

Efficacy and Safety of GLP-1 RAs in Children and Adolescents With Obesity or Type 2 Diabetes

A Systematic Review and Meta-Analysis

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 Supplemental content

IMPORTANCE Obesity affects 1 in 5 children and adolescents, increasing the risk of type 2 diabetes (T2D). Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are among the few pharmacotherapy options available for this population, necessitating a comprehensive evaluation of efficacy and safety.

OBJECTIVE To assess the efficacy and safety of GLP-1 RAs in children and adolescents (<18 years) with obesity, prediabetes, or T2D.

DATA SOURCES A systematic search was conducted in PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) for randomized clinical trials (RCTs) published from inception until February 28, 2025. Data analysis was completed from January 2025 to April 2025.

STUDY SELECTION RCTs comparing GLP-1 RAs to placebo in children and adolescents with obesity, overweight, prediabetes, or T2D with reported safety and efficacy data were included.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently extracted data on sample size, population, interventions, follow-up, and outcomes. Risk of bias was assessed using version 2 of the Cochrane risk of bias tool (RoB2). Efficacy outcomes (except lipids) were analyzed as estimated treatment differences, lipids as estimated treatment ratios, and safety via rate ratios. A random-effects inverse variance model was used for all outcomes.

MAIN OUTCOMES AND MEASURES The primary efficacy outcomes were change in hemoglobin A_{1c} (HbA_{1c}) (in percentage points), fasting glucose (in milligrams per deciliter), body weight (in kilograms), body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), BMI z scores or percentiles, BMI standard deviation score (SDS), lipid outcomes, and blood pressure. Exploratory efficacy outcomes included obstructive sleep apnea and metabolic dysfunction–associated steatohepatitis or metabolic dysfunction–associated steatotic liver disease. Safety outcomes included gastrointestinal adverse effects (GI AEs), infections, hepatobiliary disorders, suicidal ideation or behaviors, depression, hypoglycemia, and adverse event discontinuations.

RESULTS A total of 18 RCTs (11 in obesity, 6 in T2D, and 1 in prediabetes) with 1402 participants (838 GLP-1 RA users and 564 placebo) were included (mean [range] age, 13.7 [6–17] years; 831 female participants (59.3%); median [IQR] treatment duration, 0.51 [0.25–1.00] years). GLP-1 RAs significantly reduced HbA_{1c} (−0.44%; 95% CI, −0.68% to −0.21%), fasting glucose (−9.92 mg/dL; 95% CI, −16.20 to −3.64), body weight (−3.02 kg; 95% CI, −4.98 to −1.06), BMI (−1.45; 95% CI, −2.40 to −0.49), BMI SDS (−0.20; 95% CI, −0.36 to −0.05), BMI percentile (−7.24%; 95% CI, −12.97% to −1.51%), and systolic blood pressure (−2.73 mm Hg; 95% CI, −4.04 to −1.43) and increased GI AE (log[rate ratio] [RR], 0.75). Other AEs, including suicidal ideation or behaviors, showed no significant differences.

CONCLUSIONS AND RELEVANCE In this systematic review and meta-analysis of 18 trials, GLP-1 RAs significantly improved glycemic, weight, and cardiometabolic outcomes in children and adolescents with T2D or obesity. Available data over a relatively short follow-up suggested suicidal ideation or behaviors were not significantly different, although GI AEs warrant attention in long-term management.

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Childhood obesity has reached epidemic levels, affecting 1 in 5 children and adolescents younger than 18 years.¹ This rise has paralleled a steady increase in type 2 diabetes (T2D) cases among youth, with projections indicating continued growth.²⁻⁴ Additionally, the risk of developing other comorbidities like liver disease, hypertension, and dyslipidemia is also higher. As a result, these individuals could experience a prolonged duration of chronic disease in their lives.^{3,5-7} Given the important public health concern, early intervention is crucial in children and adolescents with obesity or T2D.

Despite the need, treatment has remained limited to metformin and insulin for more than 3 decades.^{8,9} The US Food and Drug Administration (US FDA) first approved liraglutide, a glucagon-like peptide-1 receptor agonist (GLP-1 RA), for use in children and adolescents with T2D in 2019, followed by approval of liraglutide, semaglutide, dulaglutide, and extended-release exenatide for obesity and T2D, while tirzepatide, a dual GLP-1 RA/glucose-dependent insulinotropic polypeptide receptor agonist, is under investigation for T2D and obesity in this population.^{8,9} Pediatric guidelines for obesity and T2D have also expanded to include GLP-1 RAs as a pharmacotherapy option.¹⁰ The gap in treatment options and availability of GLP-1 RAs has led to an exponential increase in the use of GLP-1 RAs from 2020 to 2023 in this young population.^{8,11}

The psychological impact of GLP-1 RAs is a growing concern.^{12,13} Suicide rates in US youth nearly tripled from 2007 to 2017, with 17% of US youth reporting suicidal ideation and 7% to 8% attempting suicide annually.¹⁴ Regulatory agencies like the US FDA and the European Medicines Agency are reviewing possible links between GLP-1 RAs and suicidal behaviors.^{12,13} Additionally, findings from a meta-analysis of randomized clinical trials (RCTs) in adults have shown a reduced risk of depression in the GLP-1 RA group.¹⁵ With 15.1% of adolescents reporting major depressive episodes in 2018 to 2019, GLP-1 analogs' antidepressant effects, linked to reduced neuroinflammation, enhanced neurogenesis, and brain modulation, warrant exploration.^{16,17} Although animal models show reduced depression-like behaviors, human data are lacking.¹⁸ Therefore, exploring the potential antidepressant effects of GLP-1 RAs in children and adolescents could be a valuable area of interest. Additionally, GLP-1 RAs have demonstrated benefits in managing obstructive sleep apnea (OSA) in adults with obesity or T2D, yet these effects remain unexplored in pediatric populations.^{19,20} We aim to explore these outcomes as safety events and to evaluate the potential repurposing of GLP-1 RAs in children and adolescents with these conditions.

Existing systematic reviews and meta-analyses on GLP-1 RAs in children and adolescents are limited in scope, with several critical gaps.²¹⁻²³ This meta-analysis updates efficacy and safety data by incorporating studies published between 2023 and 2025, including trials in children as young as 6 years, beyond the previous focus on adolescents aged 10 to 12 years or older. Recent FDA approvals of dulaglutide and semaglutide for pediatric use underscore the need for reevaluation. Additionally, prior reviews have focused mainly on gastrointestinal adverse effects, lacking evaluation of other adverse events

Key Points

Question What are the efficacy and safety of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in children and adolescents?

Findings In this systematic review and meta-analysis of 18 randomized clinical trials involving 1402 participants aged 6 to 17 years, GLP-1 RAs significantly reduced hemoglobin A_{1c}, fasting glucose, body weight, body mass index (BMI), BMI standard deviation score, BMI percentile, and systolic blood pressure. Gastrointestinal adverse events were significantly more common among those taking GLP-1 RAs, while rates of discontinuation, depression, suicidal ideation or behaviors, and hepatobiliary disorders were not significantly different from placebo.

Meaning GLP-1 RAs were effective in improving glycemic control, weight, and cardiometabolic outcomes in children and adolescents. Suicidal ideation and behaviors and depression showed no significant differences, although gastrointestinal adverse effects remain a consideration for long-term use.

and events of regulatory concerns, such as suicidal behaviors.²¹⁻²³

This systematic review and meta-analysis synthesizes RCT evidence on the efficacy and safety of GLP-1 RAs in children and adolescents with T2D, prediabetes, and/or obesity, providing an updated evaluation of GLP-1 RAs' therapeutic potential and risks.

Methods

Literature Search

A systematic search was conducted in PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify relevant RCTs published from inception until February 28, 2025. The search included studies evaluating the efficacy and safety of approved anti-obesity drugs in children and adolescents with obesity, overweight, prediabetes, or T2D. The search used controlled vocabulary (eg, MeSH in PubMed, Emtree in Embase) and free-text keywords related to obesity, T2D, children, adolescents, and GLP-1 RAs. Terms for obesity, T2D, age groups, GLP-1 RA components or brand names, and RCT filters were combined. Full strategies are provided in eTable 1 in Supplement 1.

We included RCTs of approved GLP-1 RAs in individuals younger than 18 years with obesity, overweight, prediabetes, or T2D assessing GLP-1 RAs alone or with lifestyle modification vs placebo. We excluded post hoc analyses and studies lacking both efficacy and safety outcomes. A study author (P.K.) deduplicated results before importing into Covidence, which helped minimize inconsistencies in study exclusion criteria.^{24,25}

Data Screening and Extraction

Data screening and extraction were performed by 4 study authors (P.K., W.H., Y.Y.Y., and V.M.N.) Title and abstract screening of all search results was conducted independently by 2 reviewers using Covidence. Full-text screening of eligible studies

was also done by 2 independent reviewers, with a third resolving any conflicts. Systematic reviews meeting the inclusion criteria were examined for relevant component studies.

A prespecified set of variables streamlined data extraction. Extracted data included first author, year, sample size, population, GLP-1 RA type, treatment duration, follow-up, country(ies), and key efficacy or safety measures. The efficacy measures included hemoglobin A_{1c} (HbA_{1c}, in percentage points); fasting plasma glucose (FPG, in milligrams per deciliter); weight outcomes (body weight [in kilograms], body mass index [BMI, calculated as weight in kilograms divided by height in meters squared], and BMI z scores); blood pressure, reported as estimated treatment difference with 95% confidence intervals; and lipid profile, reported using estimated treatment ratio (ETR) with 95% confidence intervals. Metabolic dysfunction-associated steatohepatitis or metabolic dysfunction-associated steatotic liver disease (MASH/MASLD) and OSA were assessed as exploratory efficacy outcomes.

Suicidal ideation and behavior were assessed prospectively in the RCTs using the Columbia-Suicide Severity Rating Scale (C-SSRS), in alignment with the US FDA guidance for industry.²⁶ The guidance classifies this into 3 categories: suicidal ideation, suicidal behavior, and self-injury without intent. Ideation includes 5 severity levels; behavior includes preparatory actions, aborted or interrupted attempts, attempts, and completed suicide. The trials report these 3 groups together and will be hereafter be referred to as *suicidal ideation or behaviors*.

All safety outcomes, including those related to exploratory efficacy, such as MASH/MASLD and OSA, were classified according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology by the RCTs and accounted for throughout each trial's follow-up period. Safety measures were reported as total number of events in each group and included gastrointestinal adverse events, hepatobiliary disorders, infections, suicidal ideation or behaviors, depression, hypoglycemia, and discontinuation due to adverse events.

One reviewer compiled data into a standardized format, capturing study details, inclusion and exclusion criteria, follow-up duration, and reported outcomes. If outcome data were unavailable in the published article, data were retrieved from ClinicalTrials.gov. A second reviewer cross-checked and validated the extracted data, resolving discrepancies through consensus discussions.

Data Synthesis and Analysis

Fasting glucose concentrations in millimoles per liter were converted to milligrams per deciliter by multiplying by 18.0182.²⁷ If standard deviations at follow-up were missing, they were imputed using reported baseline standard deviations.²⁸ Effect estimates for the meta-analysis were based on the difference between treatment groups in change from baseline for continuous variables. In case of zero safety events, a 0.5 continuity correction was applied. Missing effect estimates or confidence intervals were imputed using available baseline, follow-up, or

change from baseline data for both intervention and placebo groups following Cochrane guidelines.²⁸ Pooled standard deviation and standard error were calculated using formulas from Cochrane guidelines and RevMan Web (Cochrane).^{28,29} The number of events was used to calculate rate ratios for safety events, as these were more commonly reported than the number of patients experiencing those events.³⁰

All outcomes of GLP-1 RA vs placebo were summarized for the type 2 diabetes or prediabetes population, the obesity population, and overall.

All measures were assessed using random-effects inverse variance-weighted models that allow for heterogeneity among individual study effect estimates.³⁰

We carried out a sensitivity analysis following the leave-one-out approach for the main efficacy outcomes of interest (ie, HbA_{1c}, FPG, BMI, and BMI-SDS) to assess the robustness of our findings.

Risk of Bias Assessment

The risk of bias for RCTs was assessed using the Cochrane Risk of Bias in Randomized Trials version 2 (RoB2) tool by 2 reviewers.³¹ Each study's risk of bias scores were compiled, and if consensus was not reached between the 2 reviewers, the final classification was determined by a third reviewer (P.K. or J.G.)

Results are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines.³² The study protocol is registered on PROSPERO (CRD42024583356).³³ Statistical analyses were performed using Stata version 16.0 (StataCorp).

Results

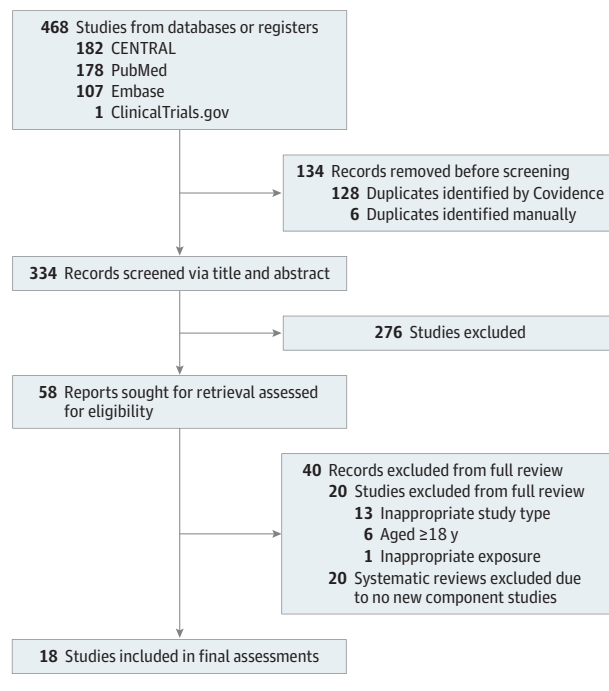
Study Characteristics

A total of 18 (11 in obesity, 6 in T2D, and 1 in prediabetes) randomized placebo-controlled trials with 1402 participants (838 GLP-1 RA users and 564 placebo) investigating the efficacy and safety of GLP-1 RAs met the inclusion criteria (**Figure 1**). Across the 18 trials, the mean (range) age of included participants was 13.7 years (6-17), with 59.3% of participants being female (range, 31%-83.3%), 67.9% being White (range, 20.5%-93.2%), a median (IQR) treatment duration of 0.51 years (0.25-1.00), and a median (IQR) follow-up duration of 0.19 years (0.05-0.49). A total of 5, 15, and 6 trials reported the use of either dose-stabilized metformin or basal insulin at baseline, concomitant lifestyle intervention during the trial, and treatment adherence, respectively. The characteristics of the included trials are summarized in the **Table**. All trials (except Zhou and colleagues⁴⁹ and Fox and colleagues⁵¹) were sponsored by pharmaceutical companies.³⁴⁻⁵¹

The overall heterogeneity remained high across most outcomes when accounting for both populations (ie, T2D and obesity together) (**Figures 2, 3, and 4**).

Overall, of 18 trials most showed some concern for the risk of bias (8 trials), followed by low concerns (6 trials) and high concerns (4 trials). The categorization of bias by category for all included trials can be found in eTable 2 in **Supplement 1**.

Figure 1. PRISMA Flow Diagram Displaying Results of the Literature Search



Efficacy Outcomes

Glycemic Outcomes

GLP-1 RAs demonstrated significant reductions in HbA_{1c} compared to placebo across trials. Overall, treatment with GLP-1 RAs resulted in an absolute reduction of HbA_{1c} by -0.44% of absolute HbA_{1c} (95% CI, -0.68% to -0.21%), with T2D trials showing a greater absolute reduction of -0.94% (95% CI, -1.25% to -0.62%) and obesity trials showing a comparatively smaller but significant absolute reduction in HbA_{1c} (-0.10% ; 95% CI, -0.18% to -0.02%).

The reduction was also notable in another glycemic parameter (ie, FPG) in the GLP-1 RA group, with significant reductions in the overall population (-9.92 mg/dL; 95% CI, -16.20 to -3.64) (to convert from milligrams per deciliter to millimoles per liter, multiply by 0.0555) and the T2D subgroup (-22.56 mg/dL; 95% CI, -35.33 to -9.78), whereas the obesity trials showed a nonsignificant reduction in FPG (-1.39 mg/dL; 95% CI, -3.10 to 0.31) (Figure 2; eFigure 1 in Supplement 1).

Weight-Related Outcomes

BMI reduced significantly in the overall population and the obesity subgroup. Overall, GLP-1 RA treatment resulted in a significant decrease in BMI by -1.45 (95% CI, -2.40 to -0.49), with the obesity trials showing a larger effect (-1.71 ; 95% CI, -2.84 to -0.58) compared to the T2D trials (-0.42 ; 95% CI, -1.10 to 0.27). BMI percentile also showed a similar trend, with the overall effect being -7.24% (95% CI, -12.97% to -1.51%) and the obesity trials exhibiting a greater reduction (-8.78% ; 95% CI, -14.90% to -2.67%), whereas the T2D trials showed a nonsignificant reduction of -0.23% (95% CI, -0.76% to 0.30%). Simi-

larly, BMI-SDS decreased by -0.20 (95% CI, -0.36 to -0.05) overall, with obesity trials demonstrating a more pronounced reduction (-0.26 ; 95% CI, -0.47 to -0.06) compared to T2D trials (-0.05 ; 95% CI, -0.13 to 0.04) (Figure 2; eFigure 2 in Supplement 1).

The reduction in waist circumference was significant in the GLP-1 RA group compared to placebo in obesity trials (-3.81 cm; 95% CI, -6.76 to -0.87), with no available data from T2D trials. In terms of body weight, the overall reduction was -3.02 kg (95% CI, -4.98 to -1.06), while the obesity trials saw a greater reduction of -4.72 kg (95% CI, -7.62 to -1.83). The T2D trials showed a nonsignificant reduction of -0.40 kg (95% CI, -1.10 to 0.31) (Figure 2; eFigure 3 in Supplement 1).

Lipid Outcomes

In terms of lipid profile, changes across trials were generally modest when analyzed using ETR. Overall, total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) demonstrated minimal differences in the overall analysis (total cholesterol: 1.00 ; 95% CI, 0.98 - 1.02 ; LDL: 1.00 ; 95% CI, 0.99 - 1.04 ; HDL: 1.00 ; 95% CI, 0.97 - 1.04). The trends for total cholesterol, LDL, and HDL remained consistent in obesity and T2D trials. Triglyceride and very low-density lipoprotein levels showed a nonsignificant reduction in the GLP-1 RA group vs placebo, with overall ETRs of 0.95 (95% CI, 0.90 - 1.01) and 0.97 (95% CI, 0.90 - 1.04), respectively (Figure 3; eFigure 4 in Supplement 1).

Blood Pressure Outcomes

There was a significant overall reduction of systolic blood pressure (SBP) in the GLP-1 RA group by -2.73 mm Hg (95% CI, -4.04 to -1.43), with a slightly more pronounced effect in 9 obesity trials (-2.85 mm Hg; 95% CI, -4.32 to -1.38) compared to 2 T2D trials (-2.29 mm Hg; 95% CI, -5.14 to 0.56). Diastolic BP (DBP) showed nonsignificant reductions overall by -1.21 mm Hg (95% CI, -2.81 to 0.39), with a nonsignificant reduction in 9 obesity trials by -1.49 mm Hg (95% CI, -3.39 to 0.41). However, the effect in 1 T2D trial was minimal (-0.26 mm Hg; 95% CI, -3.11 to 2.59) (Figure 2; eFigure 5 in Supplement 1).

Exploratory Efficacy Outcomes

GLP-1 RAs demonstrated a reducing nonsignificant trend for OSA outcomes (ie, log[rate ratio] [logRR]): -0.70 (95% CI, -2.75 to 1.35). The information for this outcome was only available from 2 obesity trials. For MASH/MASLD, data were only available from 1 T2D trial, but with 3 dose periods (0.75 mg, 1.5 mg, and pooled), and we summarized the overall estimate, which showed no significant difference in rate between the GLP-1 RA group and placebo (logRR, 0.24 ; 95% CI, -1.80 to 2.29) (Figure 4; eFigure 6 in Supplement 1).

Safety Outcomes

Gastrointestinal Adverse Events, Hepatobiliary Disorders, and Infections

Gastrointestinal adverse events showed a significantly increasing trend with GLP-1 RA treatment vs placebo overall (logRR, 0.73 ; 95% CI, 0.38 - 1.07) across 14 RCTs. In T2D trials, no mean-

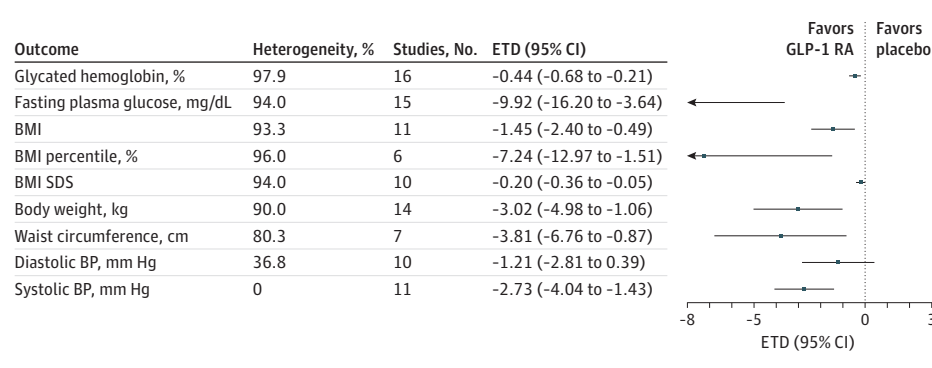
Table. Baseline Characteristics of 18 Randomized Placebo-Controlled Glucagon-Like Peptide-1 Receptor Agonist (GLP-1RA) Trials in Children and Adolescents

Source	National clinical trial identifier	GLP-1 RA type	No. of patients (GLP-1 RA/placebo)	Dose per day (maximum)	Population	Mean (range) age, y	% Female	White	Lifestyle intervention	Any concomitant treatment for T2D?	Duration of treatment, y	Follow-up, y	Adherence to treatment
Kelly et al, ³⁴ 2012	NCT00886626	Exenatide	6/6	10.0 µg	Extreme obesity	12.5 (9-16)	83.3	75	Yes	No	0.5	NA	"Excellent"
Kelly et al, ³⁵ 2013	NCT01237197	Exenatide	13/13	10.0 µg	Severe obesity	15.2 (12-19)	61.5	76.9	Yes	No	0.25	0.25	"Excellent"
Kelly et al, ³⁶ 2020	NCT02918279	Liraglutide	125/126	3.0 mg	Obesity	14.5 (12-17)	59.4	88	Yes	Yes, dose-stabilized metformin or basal insulin during the trial	1.08	0.49	>80%
Diene et al, ³⁷ 2022	NCT02527200	Liraglutide	36/19	3.0 mg	Prader-Willi syndrome and obesity	11.4 (6-17)	51.3	62.8	Yes	No	1	0.04	NA
Tamborlane et al, ³⁸ 2019	NCT01541215	Liraglutide	66/68	1.8 mg	T2D	14.6 (10-17)	61.9	64.9	Yes	Yes, dose-stabilized metformin during the trial	1	NA	NA
Tamborlane et al, ³⁹ 2022	NCT01554618	Exenatide	58/24	2.0 mg	T2D	15 (10-17)	59	42.7	Yes	No	0.47	0.7	NA
Danre et al, ⁴⁰ 2017	NCT01789086	Liraglutide	14/7	3.0 mg	Obesity	14.75 (12-17)	66.7	NA	NA	No	0.1	0.13	NA
Fox et al, ⁴¹ 2025	NCT04775082	Liraglutide	56/26	1.8 mg	Obesity	10 (6-11)	46	72	Yes	No	1.08	0.49	NA
Weghuber et al, ⁴² 2020	2015-001628-45 ^a	Exenatide	22/22	2.0 mg	Obesity	14 (10-18)	50	93.2	Yes	No	0.47	0.04	"Good to excellent"
Weghuber et al, ⁴³ 2022	NCT04102189	Semaglutide	134/67	2.4 mg	Obesity	15.4 (12-18)	62	79	Yes	Yes, metformin	1.31	0.13	NA
Klein et al, ⁴⁴ 2014	NCT00943501	Liraglutide	14/7	1.8 mg	T2D	14.8 (10-17)	66.7	66.7	Yes	Yes, dose-stabilized metformin during the trial	0.1	0.1	NA
Mastrandrea et al, ⁴⁵ 2019	NCT02696148	Liraglutide	16/8	3.0 mg	Obesity	9.9 (7-11)	38	58.3	NA	No	0.25	0.05	NA
Arslanian et al, ⁴⁶ 2022	NCT02963766	Dulaglutide	103/51	1.5 µg	T2D	14.5 (10-17)	70	55	Yes	Yes, dose-stabilized metformin or basal insulin during the trial	1	0.1	99.4% Overall
Barrientos-Pérez et al, ⁴⁷ 2022	NCT02803918	Lixisenatide	18/5	12.0 µg	T2D	15.5 (10-17)	69.6	70	Yes	No	0.12	0.01	NA
Roth et al, ⁴⁸ 2021	NCT02664441	Exenatide	23/19	2.0 mg	Hypothalamic obesity	16.9 (10-25) ^b	61	85.7	NA	No	0.69	NA	Excluding parent report: exenatide: 89% ± 14%, placebo: 85% ± 20% Including parent report: exenatide 96% ± 8%, placebo: 93% ± 14%
Zhou et al, ⁴⁹ 2017	NA	Liraglutide	21/21	1.2 mg	Prediabetes	11.2 (6-18)	31	NA	Yes	No	0.25	NA	NA
Astrazeneca ⁵⁰	NCT00658021	Exenatide	80/42	10.0 µg	T2D	14 (10-17)	67	20.5	Yes	No	0.54	3	NA
Fox et al, ⁵¹ 2022	NCT02496611	Exenatide extended release	33/33	2.0 mg	Severe obesity	16 (12-18)	47	82	Yes	No	0.99	NA	NA

Abbreviations: NA, not available; T2D, type 2 diabetes.

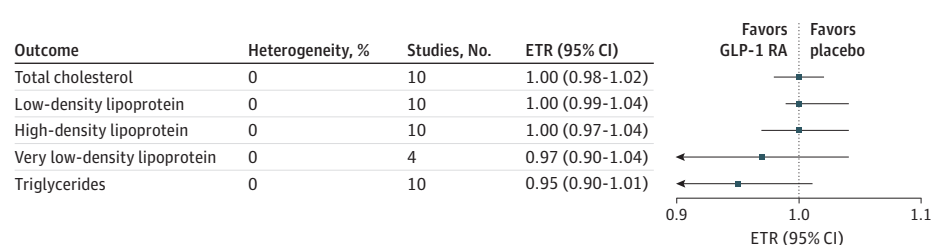
^a EUDRA-CT number.^b Although Roth and colleagues' trial⁴⁸ included participants up to 25 years of age, it was included in the analysis because most of the participants (approximately 72%) were younger than 18 years of age. Additionally, the efficacy outcomes were reanalyzed by excluding this trial in the sensitivity analysis.

Figure 2. Overall Estimated Treatment Differences (ETDs) for Efficacy Estimates



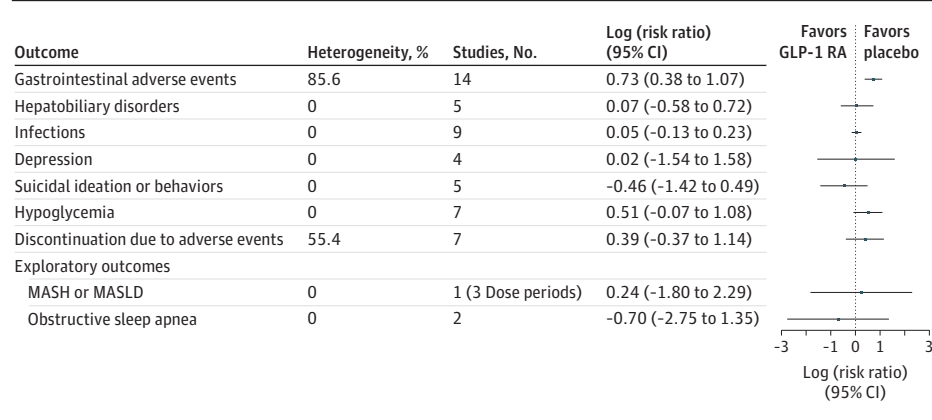
Breakdown by study and subgroup of diabetes and obesity is available in [Supplement 1](#). BMI indicates body mass index, calculated as weight in kilograms divided by height in meters squared; BP, blood pressure; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SDS, standard deviation score.

Figure 3. Overall Estimated Treatment Ratios (ETRs) for Lipid Outcomes



Breakdown by study and subgroup of diabetes and obesity is available in [Supplement 1](#). GLP-1 RA indicates glucagon-like peptide-1 receptor agonist.

Figure 4. Overall Risk of Selected Adverse Events



Suicidal behaviors encompassed suicide attempt, plan, or self-harm. Breakdown by study and subgroup of diabetes and obesity is available in [Supplement 1](#). GLP-1 RA indicates glucagon-like peptide-1 receptor agonist; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease.

ingful effect was observed (logRR, 0.31; 95% CI, -17 to 0.78). However, obesity trials showed a notable increase in gastrointestinal adverse events in the GLP-1 RA group compared to the placebo group (logRR, 1.02; 95% CI, 0.65-1.40) (Figure 4; eFigure 7 in [Supplement 1](#)).

GLP-1 RAs demonstrated a nonsignificant trend for hepatobiliary outcomes (logRR, 0.07; 95% CI, -0.58 to 0.72). For infections, the overall analysis across 9 RCTs suggested a possible increased rate (logRR, 0.05; 95% CI, -0.13 to 0.23), but the effect was not statistically significant. No significant difference was observed between the treatment groups in T2D trials (logRR, -0.03; 95% CI, -0.40 to 0.33), as well as in obesity trials (logRR, 0.26; 95% CI, -0.15 to 0.66) (Figure 4; eFigure 8 in [Supplement 1](#)).

Psychological Outcomes

There was no significant difference in depression in the GLP-1 RA group compared to placebo, with an overall logRR of 0.02 (95% CI, -1.54 to 1.58). Similarly, no significant effect was observed in T2D trials (logRR, 0.27; 95% CI, -2.13 to 2.67) or obesity trials (logRR, -0.16; 95% CI, -2.20 to 1.89).

Only 5 of 18 trials mentioned the use of the C-SSRS at baseline and follow-up; it remains unclear if C-SSRS was used in other trials. GLP-1 RAs were associated with a trend toward a decreased rate of suicidal ideation or behaviors, with an overall logRR of -0.46 (95% CI, -1.42 to 0.49), although this was not statistically significant. Similar trends were observed in T2D trials (logRR, -0.62; 95% CI, -2.07 to 0.82) and obesity trials (logRR, -0.34; 95% CI, -1.62 to

0.94), but neither reached statistical significance (Figure 4; eFigure 7 in Supplement 1).

Hypoglycemia

GLP-1 RA therapy showed a trend toward increased rates of hypoglycemia across 7 RCTs overall (logRR, 0.51; 95% CI, -0.07 to 1.08), but the effect was not statistically significant. The risk of hypoglycemia showed a higher trend but remained nonsignificant in the GLP-1 RA group vs placebo in T2D trials (logRR, 0.40; 95% CI, -0.71 to 1.51) and obesity trials (logRR, 0.51; 95% CI, -0.07 to 1.08) (Figure 4; eFigure 7 in Supplement 1). Diene and colleagues³⁷ and Tamborlane and colleagues³⁸ reported 1 serious hypoglycemia adverse event each, 1 in the treatment group (due to age) and placebo group, respectively.

Treatment Discontinuation Due to Adverse Events

Discontinuation due to adverse events showed a trend toward an increased rate overall (logRR, 0.39; 95% CI, -0.37 to 1.14) across 7 RCTs, although this was not statistically significant. No notable effect was observed in T2D trials (logRR, -0.01; 95% CI, -1.13 to 1.10); however, obesity trials showed a nonsignificant increasing trend (logRR, 0.93; 95% CI, -0.38 to 1.14) (Figure 4; eFigure 7 in Supplement 1).

Leave-One-Out Sensitivity Analysis

We performed a leave-one-out sensitivity analysis by excluding the Roth and colleagues⁴⁸ trial, as it included a small proportion of patients aged between 18 and 25 years.⁴⁸ The results for the efficacy outcomes of HbA_{1c}, FPG, BMI, and BMI-SDS remained consistent with the main analysis, with significant reductions in the GLP-1 RA group compared to placebo (eFigure 9 in Supplement 1).

Discussion

This extensive meta-analysis of 18 clinical trials evaluating the use of GLP-1 RAs in the pediatric population with diabetes or obesity offers a thorough synthesis of the benefits and risks associated with GLP-1 RAs in this underresearched group and may contribute to informed clinical decision-making.

This meta-analysis found that GLP-1 RAs significantly reduced HbA_{1c} and FPG overall and in T2D trials, with smaller, nonsignificant effects in obesity trials. These findings are consistent with existing findings from limited reviews in this population, as well as findings from the adult population.^{21,52} Additionally, reduction in weight-related parameters, such as BMI, body weight, waist circumference, BMI percentile, and BMI-SDS, was observed overall, but was significant only in the obesity trials. This was consistent with the GLP-1 RA meta-analysis performed by Wong and colleagues⁵³ in the adult population, which demonstrated greater reduction in patients without diabetes than in patients with diabetes. Overall, the lipid profile demonstrated nonsignificant increases by less than 0.1 ETR, which suggests limited clinical significance. The results were consistent with Rivera and colleagues' meta-analysis⁵⁴ comparing lipid profiles between the GLP-1 RA group and the placebo group in adults. The signifi-

cant reduction in SBP and nonsignificant reduction in DBP across populations was similar to existing reviews in children and adults.^{22,55}

We also observed a reducing trend in OSA in the GLP-1 RA group with obesity. Although this difference was not significant, possibly because of different doses, fewer trials, or heterogeneity among trials, the lowering trend warrants further research in this population. This could be of particular interest, as some studies in adults have shown benefits for OSA, leading to the first approval of GLP-1 RAs for OSA by the US FDA in December 2024.^{20,56}

The risk of gastrointestinal adverse events remained significantly elevated in the GLP-1 RA group compared to placebo; this could be attributed to the mechanism of action of GLP-1 RAs, and the findings were consistent with existing literature.²¹ There was a nonsignificant increase in the rate of treatment discontinuation due to adverse events in the GLP-1 RA group. Hypoglycemia events showed an elevated nonsignificant risk.

It is noteworthy that FDA guidance for industry requires trials to document any suicide-related behaviors using C-SSRS at baseline, during the trial, and at follow-up.²⁶ However, only 5 of 18 trials document using this in publicly available publications or on ClinicalTrials.gov.^{36,37,39,46,50} In the trials that assessed and published this safety outcome, the risk of suicide ideation or behaviors was not significantly different between the 2 groups. This is important given the growing concerns about the use of GLP-1 RAs and suicidal behaviors and the limited knowledge of this outcome in the pediatric population.^{12,13} However, continued surveillance is warranted through RCTs and real-world evidence. There was no significant difference in the risk of depression between the 2 groups. The nonsignificant findings of suicide ideation or behaviors and depression were consistent with a meta-analysis of GLP-1 RA use in adults by Tang and colleagues.⁵⁷⁻⁵⁹

To the best of our knowledge, this is the first meta-analysis capturing 18 trials in the pediatric population assessing GLP-1 RAs and assessing 23 outcomes—specifically, the risks of suicidal behaviors and depression—and exploring OSA and MASH/MASLD across available RCT data in this population.

Limitations

This meta-analysis also has limitations. First, outcomes like suicidal ideation or behaviors, depression, and MASLD/MASH were not primary outcomes in the included trials, possibly leading to underreporting, unclear classifications, or low precision. Second, we used aggregated data rather than individual participant data, limiting subgroup analysis (eg, by comedications) and confounding control. Third, variations in study design, populations, and outcome definitions may have introduced heterogeneity. Additionally, some data were extracted from ClinicalTrials.gov due to the lack of reported outcomes in published literature, potentially resulting in incomplete outcome capture. Some adverse events planned for extraction (eg, eating disorders) could not be extracted due to limited reporting. BMI-related efficacy by lifestyle intervention could not be assessed, as most trials reported concomitant lifestyle interventions at baseline or during the trial. Lastly, the variability in reporting

of adherence and adverse events limited stratification by severity or evaluation of adherence effects. These factors may affect the robustness and generalizability of our findings.

Conclusions

In conclusion, this systematic review and meta-analysis provides a comprehensive evaluation of the benefits and risks associated with GLP-1 RAs in the pediatric population, enabling

patients, caregivers, and clinicians to make more informed treatment decisions. However, to build on these findings, future clinical trials and real-world studies could assess treatment adherence with respect to patient preferences (eg, problems with self-management related to injectables or cost) and their effect on safety (severity of gastrointestinal and other adverse events) and efficacy/effectiveness outcomes. Moreover, longer follow-up from future RCTs and real-world studies is essential to establish the long-term effects of GLP-1 RAs in children and adolescents.

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