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Research Article

Efficacy of Glucagon-like Peptide-1 Receptor Agonists in Overweight/Obese and/or T2DM Adolescents: A Meta-analysis Based on Randomized Controlled Trials

Dai M et al. GLP-1RAs and Adolescents

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What is already known about this topic?

In adolescents, previous meta-analyses of GLP-1RAs in patients with T2DM and obesity have demonstrated that GLP-1RAs were beneficial for glycemic control and weight loss. However, only nine RCTs were included. Meanwhile, limited sample size prevented further subgroup analyses.

What this study adds to the literature?

This study expanded the sample size included. Meanwhile, our study confirms that GLP-1RAs reduced HbA1c, FPG, and weight loss in overweight/obese and/or T2DM adolescents. The GLP-1RAs have a no significant effect on lower blood sugar in adolescents with simple obesity. Based on subgroup, liraglutide is better than exenatide in terms of glucose reduction. Nevertheless, in terms of weight control, exenatide is better than liraglutide.

Abstract

Objective: This meta-analysis aimed to investigate the effect of glucagon-like peptide-1 receptor agonists (GLP-1RAs) on blood glucose and weight in overweight/obese and/or type 2 diabetes mellitus (T2DM) adolescents aged <18 years.

Methods: Herein, we searched PubMed, Embase, Web of Science, and Cochrane Library for all randomized controlled trials (RCTs) comparing GLP-1RAs with placebo in overweight/obese and/or T2DM adolescents and extracted relevant data up to August 2023 for meta-analysis.

Results: Fourteen RCTs were included in the meta-analysis with a total of 1262 participants. Results revealed that the GLP-1RAs group had a more significant reduction in glycosylated hemoglobin A1c (HbA1c; risk difference (RD)=–0.34%, P<0.001) than the control group. However, there was no difference in fasting blood glucose (FPG; RD=–2.07mg/dL, P=0.065) between the two groups. Nonetheless, the experimental group that administered exenatide showed a no significant reduction in HbA1c (P=0.253) and FPG (P=0.611) between the two groups. The GLP-1RAs group had a more significant decline in body weight (RD=–4.28kg, P=0.002) and BMI (RD=–1.63kg/m2, P=0.002) compared to the control group. The experimental group was adopted with liraglutide (RD=–2.31kg, P=0.038) or exenatide (RD=–2.70kg, P<0.001). Compared to the control group, the experimental group had a more significant drop in body weight than the control group. But for the experimental group that received liraglutide, the BMI had a no significant reduction between the two groups (RD=–0.81kg/m2, P=0.260). For the experimental group that was adopted with exenatide, BMI revealed a more significant decline in the intervention group than in the control group (RD=–1.14kg/m2, P<0.001).

Conclusion: This study showed that GLP-1RAs reduced HbA1c, FPG, and weight loss in overweight/obese and/or T2DM adolescents. Liraglutide is better than exenatide in terms of glucose reduction. Nevertheless, in terms of weight control, exenatide is better than liraglutide.

Keywords: glucagon-like peptide-1 receptor agonists; overweight; obesity; type 2 diabetes; HbA1c; weight loss; FPG

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Introduction

Obesity has always been a global public health problem. More than two billion people worldwide suffer from obesity, and the number continues to increase [1]. The global obese adolescent population was estimated to exceed 100 million [2]. Adolescent obesity has always tracked obesity in adulthood and has been related to many chronic diseases, including type 2 diabetes mellitus (T2DM), cardiovascular disease, and cancer [3]. Unfortunately, most treatments for childhood obesity are based only on prevention and lifestyle interventions. Until 2020, the European Medicines Agency (EMA) had not approved any pharmacological treatments for treating obesity in pediatric patients. In January 2021, the EMA authorized the use of a glucagon-like peptide (GLP)-1 analog liraglutide for treating adolescent (12–17 years) obesity [4]. Morbidly obese adolescents could consider bariatric surgery, but both surgical complications and safety limited the promotion of surgery in adolescents [5].

The T2DM prevalence was low in adolescents, but as obesity increased, T2DM became increasingly prevalent in adolescents [2]. The T2DM in adolescence is manifested by severe progressive diabetes mellitus with frequent complications, such as diabetic retinopathy, cardiovascular disease, and nephropathy [6, 7]. Common clinical drugs used to treat T2DM include: metformin, insulin and Sodium-glucose cotransporter-2 (SGLT-2) inhibitors. Although insulin is used to treat diabetes, insulin resistance is often present in obese adolescents; therefore, its efficacy is limited [8].

As mentioned earlier, liraglutide is a glucagon-like peptide-1 receptor agonists (GLP-1RAs) recently approved for T2DM treatment in adolescents aged ten years and older [9]. The GLP-1RAs stimulated postprandial insulin secretion, reduced glucagon secretion, delayed gastric emptying, and reduced appetite, thereby improving blood glucose control [10]. In adolescents, previous meta-analyses of GLP-1RAs in patients with T2DM and obesity have demonstrated that GLP-1RAs were beneficial for glycemic control and weight loss [11, 12]. However, only nine randomized controlled trials (RCTs) were included because of the limited RCT number. Therefore, conducting further subgroup analyses to explore the effect of therapeutic regimen, treatment duration, and subject participants on the efficacy of GLP-1RAs was unfeasible. Recently, as more pertinent RCTs have been reported, this meta-analysis must be updated. This meta-analysis aimed to investigate the effectiveness of GLP-1RAs in managing overweight/obese and/or T2DM in adolescents under 18, along with exploring the factors influencing efficacy.

Methods

Search strategy

This meta-analysis design and reporting followed the PRISMA 2020 updated guidelines [13] and was registered in PROSPERO 2023 (CRD42023467678). Our study aimed to investigate the effects of GLP-1RAs on blood glucose and weight in adolescents with overweight/obese and/or T2DM.

From establishing the library to August 2023, two researchers independently searched four databases, including PubMed, Web of Science, Embase, and Cochrane Library. The search terms were as follows: glucagon-like peptide-1 receptor agonist OR exenatide OR liraglutide OR dulaglutide OR lixisenatide OR semaglutide OR albiglutide OR taspoglutide OR loxenatide) AND (Children OR Adolescents OR Teens OR Teenagers OR Youths OR Adolescents, Female OR Adolescents, male. Moreover, reference lists in all retrieved articles were

searched. The primary outcomes of the included articles involved glycosylated hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), and body weight. Filter articles according to PICOS principles. When a dissenting opinion is encountered, a third person will be recruited.

Inclusion and exclusion criteria

The included studies were based on the following PICOS principle: 1) overweight/obese and/or T2DM in adolescents aged <18 years; 2) the intervention group received GLP-1RAs; 3) the control group received placebo; 4) the primary outcomes were HbA1c, FPG, and body weight; 5) RCT studies.

The exclusion criteria were as follows: 1) uncomplete available text; 2) participants included adults; 3) non-English articles; 4) unextracted data; 5) updated RCTs. When updating published articles for the same study cohort, the most recent or largest population studies were selected.

Data extraction and quality assessment

Two researchers extracted the data separately using pre-designed forms. Extracted data included: 1) the authors, publication year, country, and registration number of the study; 2) subject participants, such as comorbidity, mean body mass index (BMI), age; 3) recruitment time, therapeutic regimen, treatment duration, sample sizes for experimental and control groups; 4) outcomes, HbA1c, FPG, and body weight. Following Cochrane guidelines, RCTs were assessed by two review authors. The labels "high risk," "low risk," and "unclear risk" were used to describe several bias types, including random serial generation, allocation concealment, blinding of participants and staff, blinding of outcome assessment, insufficient outcome data, and selective reporting, among others. In the case of a disagreement, the two researchers solved the problem through discussion. When necessary, a third person would be enlisted.

Statistical analysis

This meta-analysis was explored using Stata Software 12.0 (Stata Corporation, College Station, TX, United States) and Review Manager 5.3 (RevMan version 5.3; Oxford, UK). The definition of Risk difference (RD) is actually the mean difference. RD and 95% confidence intervals (CI) were used to assess the association of GLP-1RAs with HbA1c, FPG, and body weight. Heterogeneity between studies was assessed by the chi-square test with an inconsistency index (I^2): $I^2 < 25\%$ indicated low heterogeneity; $I^2 = 25\%–50\%$ indicated moderate heterogeneity; $I^2 > 50\%$ indicated significant heterogeneity [14]. Due to potential heterogeneity in the participant population and experimental design, this study was analyzed using a unified random-effects model to increase our result credibility. All tests were two-sided; $p < 0.05$ was considered a significant value [15].

Results

Description of the studies

In accordance with the search criteria, 3120 records from four databases were thoroughly examined, and no more studies could be located in other sources. A number of 2235 records were kept after duplicate articles were removed, while 2111 irrelevant articles were removed by investigating article titles and abstracts. Through reading the complete papers, we eliminated 110 studies, of which 45 were not RCTs, 42 included adults, 10 had no reported outcomes of interest, 5 were not in English, 5 were updated articles, and 3 were inaccessible data. Eventually, fourteen RCTs were included in the meta-analysis (**Fig. 1**) [16-29].

The 14 RCTs were selected to research GLP-1RAs in adolescents who were overweight/obese and/or T2DM. In these studies, most participants were aged 12–18, with an average BMI greater than 30. All studies were in Western countries or predominantly Western multicenter studies with a treatment duration of 5–68 weeks. Six studies adopted liraglutide, five adopted exenatide, two adopted semaglutide, and one adopted dulaglutide. All participants included obesity, T2DM, and overweight combined with T2DM. In total, 754 adolescents were allocated to GLP-1RAs therapy, and 508 were treated with the placebo. Patients with T2DM have previously received metformin, insulin, or exercise therapy. Most trials combined lifestyle, diet, and exercise interventions. **Table 1** and **Supplementary Table 1** contain a list of the characteristics of the analyzed studies in this meta-analysis.

Quality evaluation

Figs. S1–2 depict the included studies assessments. Herein, we used the Cochrane Collaboration method to assess each RCT quality. All included studies were assessed as low risk regarding random sequence generation and allocation concealment. Most studies were rated as low risk in blinding of participants and personnel and selective reporting, whereas a small number were rated as unclear. Most studies

were classified as low risk, while only a small number were evaluated as high risk, and a few were at unknown risk concerning blinding of outcome assessment and incomplete outcome data. For other biases, the included studies were assessed as being at unclear risk.

Result analysis

Fig. 2 summarizes the effects of GLP-1RAs on HbA1c and FPG in the whole population. Nine studies reported HbA1c results, revealing that participants in the GLP-1RAs group had a more significant reduction in HbA1c compared to the control group (RD=–0.34%, P<0.001, 95%Cl=[–0.51, –0.18]; **Fig. 2a**). However, the heterogeneity was 91.2%. Ten studies reported FPG findings, indicating that FPG had a greater decrease in the intervention group than in the control group (RD=–2.07mg/dL, 95%Cl=[–4.28, 0.13]), but the difference was no significant (P=0.065; **Fig. 2b**). The heterogeneity was 57.7%.

For HbA1c, subgroup analysis was performed by participant type, showing that HbA1c exhibited no significant reduction between the two groups for obese participants (non-T2DM) (P=0.087; **Fig. 3a**). Notably, for T2DM patients, HbA1c showed a more significant decrease in the intervention group than in the control group (RD=–1.10%, P<0.001, 95%Cl=[–1.38, –0.83]; **Fig. 3b**). Further subgroup analysis was conducted in terms of HbA1c in the whole population (**Table 2-1**). For the study of the participant number in the experimental group < 50, HbA1c revealed a no significant decrease between the two groups (P=0.079). For the study of the participant number in the experimental group ≥ 50, the GLP-1RAs group had a more significant reduction than the control group (RD=–0.55%, P<0.001). For the experimental group that was adopted with liraglutide, HbA1c indicated a more significant decline in the intervention group than the control group (RD=–0.47%, P=0.011). However, for the experimental group that was adopted with exenatide, HbA1c showed a no significant reduction between the two groups (P=0.253). For treatment duration, both < 52 (RD=–0.66%, P<0.001) and ≥ 52 weeks (RD=–0.23%, P=0.034), the experimental group had a more significant decrease than the control group in HbA1c.

The FPG was analyzed in subgroups, indicating that for adolescents with obesity, no significant differences were found in FPG reduction between the two groups (P=0.119) (**Fig. 4a**). For T2DM adolescents, FPG level exhibited a greater decrease in the intervention group than in the control group (RD=–19.48mg/dL, 95%Cl=[–41.20, 2.24]), but the difference did not reach statistical significance (P=0.079; **Fig. 4b**). Further subgroup analysis was performed in terms of FPG in the whole population (**Table 2-1**). For the study of participant number in the experimental group, both < 50 (P=0.421) and ≥ 50 (P=0.070), FPG levels had a no significant reduction between the two groups. For the experimental group that was adopted with liraglutide, FPG represented a more significant decline in the intervention group than the control group (RD=–1.91mg/dL, P=0.001). For the experimental group that was adopted with exenatide, there was a no statistically significant reduction in FPG between the two groups (P=0.611). For treatment duration, both < 52 (RD=3.51mg/dL, P=0.056) and ≥ 52 weeks (RD=–1.52mg/dL, P=0.007), FPG had a more significant decrease in the intervention group than in the control group, but the former difference was not statistically significant.

Fig. 5 summarizes the effects of GLP-1RAs on body weight and BMI in the whole population. Nine studies reported results for body weight. Participants in the GLP-1RAs group had a more significant decline in body weight compared to the control group (RD=–4.28kg, P=0.002, 95%Cl=[–6.95, –1.60]; **Fig. 5a**). Eight studies reported BMI, and BMI was a more significant decrease in the intervention group treated with GLP-1RAs compared with controls (RD=–1.63kg/m^2, P=0.002, 95%Cl=[–2.68, –0.57]; **Fig. 5b**).

Table 2-2 lists further subgroup analyses of body weight and BMI. For the study of the participant number in the experimental group < 50 (RD=–2.64kg, P<0.001) and ≥ 50 (RD=–7.64kg, P=0.070), body weight had a more significant decrease in the intervention group than in the control group, but the latter difference was no significant. The experimental group was adopted with liraglutide (RD=–2.31kg, P=0.038) or exenatide (RD=–2.70kg, P<0.001). The experimental group had a more significant drop in body weight than the control group. For treatment duration < 52 (RD=–2.09kg, P<0.001) and ≥ 52 weeks (RD=–8.86kg, P=0.045), the experimental group had a more significant decrease in body weight than the control group.

For the study of the participant number in the experimental group < 50, the BMI decline in the experimental group was more significant than in the control group (RD=–0.88kg/m^2, P=0.015). For the study of participant number in the experimental group ≥ 50, BMI had a no significant reduction between the two groups (P=0.089). For the experimental group that was adopted with liraglutide, BMI showed a no significant reduction between the two groups (P=0.260). For the experimental group that was adopted with exenatide, BMI revealed a more significant decline in the intervention group than in the control group (RD=–1.14kg/m^2, P<0.001). For treatment durations, both < 52 (RD=–0.56kg/m^2, P=0.034) and ≥ 52 weeks (RD=–2.79kg/m^2, P=0.039), BMI exhibited a more significant decrease in the intervention group than in the control group. Furthermore, this study was further analyzed from a BMI perspective (%) (**Table 2-2**).

Subgroup analysis was performed for participants with obesity regarding body weight (kg) and BMI (kg/m^2 and %). Body weight was a more significant decrease in the intervention group than in the control group (RD=–4.72kg, P=0.002; **Fig. 6a**). The BMI was a more significant drop in magnitude in the experimental group than in the control group (RD=–1.93kg/m^2, P=0.003; RD=–7.31%, P=0.004; **Figs. 6b–c**).

Discussion

This study indicated that GLP-1RAs, compared to placebo, decrease HbA1c, FPG, and body weight in adolescents with overweight/obese and/or T2DM. Remarkably, GLP-1RAs had a no significant effect on HbA1c and FPG in adolescents with obesity (non-T2DM). In T2DM, our study manifested that liraglutide was more effective in adolescents than exenatide in lowering HbA1c and FPG. In contrast, exenatide was more effective than liraglutide in weight control. With the treatment prolongation, the efficacy of GLP-1RAs on glucose control decreased; conversely, weight control was more effective. Moreover, Daniel *et al*. demonstrated that in obese adolescents, semaglutide plus lifestyle intervention treatment resulted in a more significant reduction in BMI than lifestyle intervention alone [17]. William *et al.* showed that liraglutide effectively improves blood sugar in T2DM adolescents [19]. These results are consistent with our study.

The GLP-1RAs mainly reduce glucose through the following aspects: (1) GLP-1RAs can stimulate insulin secretion to lower blood sugar [30]. The GLP-1RAs increase intracellular Ca^{2+} concentration through ligand-gated calcium channels or voltage-dependent Ca^{2+} channels on the endoplasmic reticulum (ER), enhancing insulin secretion [31, 32]. Notably, GLP-1RAs only increase insulin release in cases of hyperglycemia; accordingly, it does not cause hypoglycemia [33], which is confirmed again in our study. In obesity (non-T2DM), GLP-1RAs did not significantly decrease blood glucose. Studies have suggested that GLP-1RAs induce an increase in β-cell mass through enhanced cellular regeneration and apoptosis inhibition [34, 35]. (2) GLP-1RAs can inhibit glucagon secretion in a glucose concentration-dependent manner, lowering blood sugar. Some studies have reported the possibility that GLP-1R directly mediates α cell inhibition to suppress glucagon secretion [36]. The GLP-1R can also indirectly inhibit glucagon by directly stimulating the increased somatostatin secretion [37, 38]. (3) GLP-1RAs promote glycogen synthesis in liver cells, lowering blood glucose concentrations [39]. (4) GLP-1RAs balance food intake by activating multiple nuclei of the hindbrain and hypothalamus (periventricular nuclei, posterior brain area, and nucleus tractus solitarius). Moreover, GLP-1RAs activated brain regions of the mid-limbic system to inhibit reward behavior and palatability. The combined effect of GLP-1RAs on homeostasis and hedonic eating may contribute to their appetite suppression [40]. (5) GLP-1RAs could also delay gastric emptying and peristalsis of the gastrointestinal tract and reduce gastric acid secretion stimulated by pentapeptide gastrin [41].

Our study indicated that liraglutide was more effective in adolescents than exenatide regarding sugar control. In LEAD-6, liraglutide lowers more HbA1c than exenatide [42]. The probable cause is that exenatide has a short half-life and a higher plasma concentration within 4–8 h after a single subcutaneous injection [43]. However, approximately 99% of the liraglutide molecules are typically bound to plasma albumin, and the bound molecule has a half-life of 11–13 h [41]. Therefore, the liraglutide drug concentration in plasma has been high, and the hypoglycemic effect is better. Our research demonstrated that the degree of glucose reduction declines with prolonged treatment duration. The probable cause is that blood sugar does not drop continuously. Only in cases of hyperglycemia do GLP-1RAs raise insulin release to reduce blood sugar. When blood sugar drops to the normal range, the ability of GLP-1Ra to lower blood sugar only plays a role in maintaining blood sugar concentration [44].

Our research illustrates that GLP-1RAs can lower weight in adolescents compared to a placebo. The weight loss mechanism is as follows: (1) As mentioned earlier, GLP-1RAs promote weight loss by reducing food intake and prolonging gastric emptying [40, 41]. (2) GLP-1RAs activate brown fat and increase rodent energy expenditure independently of locomotor activity through sympathetic nervous system (SNS) pathways. (3) GLP-1RAs also reduce peripheral lipid storage in white adipocytes in mice by a mechanism that relies on SNS activation [45]. (4) In mice and monkeys, GLP-1RAs target pathways that reduce body weight and improve many metabolic parameters by producing GLP-1 bispecific molecules [46]. (5) Studies have demonstrated that obese teenagers can lose weight through these mechanisms, as well as increased fat and reduced carbohydrate oxidation [47]. Our study indicated that exenatide was more effective than liraglutide in weight loss. One reason is that exenatide and lowering glucose have been shown to improve lipid homeostasis, reduce body weight, improve insulin resistance, and reduce hepatic steatosis [48, 49]. Another aspect is that exenatide treats obesity by regulating CTRP3 and PPAR-γ gene expression, which are related to lipogenesis [50]. Nevertheless, the meta-analysis

conducted by Paul M. et al. has indicated that a no significant difference exists between liraglutide and exenatide in adolescent weight loss [12]. This may be due to their inclusion of a limited number of RCTs. Our research revealed that GLP-1RAs are more effective in reducing body weight with prolonged treatment. This may be because GLP-1 produces anorexia effects on the mediation of the brainstem and hypothalamic nucleus [43]. The severity of anorexia increases with therapy duration, resulting in greater weight loss.

This meta-analysis is an updated study of published RCTs on the effectiveness of GLP-1RAs in treating overweight/obese and/or T2DM adolescents. Our study once again confirms the effectiveness of GLP agonists in lowering glucose and weight in adolescents. In addition, we explored the different effects of exenatide and liraglutide on hypoglycemic and weight reduction in adolescents. Additionally, we found that prolonged treatment may affect the efficacy of controlling glucose and weight. However, our study also has some limitations. First, our study included multiple GLP-1RAs, but subgroup analyses of all drugs were impossible because of limited data. Second, a few subgroup analyses of the included studies affected credibility to some extent. Third, because there were some differences in the included studies, the heterogeneity of the final analysis was higher, which reduced credibility. Therefore, a random-effects model was used for analysis. Fourth, the included studies were all multicenter studies in Western countries; consequently, the results could not be directly generalized to other countries.

Conclusion

This study confirms that GLP-1RAs reduced HbA1c, FPG, and weight loss in adolescents with overweight/obesity and/or T2DM. GLP-1RAs had no significant effect on blood glucose reduction in obese adolescents. For adolescents with T2DM, liraglutide is superior to exenatide in lowering glucose. However, when it comes to weight control, exenatide is preferred over liraglutide. When the duration of treatment is prolonged, the magnitude of the drop in blood glucose tends to stabilize and weight loss continues.

Abbreviations

GLP-1RAs: glucagon-like peptide-1 receptor agonists; T2DM: type 2 diabetes mellitus; RCTs: randomized controlled trials; HbA1c: glycosylated hemoglobin A1c; RD: risk difference; FPG: fasting plasma glucose; EMA: European Medicines Agency; GLP: glucagon-like peptide; BMI: body mass index; CI: confidence intervals; ER: endoplasmic reticulum; SNS: sympathetic nervous system; NA: not available.

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Disclosures

Ethics approval and consent to participate

Not applicable (this paper was provided based on research in global databases).

Consent to publish

Not applicable.

Availability of data and materials

The datasets supporting the conclusions of this article are included within the article. Please contact the corresponding author for any required detailed data about this article.

Competing interests

The authors declare no conflict of interest.

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Authors' contributions

Reference

1. Caballero, B. Humans against Obesity: Who Will Win? Advances in nutrition (Bethesda, Md.) 10, S4-s9 (2019).DOI:10.1093/advances/nmy055

2. Marcus, C., Danielsson, P. & Hagman, E. Pediatric obesity-Long-term consequences and effect of weight loss. Journal of internal medicine 292, 870-891 (2022).DOI:10.1111/joim.13547

3. Lee, E.Y. & Yoon, K.H. Epidemic obesity in children and adolescents: risk factors and prevention. Frontiers of medicine 12, 658-666 (2018).DOI:10.1007/s11684-018-0640-1

4. Nicolucci, A. & Maffeis, C. The adolescent with obesity: what perspectives for treatment? Italian journal of pediatrics 48, 9 (2022).DOI:10.1186/s13052-022-01205-w

5. Dabas, A. & Seth, A. Prevention and Management of Childhood Obesity. Indian journal of pediatrics 85, 546-553 (2018).DOI:10.1007/s12098-018-2636-x

6. Amutha, A. & Mohan, V. Diabetes complications in childhood and adolescent onset type 2 diabetes-a review. Journal of diabetes and its complications 30, 951-957 (2016).DOI:10.1016/j.jdiacomp.2016.02.009

7. Viner, R., White, B. & Christie, D. Type 2 diabetes in adolescents: a severe phenotype posing major clinical challenges and public health burden. Lancet (London, England) 389, 2252-2260 (2017).DOI:10.1016/s0140-6736(17)31371-5

8. Thota, P., Perez-Lopez, F.R., Benites-Zapata, V.A., Pasupuleti, V. & Hernandez, A.V. Obesity-related insulin resistance in adolescents: a systematic review and meta-analysis of observational studies. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 33, 179-184 (2017).DOI:10.1080/09513590.2016.1273897

9. Singhal, S. & Kumar, S. Current Perspectives on Management of Type 2 Diabetes in Youth. Children (Basel, Switzerland) 8 (2021).DOI:10.3390/children8010037

10. Zhao, X. et al. GLP-1 Receptor Agonists: Beyond Their Pancreatic Effects. Frontiers in endocrinology 12, 721135 (2021).DOI:10.3389/fendo.2021.721135

11. Chadda, K.R., Cheng, T.S. & Ong, K.K. GLP-1 agonists for obesity and type 2 diabetes in children: Systematic review and meta-analysis. Obesity reviews : an official journal of the International Association for the Study of Obesity 22, e13177 (2021).DOI:10.1111/obr.13177

12. Ryan, P.M. et al. Safety and Efficacy of Glucagon-Like Peptide-1 Receptor Agonists in Children and Adolescents with Obesity: A Meta-Analysis. The Journal of pediatrics 236, 137-147.e113 (2021).DOI:10.1016/j.jpeds.2021.05.009

13. Dickson, K. & Yeung, C.A. PRISMA 2020 updated guideline. British dental journal 232, 760-761 (2022).DOI:10.1038/s41415-022-4359-7

14. Melsen, W.G., Bootsma, M.C., Rovers, M.M. & Bonten, M.J. The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 20, 123-129 (2014).DOI:10.1111/1469-0691.12494

15. Lin, L. et al. Empirical Comparison of Publication Bias Tests in Meta-Analysis. Journal of general internal medicine 33, 1260-1267 (2018).DOI:10.1007/s11606-018-4425-7

16. Weghuber, D. et al. A 6-month randomized, double-blind, placebo-controlled trial of weekly exenatide in adolescents with obesity. Pediatric obesity 15, e12624 (2020).DOI:10.1111/ijpo.12624

17. Weghuber, D. et al. Once-Weekly Semaglutide in Adolescents with Obesity. The New England journal of medicine 387, 2245-2257 (2022).DOI:10.1056/NEJMoa2208601

18. Tamborlane, W.V. et al. Once-Weekly Exenatide in Youth With Type 2 Diabetes. Diabetes care 45, 1833-1840 (2022).DOI:10.2337/dc21-2275

19. Tamborlane, W.V. et al. Liraglutide in Children and Adolescents with Type 2 Diabetes. The New England journal of medicine 381, 637-646 (2019).DOI:10.1056/NEJMoa1903822

20. Mastrandrea, L.D. 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. Pediatric obesity 14, e12495 (2019).DOI:10.1111/ijpo.12495

21. Klein, D.J. et al. Liraglutide's safety, tolerability, pharmacokinetics, and pharmacodynamics in pediatric type 2 diabetes: a randomized, double-blind, placebo-controlled trial. Diabetes technology & therapeutics 16, 679-687 (2014).DOI:10.1089/dia.2013.0366

22. Kelly, A.S. 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 pediatrics 167, 355-360 (2013).DOI:10.1001/jamapediatrics.2013.1045

23. Kelly, A.S. et al. Exenatide as a weight-loss therapy in extreme pediatric obesity: a randomized, controlled pilot study. Obesity (Silver Spring, Md.) 20, 364-370 (2012).DOI:10.1038/oby.2011.337

24. Kelly, A.S. et al. A Randomized, Controlled Trial of Liraglutide for Adolescents with Obesity. The New England journal of medicine 382, 2117-2128 (2020).DOI:10.1056/NEJMoa1916038

25. Kelly, A.S. et al. Reducing BMI below the obesity threshold in adolescents treated with once-weekly subcutaneous semaglutide 2.4 mg. Obesity (Silver Spring, Md.) 31, 2139-2149 (2023).DOI:10.1002/oby.23808

26. Fox, C.K. et al. Exenatide for weight-loss maintenance in adolescents with severe obesity: A randomized, placebo-controlled trial. Obesity (Silver Spring, Md.) 30, 1105-1115 (2022).DOI:10.1002/oby.23395

27. Diene, G. et al. Liraglutide for Weight Management in Children and Adolescents With Prader-Willi Syndrome and Obesity. The Journal of clinical endocrinology and metabolism 108, 4-12 (2022).DOI:10.1210/clinem/dgac549

28. 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. The Journal of pediatrics 181, 146-153.e143 (2017).DOI:10.1016/j.jpeds.2016.10.076

29. Arslanian, S.A. et al. Once-Weekly Dulaglutide for the Treatment of Youths with Type 2 Diabetes. The New England journal of medicine 387, 433-443 (2022).DOI:10.1056/NEJMoa2204601

30. Meier, J.J. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. Nature reviews. Endocrinology 8, 728-742 (2012).DOI:10.1038/nrendo.2012.140

31. Lu, M., Wheeler, M.B., Leng, X.H. & Boyd, A.E., 3rd The role of the free cytosolic calcium level in beta-cell signal transduction by gastric inhibitory polypeptide and glucagon-like peptide I(7-37). Endocrinology 132, 94-100 (1993).DOI:10.1210/endo.132.1.8380389

32. Holz, G.G.t., Leech, C.A. & Habener, J.F. Activation of a cAMP-regulated Ca(2+)-signaling pathway in pancreatic beta-cells by the insulinotropic hormone glucagon-like peptide-1. The Journal of biological chemistry 270, 17749-17757 (1995).

33. Nauck, M.A. et al. Effects of glucagon-like peptide 1 on counterregulatory hormone responses, cognitive functions, and insulin secretion during hyperinsulinemic, stepped hypoglycemic clamp experiments in healthy volunteers. The Journal of clinical endocrinology and metabolism 87, 1239-1246 (2002).DOI:10.1210/jcem.87.3.8355

34. Buteau, J., Roduit, R., Susini, S. & Prentki, M. Glucagon-like peptide-1 promotes DNA synthesis, activates phosphatidylinositol 3-kinase and increases transcription factor pancreatic and duodenal homeobox gene 1 (PDX-1) DNA binding activity in beta (INS-1)-cells. Diabetologia 42, 856-864 (1999).DOI:10.1007/s001250051238

35. Farilla, L. et al. Glucagon-like peptide 1 inhibits cell apoptosis and improves glucose responsiveness of freshly isolated human islets. Endocrinology 144, 5149-5158 (2003).DOI:10.1210/en.2003-0323

36. Richards, P. et al. Identification and characterization of GLP-1 receptor-expressing cells using a new transgenic mouse model. Diabetes 63, 1224-1233 (2014).DOI:10.2337/db13-1440

37. de Heer, J., Rasmussen, C., Coy, D.H. & Holst, J.J. Glucagon-like peptide-1, but not glucose-dependent insulinotropic peptide, inhibits glucagon secretion via somatostatin (receptor subtype 2) in the perfused rat pancreas. Diabetologia 51, 2263-2270 (2008).DOI:10.1007/s00125-008-1149-y

38. Waser, B., Blank, A., Karamitopoulou, E., Perren, A. & Reubi, J.C. Glucagon-like-peptide-1 receptor expression in normal and diseased human thyroid and pancreas. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc 28, 391-402 (2015).DOI:10.1038/modpathol.2014.113

39. Valverde, I. et al. Glucagon-like peptide 1: a potent glycogenic hormone. FEBS letters 349, 313-316 (1994).DOI:10.1016/0014-5793(94)00699-7

40. Müller, T.D. et al. Glucagon-like peptide 1 (GLP-1). Molecular metabolism 30, 72-130 (2019).DOI:10.1016/j.molmet.2019.09.010

41. Isaacs, D., Prasad-Reddy, L. & Srivastava, S.B. Role of glucagon-like peptide 1 receptor agonists in management of obesity. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists 73, 1493-1507 (2016).DOI:10.2146/ajhp150990

42. Buse, J.B. et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet (London, England) 374, 39-47 (2009).DOI:10.1016/s0140-6736(09)60659-0

43. Nielsen, L.L., Young, A.A. & Parkes, D.G. Pharmacology of exenatide (synthetic exendin-4): a potential therapeutic for improved glycemic control of type 2 diabetes. Regulatory peptides 117, 77-88 (2004).DOI:10.1016/j.regpep.2003.10.028

44. Green, J.B. & Feinglos, M.N. Exenatide and rimonabant: new treatments that may be useful in the management of diabetes and obesity. Current diabetes reports 7, 369-375 (2007).DOI:10.1007/s11892-007-0060-0

45. Nogueiras, R. et al. Direct control of peripheral lipid deposition by CNS GLP-1 receptor signaling is mediated by the sympathetic nervous system and blunted in diet-induced obesity. The Journal of neuroscience : the official journal of the Society for Neuroscience 29, 5916-5925 (2009).DOI:10.1523/jneurosci.5977-08.2009

46. Lu, S.C. et al. GIPR antagonist antibodies conjugated to GLP-1 peptide are bispecific molecules that decrease weight in obese mice and monkeys. Cell reports. Medicine 2, 100263 (2021).DOI:10.1016/j.xcrm.2021.100263

47. van Can, J. et al. Effects of the once-daily GLP-1 analog liraglutide on gastric emptying, glycemic parameters, appetite and energy metabolism in obese, non-diabetic adults. International journal of obesity (2005) 38, 784-793 (2014).DOI:10.1038/ijo.2013.162

48. Ding, X., Saxena, N.K., Lin, S., Gupta, N.A. & Anania, F.A. Exendin-4, a glucagon-like protein-1 (GLP-1) receptor agonist, reverses hepatic steatosis in ob/ob mice. Hepatology (Baltimore, Md.) 43, 173-181 (2006).DOI:10.1002/hep.21006

49. Tushuizen, M.E. et al. Incretin mimetics as a novel therapeutic option for hepatic steatosis. Liver international : official journal of the International Association for the Study of the Liver 26, 1015-1017 (2006).DOI:10.1111/j.1478-3231.2006.01315.x

50. Koldemir Gündüz, M., Kaymak, G., Kanbur, E., Berikten, D. & Şener, H. Exenatide increases CTRP3 gene expression in adipose cells by inhibiting adipogenesis and induces apoptosis. Toxicology in vitro : an international journal published in association with BIBRA 85, 105479 (2022).DOI:10.1016/j.tiv.2022.105479

Table 1. Characteristics of all the studies included in the meta-analysis.

Author	Year	Participants	Mean age (years)	Experimental group (number)	Control group (number)	Intervention	Target dose	Treatment duration (weeks)
Weghuber	2022	Obesity	15.4	134	67	Semaglutide	2.4 mg weekly	68
Arslanian	2022	Overweight, T2DM	14.5	103	51	Dulaglutide	0.75 mg weekly, 1.50 mg weekly	26
Tamborlane	2022	T2DM	15	58	24	Exenatide	2.00 mg weekly	24
Diene	2022	Obesity	14.3	19	12	Liraglutide	3.00mg daily	16, 52
Fox	2022	Obesity	16	33	33	Exenatide	2.00 mg weekly	52
Kelly	2023	Obesity	15.4	133	67	Semaglutide	2.40 mg weekly	75
Mastrandrea	2019	Obesity	9.9	16	8	Liraglutide	3.00 mg weekly	8
Kelly	2012	Obesity	12.7	5	6	Exenatide	0.02 mg daily	13
Klein	2014	Overweight, T2DM	14.8	14	7	Liraglutide	1.80mg daily	5
Tamborlane	2019	Overweight, T2DM	14.6	66	68	Liraglutide	1.80 mg daily	26, 52
Danne	2017	Obesity	14.9	14	7	Liraglutide	3.00 mg daily	5
Kelly	2020	Obesity	14.5	125	126	Liraglutide	3.00 mg daily	56
Weghuber	2020	Obesity	14	22	22	Exenatide	2.00 mg weekly	24
Kelly	2013	Obesity	15.2	12	10	Exenatide	0.02 mg daily	13

T2DM, type 2 diabetes mellitus.

Table 2-1. Subgroup analysis of HbA1c and fasting plasma glucose.

	No. of studies	RD	95%CI	P	Heterogeneity I^2
HbA1c (%)					
Experimental group (number)<50	4	-0.17	-0.35, 0.02	0.079	80.4%
Experimental group (number)≥50	5	-0.55	-0.82, -0.29	<0.001	93.4%
Liraglutide	4	-0.47	-0.84, -0.11	0.011	89.5%
Exenatide	3	-0.11	-0.30, 0.08	0.253	73.5%
Treatment duration<52weeks	6	-0.66	-1.03, -0.29	<0.001	88.0%
Treatment duration ≥52weeks	4	-0.23	-0.44, -0.02	0.034	94.8%
Fasting plasma glucose (mg/dl)					
Experimental group (number)<50	6	-0.83	-2.86, 1.20	0.421	0.9%
Experimental group (number)≥50	4	-4.29	-8.93, 0.35	0.070	80.3%
Liraglutide	4	-1.91	-3.07, -0.75	0.001	0.0%
Exenatide	5	-0.62	-3.00, 1.76	0.611	12.8%
Treatment duration<52weeks	8	-3.51	-7.10, 0.09	0.056	63.2%
Treatment duration≥52weeks	3	-1.52	-2.62, -0.42	0.007	0.0%

HbA1c, glycosylated hemoglobin A1c; RD, risk difference; CI, confidence interval.

Table 2-2. Subgroup analyses of body weight and BMI.

	No. of studies	RD	95%CI	P	Heterogeneity I^2
Body weight (kg)					
Experimental group (number)<50	6	-2.44	-3.64, -1.24	<0.001	0.0%
Experimental group (number)≥50	3	-7.64	-15.90, 0.61	0.070	95.8%
Liraglutide	3	-2.31	-4.50, -0.13	0.038	49.9%
Exenatide	5	-2.70	-4.05, -1.36	<0.001	0.0%
Treatment duration<52 weeks	6	-2.09	-3.18, -0.99	<0.001	0.0%
Treatment duration≥52weeks	3	-8.86	-17.52, -0.20	0.045	93.5%
BMI (kg/m^2)					
Experimental group (number) <50	5	-0.88	-1.59, -0.17	0.015	60.0%
Experimental group (number) ≥50	3	-2.50	-5.38, 0.38	0.089	96.9%
Liraglutide	2	-0.81	-2.22, 0.60	0.260	87.2%
Exenatide	4	-1.14	-1.69, -0.59	<0.001	0.0%
Treatment duration<52weeks	5	-0.56	-1.08, -0.04	0.034	70.7%
Treatment duration≥52weeks	4	-2.79	-5.44, -0.14	0.039	95.6%
BMI (%)					
Experimental group (number)<50	4	-2.47	-4.96, 0.01	0.051	77.6%
Experimental group (number)≥50	3	-13.24	-22.62, -3.87	0.006	96.2%
Exenatide	4	-2.47	-4.96, 0.01	0.051	77.6%
Treatment duration<52weeks	3	-2.15	-4.85, 0.55	0.119	81.2%
Treatment duration≥52weeks	4	-11.02	-18.71, -3.34	0.005	95.0%

RD, risk difference; BMI, body mass index; CI, confidence interval.

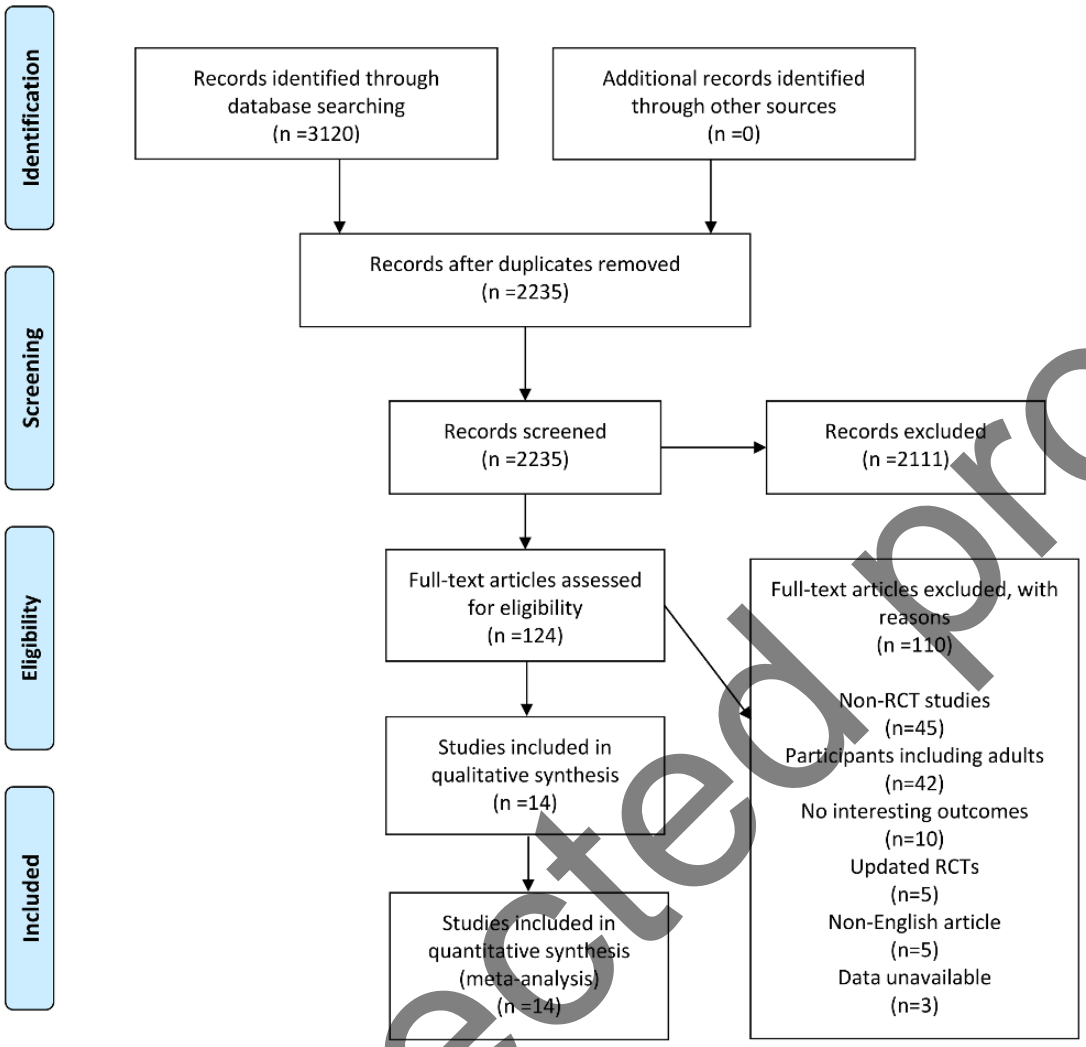


Fig. 1. Flow diagram of selection.

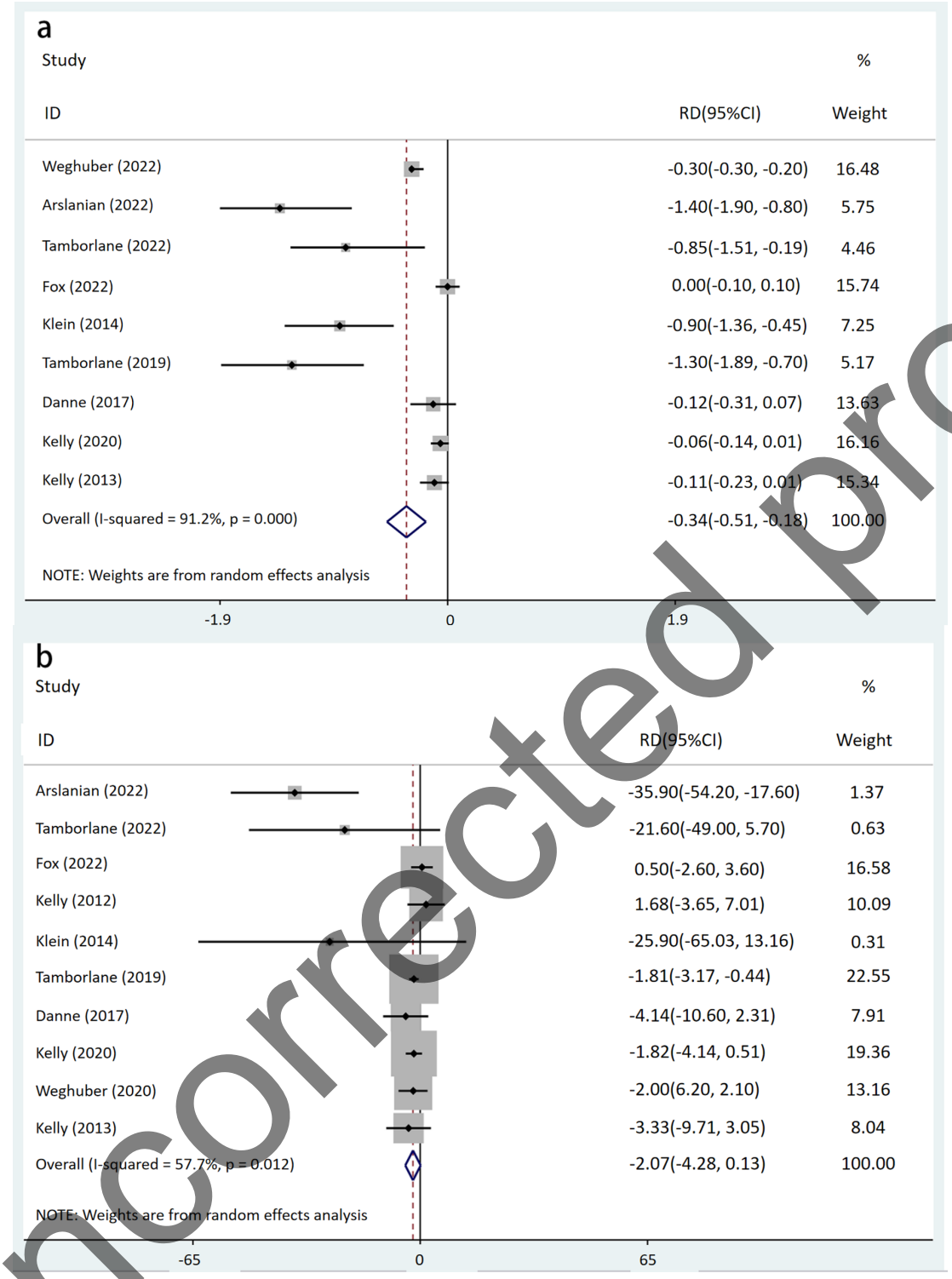


Fig. 2. Forest plot of meta-analysis of the effect of GLP-1RAs on HbA1c and FPG in all participants. (a: HbA1c, p<0.001; b: FPG, p=0.065).

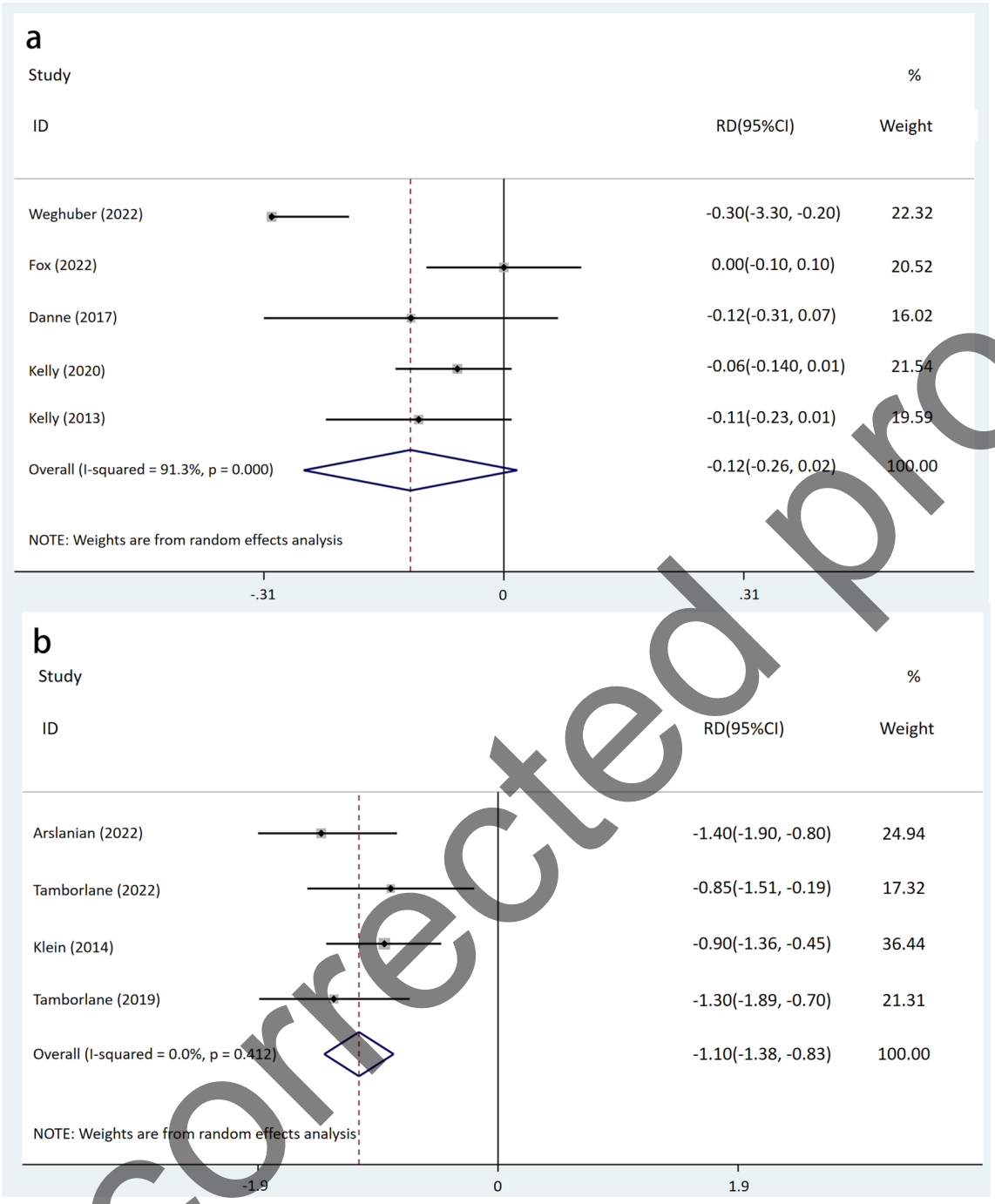


Fig. 3. Forest plot of meta-analysis of the effect of GLP-1RAs on HbA1c (a: obesity, p=0.087; b: T2DM, p<0.001).

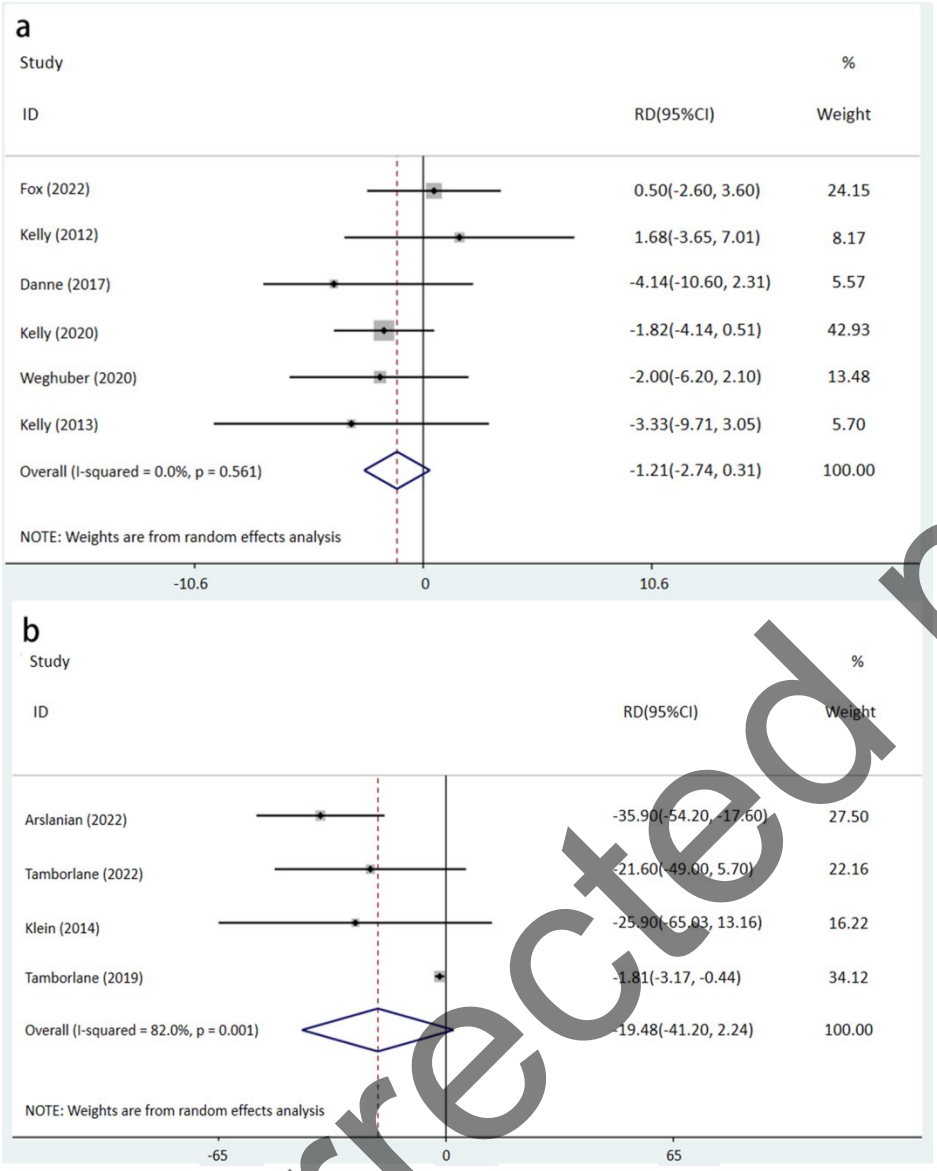


Fig. 4. Forest plot of meta-analysis of the effect of GLP-1RAs on FPG (a: obesity, p=0.119; b: T2DM, p=0.079).

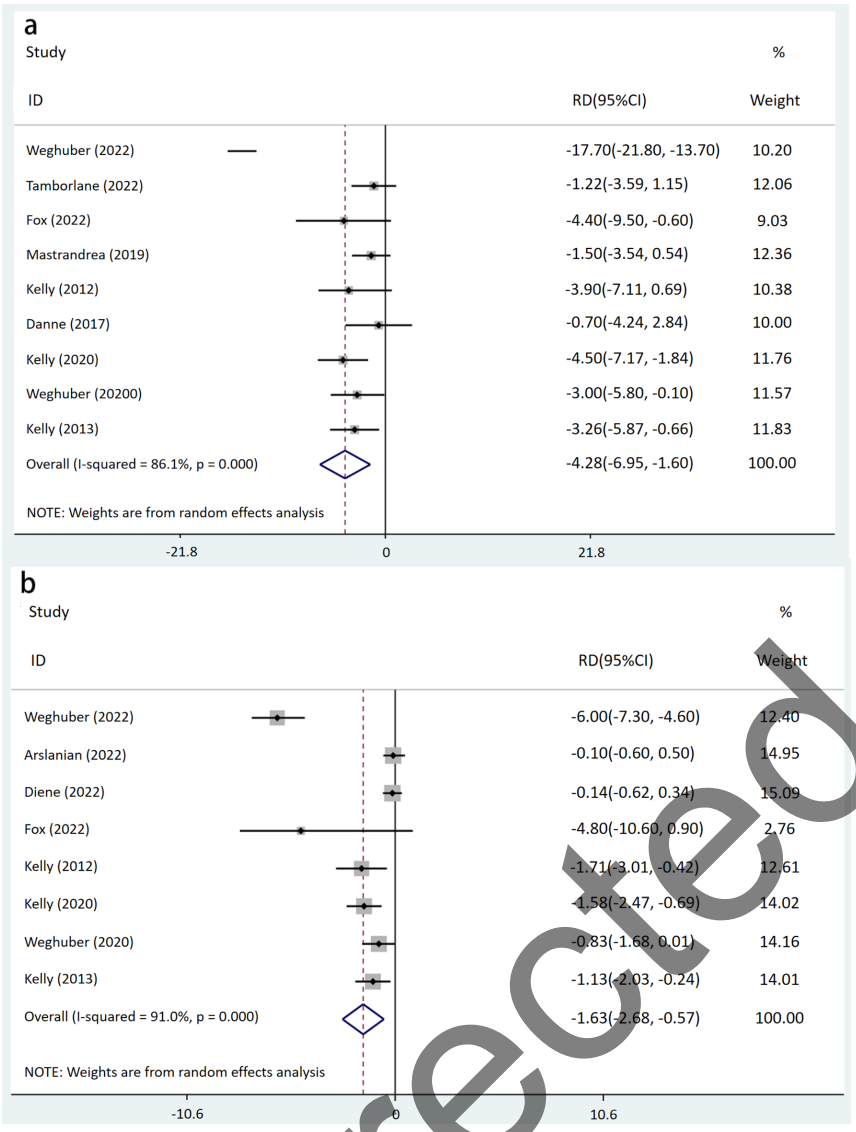


Fig. 5. Forest plot of meta-analysis of the effect of GLP-1RAs on body weight and BMI in all participants (a: body weight, p=0.002; b: BMI, p=0.002).

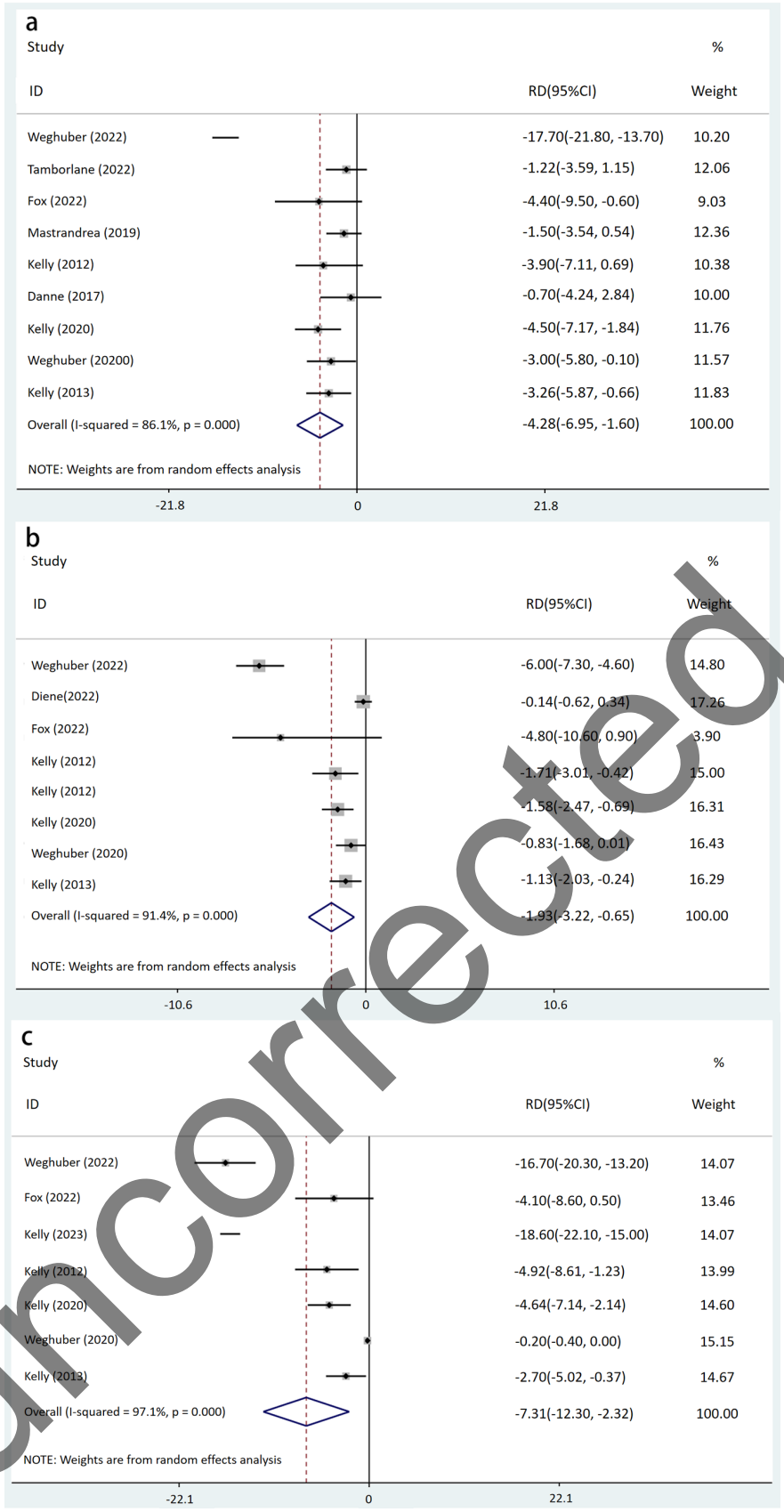


Fig. 6. Forest plot of meta-analysis of the effect of GLP-1RAs on weight control in obesity (a: body weight, p=0.002; b: BMI(kg/m^2), p=0.003; c: BMI(%), p=0.004).

Figure legends

Fig. 1. Flow diagram of selection.

Fig. 2. Forest plot of meta-analysis of the effect of GLP-1RAs on HbA1c and FPG in all participants. (a: HbA1c, p<0.001; b: FPG, p=0.065).

Fig. 3. Forest plot of meta-analysis of the effect of GLP-1RAs on HbA1c (a: obesity, p=0.087; b: T2DM, p<0.001).

Fig. 4. Forest plot of meta-analysis of the effect of GLP-1RAs on FPG (a: obesity, p=0.119; b: T2DM, p=0.079).

Fig. 5. Forest plot of meta-analysis of the effect of GLP-1RAs on body weight and BMI in all participants (a: body weight, p=0.002; b: BMI, p=0.002).

Fig. 6. Forest plot of meta-analysis of the effect of GLP-1RAs on weight control in obesity (a: body weight, p=0.002; b: BMI(kg/m^2), p=0.003; c: BMI(%), p=0.004).

Table legends

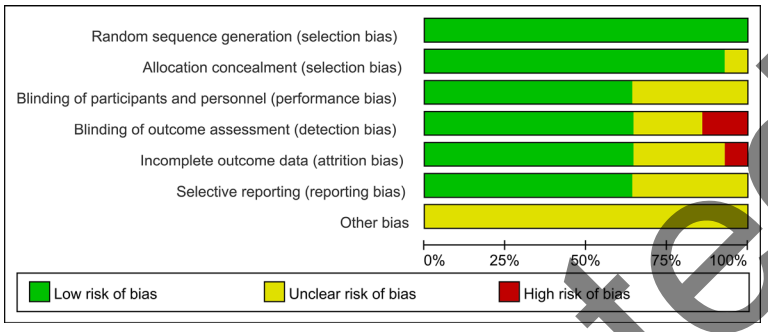
Table 1. Characteristics of all the studies included in the meta-analysis.

Table 2-1. Subgroup analysis of HbA1c and fasting plasma glucose.

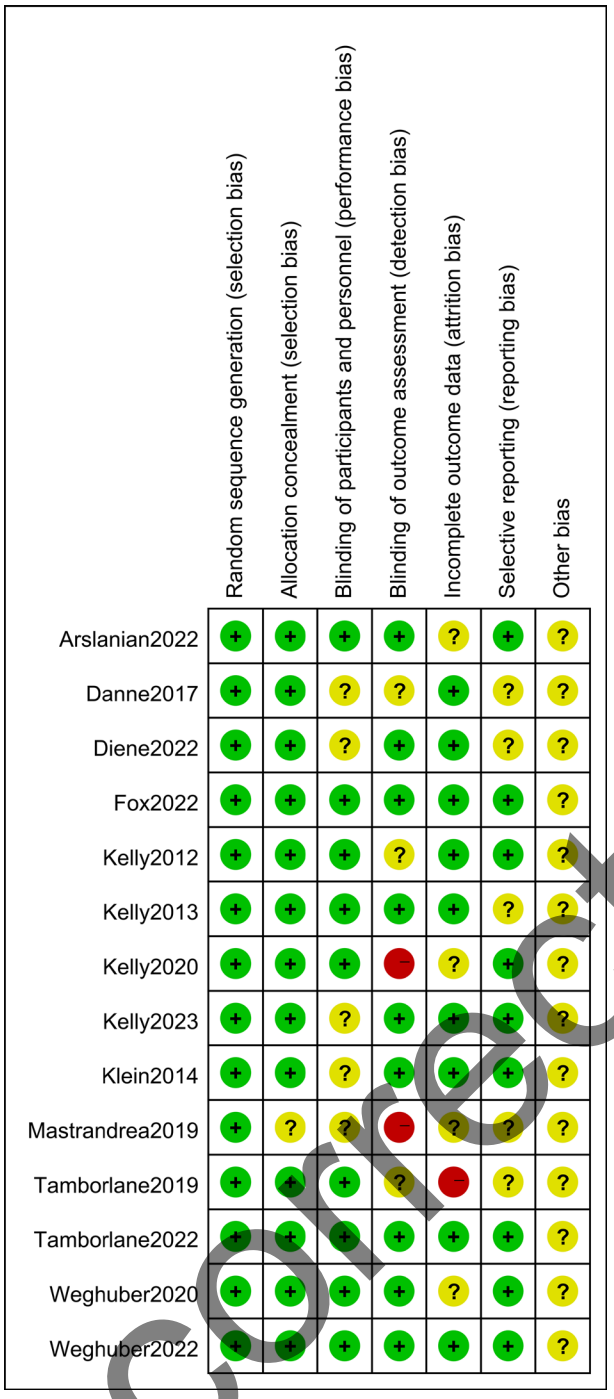
Table 2-2. Subgroup analyses of body weight and BMI.

Additional files

Supplementary Fig. 1. Risk of bias graph for quality assessment of the included RCTs.



Supplementary Fig. 2. Risk of bias summary for quality assessment of the included RCTs.



Supplementary Table 1. Characteristics of all studies included in the meta-analysis.

Supplementary Table 1. Characteristics of all the studies included in the meta-analysis.

Author	Year	Trial registration number	Country	Recruitment time	Age (year)	Mean BMI (kg/m^2)	Concurrent non-drug intervention
Weghuber	2022	NCT04102189	Multi-center	2019-2022	12–18	37	Lifestyle interventions
Arslanian	2022	NCT02963766	Multi-center	2016-2020	10–18	34.1	Diet and exercise interventions
Tamborlane	2022	NCT01554618	Multi-center	2016-2020	10–18	36.36	NA
Diene	2022	NCT02527200	Multi-center	2015-2020	12–17	37.8	Diet and exercise interventions
Fox	2022	NCT02496611	United States	2015-2019	12–18	36.9	Diet and exercise interventions
Kelly	2023	NCT04102189	Multi-center	2019-2022	12–18	37.1	Diet and exercise interventions
Mastrandrea	2019	NCT02696148	United States	2016-2017	7–11	≥ 30	NA
Kelly	2012	NCT00886626	United States	2009-2010	9–16	36.7	Lifestyle interventions
Klein	2014	NCT00943501	Multi-center	2009-2011	10–17	Liraglutide: 40 Placebo: 39.9	NA
Tamborlane	2019	NCT01541215	Multi-center	2012-2018	10–17	33.9	Diet and exercise interventions
Danne	2017	NCT01789086	Germany	2013-2014	12–17	≥ 30	NA
Kelly	2020	NCT02918279	Multi-center	2016-2019	12–18	Liraglutide: 35.3 Placebo: 35.8	Lifestyle interventions
Weghuber	2020	NA	Multi-center	2015-2016	10–18	> 30	Lifestyle interventions
Kelly	2013	NCT01237197	United States	2011-2012	12–19	42.5	Lifestyle interventions

BMI, body mass index; NA, not available.