obesity. Forest plot presenting the mean difference (MD) and 95% confidence interval (CI) for change in LDL-c level from baseline. Abbreviations: CI confidence interval, MD mean difference, GLP1RA glucagon-like peptide 1 receptor agonist.

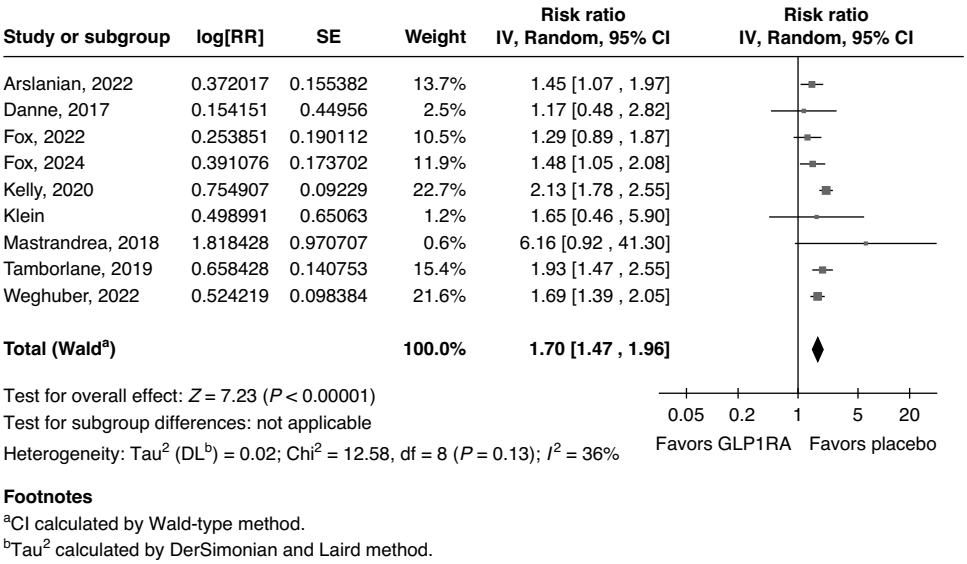


Fig. 6 Adverse gastrointestinal events in overall pediatric patients with obesity. Forest plot presenting the risk ratio (RR) and 95% confidence interval (CI) for adverse gastrointestinal events. Abbreviations: CI confidence interval, RR risk ratio, GLP1RA glucagon-like peptide 1 receptor agonist.

years, GLP-1 receptor agonists consistently decreased BMI z-score (MD −0.33; 95% CI −0.47 to −0.20; $p < 0.01$; $I^2 = 0\%$; Fig. 3) compared with placebo. HbA1c level was significantly decreased following GLP-1 receptor agonist (MD −0.21%; 95% CI −0.35 to −0.07%; $p < 0.01$; $I^2 = 91\%$; Fig. 4). There was no significant difference in LDL-c level between groups (MD −1.62; 95% CI −6.53 to 3.29; $p = 0.52$; $I^2 = 77\%$; Fig. 5).

Adverse gastrointestinal events

Treatment with GLP-1 receptor agonists significantly increased the risk of gastrointestinal adverse events in the overall population (RR 1.70; CI 1.47 to 1.96; $p < 0.01$; $I^2 = 36\%$; Fig. 6) and among patients aged less than 12 years (RR 1.52; 95% CI 1.09 to 2.12; $p < 0.01$; $I^2 = 0\%$; Fig. 7).

Risk of bias assessment

RoB-2 identified all studies at low risk of bias (Supplemental Fig. 1). There was significant evidence of publication bias for body weight ($p = 0.03$; Supplemental Fig. 2). Only 1 study was not symmetrical in the funnel plot analysis- considering this we included 9 studies in Egger's test (Supplemental Fig. 2).

Sensitivity analysis

In leave-one-out sensitivity analysis, results remained consistent after omission of all studies (Supplemental Fig. 3).

Subgroup analyses

GLP-1 therapy showed efficacy in weight reduction in patients with T2DM (MD −6.86 kg; 95% CI −13.31 to −0.40 kg; $p < 0.01$; $I^2 = 96\%$; Supplemental Fig. 4) and patients without T2DM (MD −2.26 kg; 95% CI −3.46 to −1.06 kg; $p < 0.01$; $I^2 = 0\%$; Supplemental Fig. 5).

Both exenatide (MD −3.30 kg; 95% CI −5.03 to −1.57 kg; $p < 0.01$; $I^2 = 0\%$; Supplemental Fig. 6) and liraglutide (MD −3.09 kg; 95% CI −5.39 to −0.79 kg; $p < 0.01$; $I^2 = 65\%$; Supplemental Fig. 7) demonstrated a significant weight reduction in pediatric patients.

Follow-up periods longer than 12 weeks showed greater efficacy in weight reduction (MD −6.08 kg; 95% CI −11.57 to −0.58 kg; $p = 0.03$; $I^2 = 95\%$; Supplemental Fig. 8) compared to those shorter than 12 weeks (MD −1.91 kg; 95% CI −3.29 to −0.53 kg; $p < 0.01$; $I^2 = 0\%$; Supplemental Fig. 9).

Considering frequency of administration, once daily administration of GLP-1 receptor agonists significantly decreased body weight in pediatric patients (MD −3.09 kg; 95% CI −5.39 to −0.79 kg; $p < 0.01$; $I^2 = 65\%$; Supplemental Fig. 10a). There was no significant reduction in body weight with once weekly administration of GLP-1 receptor agonists (MD −6.13 kg; 95% CI −13.01 to 0.75; $p = 0.08$; $I^2 = 96\%$; Supplemental Fig. 10b).

DISCUSSION

In this systematic review and meta-analysis of 11 RCTs and 1,024 pediatric patients, GLP-1 receptor agonists were associated with significantly reducing body weight, BMI z-score, waist circumference and HbA1C. There was no significant difference in LDL-c levels.

Obesity is directly associated with increased cardiovascular risk, and children with obesity tend to develop cardiometabolic disorders earlier in adulthood.[24] Dyslipidemia and insulin resistance are frequent comorbidities seen in patients with increased body weight. Waist circumference is another diagnostic criterion for metabolic syndrome.[25] Children with high waist circumference were 3.6 times more likely than those with normal waist status to have a low high-density lipoprotein level, 3.0 times more likely to have high triglycerides, and 3.7 times more likely to have a high fasting insulin level.[26] In this meta-analysis, waist circumference was decreased following the use of GLP-1 receptor agonists by almost four centimeters. These results indicate an overall improvement in the metabolic profile, which may ultimately reduce cardiovascular risk in this patient population.

GLP-1 receptor agonists play an important role in glycemic control.[27] Obesity is often associated with elevated fasting glucose and HbA1c levels.[28] Our meta-analysis demonstrated a significant reduction in HbA1c among children and adolescents using this medication compared with placebo, which may represent a decrease in risk of chronic complications caused by the inflammatory state of obesity and poor glycemic control.

Despite improvements in the glycemic profile observed with GLP-1 receptor agonist use, LDL-c showed a consistent downward trend that missed statistical significance. This muted effect likely reflects the fact that baseline LDL-c levels were generally on target before treatment, as obesity in youth more typically manifests as low HDL-c and hypertriglyceridemia rather than marked LDL-c

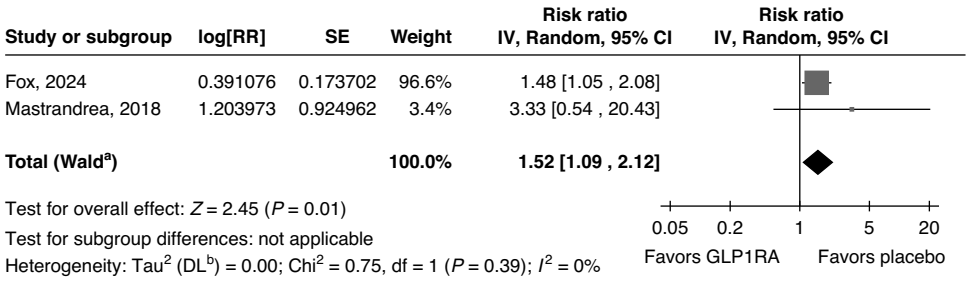


Fig. 7 Adverse gastrointestinal events in pediatric patients. Forest plot presenting the risk ratio (RR) and 95% confidence interval (CI) for adverse gastrointestinal events. Abbreviations: CI confidence interval, RR risk ratio, GLP1RA glucagon-like peptide 1 receptor agonist.

dyslipidemia. Consequently, although GLP-1 therapy appears directionally favourable for LDL-c, its clinically meaningful lipid benefits in children and adolescents may be more pronounced in other metabolic clusters such as glycemia, HDL-C and triglycerides.

Glycaemic dysregulation and its treatment can independently influence body weight, lipid fractions, appetite and gastrointestinal tolerability, potentially exaggerating or masking obesity-specific responses to GLP-1 receptor agonists. In addition, adolescents with T2DM often receive background metformin, insulin or lifestyle counselling that differs in intensity from purely obesity-focused programmes, introducing co-interventions that could confound the observed effects on anthropometry and metabolic markers. To gauge the magnitude of this bias we ran a subgroup analysis comparing patients with T2DM versus non-T2DM and weight reduction remained significant in both strata (−6.8 kg and −2.2 kg, respectively), reinforcing the strength of the obesity-specific conclusions, but also highlighting the need for future RCTs that focus solely on pediatric obesity, to yield clearer efficacy signals.

A total of six studies used liraglutide,[7–10,12,16] three studies used exenatide,[6,11,13] one study used semaglutide,[15] and one study used dulaglutide.[14] In a subgroup analysis performed, exenatide appeared to be more effective in promoting weight loss compared to liraglutide (Supplemental Figs. 6 and 7). However, it is important to note that the studies involving exenatide had a longer follow-up duration (greater than 12 weeks), which may represent a confounding factor. Regarding follow-up duration, studies lasting more than 12 weeks consistently demonstrated greater weight loss than those with shorter follow-up periods (Supplemental Figs. 8 and 9).

Our analysis reveals a dramatic difference in weight reduction observed in the study utilizing semaglutide,[15] when compared to other studies employing liraglutide.[9] While liraglutide remains the only GLP-1 analogue currently approved for the treatment of obesity in children, these findings highlight the potential of other GLP-1 analogues, such as semaglutide, in the management of this condition.[29]

This potential becomes even more relevant when considering the practical aspects of treatment. GLP-1 receptor agonists are medications administered subcutaneously, and most of the studies included in this meta-analysis used liraglutide, which requires daily administration. Although it is currently the only approved agent in this class for use in children and adolescents, its dosing regimen may pose a barrier to adherence in this population. This underscores the need for further studies evaluating other GLP-1 receptor agonists with more convenient dosing schedules, such as those administered weekly.

A study published in BMC Paediatrics observed that a 0.10 reduction in weight z-score corresponded to an ~0.15 reduction in BMI z-score, which was associated with clinically significant improvements in lipid profiles and insulin levels.[30] While studies have demonstrated significant weight loss in children undergoing appropriate physical activity and dietary interventions,[31] our meta-analysis indicates that combining these strategies with pharmacotherapy can nearly double the weight loss. This enhanced effect may be particularly important for children with severe obesity who struggle with basic daily activities and face challenges in social integration.

The subgroup analysis for participants under 12 years of age included only two studies[9,16] with a limited sample size, representing a critical limitation in the evidence base for this population. The small number of studies and participants significantly restricts the reliability and generalisability of the findings. As such, conclusions regarding the efficacy and safety of the intervention in children under 12 should be interpreted with caution, and any extrapolation should be avoided to prevent overstating the available evidence.

The maximum follow-up duration in the study was 68 weeks, highlighting a significant limitation regarding the evaluation of long-term outcomes. Specifically, there is a lack of data on the sustained safety profile of the intervention, including its potential effects on critical developmental aspects such as growth, puberty and bone health. Additionally, the durability of weight loss beyond the 1-year mark remains uncertain. Therefore, caution is warranted when attempting to extrapolate these findings to longer timeframes, as the long-term risks and benefits have not been adequately assessed.

Our study identified high heterogeneity in the generated plots. This is likely attributable, in part, to the inclusion of a study that used semaglutide and had a significantly longer follow-up period (68 weeks) compared to the others.[15] Furthermore, the studies varied not only in the specific GLP-1 analogues used but also in dosing regimens and administration frequency. Notably, studies that employed higher doses and longer follow-up durations[12,16] demonstrated greater weight reduction, whereas studies with lower doses and shorter follow-up periods[8,9] reported more modest outcomes. Furthermore, heterogeneity (I^2) fell from >80% in the primary analysis to <35% when diabetes trials were removed, suggesting that part of the variability stemmed from the mixed metabolic phenotypes.

The main adverse effect of GLP-1 receptor agonists in adults is gastrointestinal.[29] According to the included trials, the safety profile of GLP-1 receptor agonists among children and adolescents was consistent with that observed among adults and with that of this medication in general.[15] No new safety concerns were identified and permanent discontinuations because of gastrointestinal disorders were very low or null [Table 2].

Table 2. Adverse Events of Included Studies.[6–16]

Study, year	*Any adverse event (%)*	*Serious adverse event (%)*	*Diarrhea (%)*	*Nausea (%)*	*Hypoglycemia (%)*	*Discontinuation rate (%)*
Arslanian, 2022	GLP-1 (74) Placebo (69)	GLP-1 (2) Placebo (6)	GLP-1 (14) Placebo (18)	GLP-1 (8) Placebo (15)	GLP-1 (8) Placebo (12)	GLP-1 (3) Placebo (2)
Danne, 2017	GLP-1 (100) Placebo (57)	GLP-1 (21) Placebo (0)	GLP-1 (21) Placebo (0)	GLP (50) Placebo (0)	GLP-1 (14) Placebo (0)	n/a
Fox, 2022	GLP-1 (96) Placebo (90)	GLP-1 (3) Placebo (0)	GLP-1 (33) Placebo (18)	GLP-1 (39) Placebo (21)	n/a	n/a
Fox, 2024	GLP-1 (89) Placebo (88)	GLP-1 (12) Placebo (8)	n/a*	n/a*	n/a	GLP-1 (11) Placebo (0)
Kelly, 2020	GLP-1 (88) Placebo (84)	GLP-1 (2) Placebo (4)	GLP-1 (22) Placebo (14)	GLP-1 (42) Placebo (14)	n/a	GLP-1 (10) Placebo (0)
Klein, 2014	GLP-1 (57) Placebo (28)	GLP-1 (0) Placebo (0)	GLP-1 (42) Placebo (14)	GLP-1 (21) Placebo (14)	GLP-1 (28) Placebo (14)	n/a
Mastrandrea, 2018	GLP-1 (56) Placebo (62)	GLP-1 (6) Placebo (12)	GLP-1 (6) Placebo (0)	GLP-1 (12) Placebo (0)	GLP-1 (25) Placebo (12)	n/a
Kelly, 2013	n/a	GLP-1 (0) Placebo (0)	GLP-1 (8) Placebo (31)	GLP-1 (62) Placebo (31)	GLP-1 (0) Placebo (0)	GLP-1 (0) Placebo (0)
Tamborlane, 2019	GLP-1 (84) Placebo (80)	GLP-1 (13) Placebo (5)	GLP-1 (22) Placebo (16)	GLP-1 (28) Placebo (13)	GLP-1 (45) Placebo (25)	GLP-1 (1) Placebo (1)
Weghuber, 2020	n/a	GLP-1 (0) Placebo (0)	n/a*	n/a*	GLP-1 (0) Placebo (0)	n/a
Weghuber, 2022	GLP-1 (79) Placebo (82)	GLP-1 (11) Placebo (9)	GLP-1 (22) Placebo (13)	GLP-1 (42) Placebo (18)	n/a	GLP-1 (5) Placebo (4)

n/a not available.
[a]Did not differentiate between individual gastrointestinal symptoms; instead, it grouped the symptoms collectively.

Limitations

Our analysis has some limitations. First, most of the included studies had shorter follow-up periods, with the maximum duration of follow-up of 68 weeks. Therefore, we cannot assess the long-term safety, efficacy and sustainability of weight and metabolic improvements with GLP-1 receptor agonists in children and adolescents. Second, the significant heterogeneity observed in our analysis suggests variability across studies, possibly due to differences in study age populations, doses, treatment durations, or GLP-1 receptor agonist formulations. To mitigate this limitation, we conducted a sensitivity analysis and subgroup analyses that showed consistent findings with the overall analysis.

CONCLUSION

In this systematic review and meta-analysis of RCTs among children and adolescents with obesity, GLP-1 receptor agonists significantly reduced body weight, BMI z-score, waist circumference and HbA1c levels in children and adolescents.

REFERENCES

1. Luli, M. et al. The implications of defining obesity as a disease: a report from the Association for the Study of Obesity 2021 annual conference. *eClinicalMedicine* **58**, 101962 (2023).
2. Smith, J. D., Fu, E. & Kobayashi, M. A. Prevention and management of childhood obesity and its psychological and health comorbidities. *Annu. Rev. Clin. Psychol.* **16**, 351–378 (2020). May 07.
3. Maffeis, C. et al. The treatment of obesity in children and adolescents: Consensus position statement of the Italian society of pediatric endocrinology and diabetology, Italian Society of Pediatrics and Italian Society of Pediatric Surgery. *Ital. J. Pediatr.* **49**, 69 (2023).
4. Chung, Y. L. & Rhie, Y.-J. Severe obesity in children and adolescents: metabolic effects, assessment, and treatment. *J. Obes. Metab. Syndr.* **30**, 326–335 (2021).
5. Collins, L., & Costello, R. A. *Glucagon-Like Peptide-1 Receptor Agonists*. Em *StatPearls* (StatPearls Publishing, 2024).
6. Kelly, A. et al. The effect of glucagon-like peptide-1 receptor agonist therapy on body mass index in adolescents with severe obesity: A randomized, placebo-controlled, clinical trial. *JAMA Pediatr.* **167**, 355–360 (2013).
7. Klein, D. et al. Liraglutide's safety, tolerability, pharmacokinetics, and pharmacodynamics in pediatric type 2 diabetes: A randomized, double-blind, placebo-controlled trial. *Diab. Technol. Ther.* **16**, 679–687 (2014).
8. Danne, T. et al. Liraglutide in an adolescent population with obesity: a randomized, double-blind, placebo-controlled 5-week trial to assess safety, tolerability, and pharmacokinetics of liraglutide in adolescents aged 12-17 years. *J. Pediatr.* **181**, 146–153.e3 (2017).
9. Mastrandrea, L. et al. Liraglutide effects in a paediatric (7-11 y) population with obesity: a randomized, double-blind, placebo-controlled, short-term trial to assess safety, tolerability, pharmacokinetics, and pharmacodynamics. *Pediatr. Obes.* **14**, e12495 (2019).
10. Tamborlane, W. et al. Liraglutide in children and adolescents with type 2 diabetes. *N. Engl. J. Med.* **381**, 637–646 (2019).
11. Weghuber, D. et al. A 6-month randomized, double-blind, placebo-controlled trial of weekly exenatide in adolescents with obesity. *Pediatr. Obes.* **15**, e12624 (2020).
12. Kelly, A. et al. A randomized, controlled trial of liraglutide for adolescents with obesity. *N. Engl. J. Med.* **382**, 2117–2128 (2020).
13. Fox, C. et al. Exenatide for weight-loss maintenance in adolescents with severe obesity: a randomized, placebo-controlled trial. *Obesity* **30**, 1105–1115 (2022).
14. Arslanian, S. et al. Once-weekly dulaglutide for the treatment of youths with type 2 diabetes. *N. Engl. J. Med.* **387**, 433–443 (2022).
15. Weghuber, D. et al. Once-weekly semaglutide in adolescents with obesity. *N. Engl. J. Med.* **387**, 2245–2257 (2022).
16. Fox, C. et al. Liraglutide for children 6 to <12 years of age with obesity—a randomized trial. *N. Engl. J. Med.* **392**, 555–565 (2024).
17. Liu, L. et al. Comparative efficacy and safety of glucagon-like peptide-1 receptor agonists in children and adolescents with obesity or overweight: a systematic review and network meta-analysis. *Pharmaceuticals* **17**, 828 (2024).
18. Ryan, P. et al. Safety and efficacy of glucagon-like peptide-1 receptor agonists in children and adolescents with obesity: a meta-analysis. *J. Pediatr.* **236**, 137–147.e13 (2021).
19. Higgins, J. et al. *Cochrane Handbook for Systematic Reviews of Interventions* 2nd edn (John Wiley & Sons, 2019).
20. Page, M. et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ **372**, n71 (2021)
21. Higgins, J. P., Savović, J., Page, M. J., Elbers, R. G., Sterne, J. A. Assessing risk of bias in a randomized trial. In *Cochrane Handbook for Systematic Reviews of Interventions* [Internet]. 1st edn (eds Higgins J. P. T.) Ch. 8, 205–228, accessed 22 April 2023 Available from: https://onlinelibrary.wiley.com/doi/10.1002/9781119536604.ch8 (Wiley, 2019).
22. Egger, M., Smith, G. D., Schneider, M. & Minder, C. Bias in meta-analysis detected by a simple, graphical test. *Br. Med. J.* **315**, 629–634 (1997).
23. McGrath, S., Zhao, X., Steele, R., Thombs, B. D. & Benedetti, A. the DEPRESsion Screening Data (DEPRESSD) Collaboration, et al. Estimating the sample mean and standard deviation from commonly reported quantiles in meta-analysis. *Stat. Methods Med. Res.* **29**, 2520–2537 (2020).
24. Skinner Asheley, C., Perrin Eliana, M., Moss Leslie, A. & Skelton Joseph, A. Cardiometabolic risks and severity of obesity in children and young adults. *N. Engl. J. Med.* **373**, 1307–1317 (2015).
25. Alberti, K. G. M. M., Zimmet, P. & Shaw, J. IDF Epidemiology Task Force Consensus Group: the metabolic syndrome—a new worldwide definition. *Lancet* **366**, 1059–1062 (2005).
26. Bassali, R., Waller, J. L., Gower, B., Allison, J. & Davis, C. L. Utility of waist circumference percentile for risk evaluation in obese children. *Int. J. Pediatr. Obes.* **5**, 97–101 (2010).
27. Yao, H. et al. Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: Systematic review and network meta-analysis. *BMJ* **384**, e076410 (2024).
28. Chandrasekaran, P. & Weiskirchen, R. The role of obesity in type 2 diabetes mellitus-an overview. *Int. J. Mol. Sci.* **25**, 1882 (2024).
29. Coutinho, W. & Halpern, B. Pharmacotherapy for obesity: moving towards efficacy improvement. *Diabetol. Metab. Syndr.* **16**, 6 (2024).
30. Cason-Wilkerson, R., Thompson, D. & Mitchell, N. Weight change for pediatric completers in a national weight loss program. *Glob. Pediatr. Health* **8**, 2333794X211057716 (2021).
31. Ruebel, M. L., Heelan, K. A., Bartee, T. & Foster, N. Outcomes of a family based pediatric obesity program—preliminary results. *Int. J. Exerc. Sci.* **4**, 217–228 (2011).

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AUTHOR CONTRIBUTIONS

L.M.R., *Estácio de Sá University, RJ, Brazil* (first author)—contributed to the search strategy, study triage, data and outcome extraction, systematic review, statistical analysis and drafting of the manuscript. A.A.C.d.M., *Catholic University of Pernambuco, PE, Brazil*—contributed to the search strategy, triage, data and outcome extraction and preparation of figures. E.F., *Trinity College Dublin, Ireland*—contributed to the risk of bias assessment, data and outcome extraction. Y.M., *Federal University of Rio de Janeiro, Macaé, RJ, Brazil*—contributed to data extraction and preparation of tables and figures. C.C.P.S.J., *Division of Endocrinology, Federal University of São Paulo/Escola Paulista de Medicina, SP, Brazil* (senior author)—contributed to manuscript writing, critical revision and statistical analysis.

COMPETING INTERESTS

The authors declare that they have no competing interests. All authors report no relationships that could be construed as a conflict of interest. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. There were no external funding sources for this study.

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