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Safety and Efficacy of Glucagon-Like Peptide-1 Receptor Agonists in Children and Adolescents with Obesity: A Meta-Analysis

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Objectives To determine the weight, body mass index (BMI), cardiometabolic, and gastrointestinal effects of glucagon-like peptide-1 (GLP-1) receptor agonists in children with obesity.

Study design Web of Science, PubMed/MEDLINE, and Scopus databases from 01/01/1994-01/01/2021 for randomized control trials examining the weight, BMI, cardiometabolic, or gastrointestinal effects of GLP-1 receptor agonists in children and adolescents with obesity. Data were extracted by 2 independent surveyors and a random effects model was applied to meta-analyze generic inverse variance outcomes. Primary outcomes were related to weight and cardiometabolic profile, and secondary outcomes of interest were gastrointestinal-related treatment-emergent adverse events.

Results Nine studies involving 574 participants were identified, of which 3 involved exenatide and 6 involved liraglutide. GLP-1 receptor agonists use caused a modest reduction in body weight (mean difference [MD] -1.50 [-2.50,-0.50] kg, I^2 64%), BMI (MD -1.24 [-1.71,-0.77] kg/m^2, I^2 0%), and BMI z score (MD -0.14 [-0.23,-0.06], I^2 43%). Glycemic control was improved in children with proven insulin resistance (glycated hemoglobin A1c MD -1.05 [-1.93,-0.18] %, I^2 76%). Although no lipid profile improvements were noted, a modest decrease in systolic blood pressure was detected (MD -2.30 [-4.11,-0.49] mm Hg; I^2 0%). Finally, analysis of gastrointestinal-related treatment-emergent adverse events revealed an increased risk of nausea (risk ratio 2.11 [1.44, 3.09]; I^2 0%), without significant increases in other gastrointestinal symptoms.

Conclusions This meta-analysis indicates that GLP-1 receptor agonists are safe and effective in modestly reducing weight, BMI, glycated hemoglobin A1c, and systolic blood pressure in children and adolescents with obesity in a clinical setting, albeit with increased rates of nausea. *(J Pediatr 2021;236:137-47)*.

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Prevalence of pediatric obesity is approaching 1 in 5 children and adolescents age 2-19 years in the US.[1] As a direct consequence of this obesity surge, we will continue to experience a substantial adult cardiometabolic burden.[2] Public health measures to optimize lifestyle (ie, dietary/exercise) interventions and to reduce culpable environmental exposures are the primary target for governments and societies.[3] There remains a subset of children and adolescents whose obesity is resistant to this approach.[4] For these children, and particularly those with severe obesity, pediatricians have little to offer in terms of safe, effective, and durable weight-reducing pharmaceutical interventions with high-grade evidence supporting their use.[4,5]

Incretins are gut-derived hormones, such as glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1), which have been shown to confer a range of beneficial metabolism-regulating functions, ranging from increased insulin secretion and sensitivity to delayed gastric emptying and promotion of postprandial satiety.[6,7] Two discrete classes of incretin-based therapies have arisen, namely GLP-1 receptor agonists (GLP-1RAs) and dipeptidyl peptidase-4 inhibitors (DPP-4Is). Although these medication classes were designed and licensed initially for their antihyperglycemic effects, they have demonstrated weight regulating and cardioprotective potential in clinical trials involving adults.[8,9]

Research exploring the efficacy of these drugs in pediatric obesity has been accumulating over the past decade. The first drug of the class, Saxenda (liraglutide), received Food and Drug Administration approval for use in children age

BMI	Body mass index	MD	Mean difference
DPP-4I	Dipeptidyl peptidase-4 inhibitors	RCT	Randomized controlled trial
GI	Gastrointestinal	RR	Risk ratios
GLP-1	Glucagon-like peptide-1	TEAE	Treatment-emergent adverse event
GLP-1RA	GLP-1 receptor agonists		
HbA1c	Glycated hemoglobin A1c	T2D	Type 2 diabetes
LDL-C	Low-density cholesterol		

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12-17 years with obesity (weight >60 kg and BMI of >30 kg/m^2 in accordance with international standards[10]/≥95th percentile) in 2020. However, as these trials have generally been of small or modest size, the precise cardiometabolic effects and associated safety of GLP-1RAs has not been adequately established in the pediatric setting. The present systematic review and meta-analysis aimed to assess whether GLP-1RAs reduce weight or body mass index (BMI) and improve cardiometabolic profile, defined here as improvement in glycated hemoglobin A1c (HbA1c), lipid profile, or blood pressure in children with obesity when compared with placebo or no intervention in a randomized controlled trial (RCT). As a secondary aim, we sought to determine if GLP-1RAs are associated with increased gastrointestinal side effects, pancreatitis, and altered liver function in the same population.

Methods

The design and reporting of the present systematic review and meta-analysis follows the PRISMA guidelines.[11] A protocol for this meta-analysis was prospectively registered (PROSPERO ID: CRD42020195869).[12]

The literature was comprehensively searched through the Web of Science, PubMed/MEDLINE, and Scopus databases from January 1, 1995 to January 1, 2021 using the strategies outlined in **Table I** (available at www.jpeds.com) by means of the University College Cork library system. All resulting references were uploaded to the Covidence Systematic Review Manager platform (covidence.org) for screening and data extraction purposes.

We originally aimed to include all clinical trials that explored the use of GLP-1RA (eg, exenatide, lixisenatide, dulaglutide, and liraglutide) or DPP-4I (eg, sitagliptin, vildagliptin, saxagliptin, and linagliptin) in male and/or female children and adolescents age <18 years at time of randomization with obesity (mean age-adapted BMI >30 kg/m^2), with or without a diagnosis of type 2 diabetes (T2D). However, as no trials examining the use of DPP-4Is were uncovered, they will not be further discussed in this review. Only RCTs were included in the ultimate quantitative meta-analysis. Studies including participants with type 1 diabetes, obesity-associated genetic disorders (eg, Prader-Willi syndrome), hypothyroidism, or any history of an eating disorder were excluded from the present systematic review and meta-analysis. The authors functioned in 2 distinct and independent working groups of screeners who reviewed each abstract and/or full text manuscript in duplicate to ensure relevance and appropriate data reporting. Reference lists of included studies were reviewed for potential additional studies of relevance. Any discrepancies in inclusion/exclusion decisions were resolved through discussion and consensus with a third party.

As with screening, data extraction was conducted in duplicate by 2 independent authors from the working groups outlined above. Details on the baseline characteristics and demographics of the study population, as well as information on the study group and funders were collected. A range of outcomes were extracted for time points at the beginning and at intervention end. The primary outcomes for quantitative meta-analysis were cardiometabolic in nature, including reductions in body weight/BMI/z score, HbA1c, fasting plasma glucose, lipid profile (triglycerides, total cholesterol, low-density cholesterol [LDL-C]), and blood pressure attributable to the intervention. Secondary outcomes of interest related to rates of gastrointestinal-related treatment-emergent adverse events (TEAEs), such as nausea, vomiting, diarrhea, abdominal pain, and elevated pancreatic enzymes.

The generic inverse variance mean difference (MD) or risk ratios (RR) with 95% CIs representing the effect of GLP-1RAs on outcomes of interest at the longest follow-up point were produced using a random-effects DerSimonian and Laird model. This method incorporates adjustment for heterogeneity of intervention effects between the studies included and was applied given the potentially high degree of heterogeneity across pediatric study populations. Subgroup analyses exploring the effect of specific medication on the weight and BMI z score reducing capacity and TEAE rates of the interventions were also performed. Heterogeneity among results was evaluated using the Cochran Q test and the I^2 test. RevMan v 5.4 (Review Manager; The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used to conduct all statistical analyses.

Although not specified in the registered protocol a priori, it was deemed appropriate to conduct a sensitivity analysis exploring the effect of concurrent lifestyle interventions on the therapeutic effect of the medications given the presence of such adjuncts in several of the trials.

The risk of bias tool was applied to each study included by 2 independent reviewers through the Covidence platform. The overall study risk of bias assessment was used to provide context when discussing the relevant primary and secondary outcomes. Finally, funnel plots were generated and visually assessed, and Egger tests were conducted to explore any potential publication bias.

Results

In total, 737 references were uncovered through the search strategy outlined, of which 72 were removed as duplicates (**Figure 1**; available at www.jpeds.com). Subsequent abstract screening of the remaining 665 references resulted in exclusion of all but 10 studies. Review of the respective references lists revealed an additional 2 references of relevance. Following full text review, 9 studies of relevance to the research question remained, of which 2 were post-hoc analyses of data already included, and 1 was not a clinical trial. Finally, all 9 of these studies were randomized controlled trials reporting outcomes of interest in a useable manner and were, therefore, included in the meta-analysis.

Of the 9 studies included, 3 were conducted in the US,[13-15] 1 in Germany,[16] 1 in Sweden,[17] 1 in China,[18] and 3 were

international consortia[19-21] at sites in countries including Belgium, Mexico, Russia, Slovenia, Sweden, the United Kingdom, and the US, among others (**Table II**; available at www.jpeds.com). Although 8 of the studies were parallel RCTs,[13,14,16-21] 1 study used a crossover RCT design.[15] In terms of the therapeutic intervention, 3 studies involved exenatide[14,15,17] and 6 involved liraglutide.[13,16,19,20] All studies reported the use of a volume-matched placebo injection pen, and 3 of the included studies explicitly reported the application of concurrent lifestyle interventions for both the intervention and placebo groups.[15,18,20]

In total, this meta-analysis included data from 574 children and adolescents, 302 of which received a GLP-1RA. The majority of the studies were small in size, ranging from 11 to 44 participants, and short in duration, ranging from 5 to 26 weeks (**Table III**).[13-17,19] However, 2 of the studies were relatively large in scale and duration, involving 134 and 251 participants in 52- and 56-week-long interventions, respectively.[20,21] The mean (±SD) age across all included participants was 14.15 (±2.16) years, with a slight female (53.3%) majority. Mean weights of participants at baseline ranged from 71.5 kg to 124 kg, with BMI ranging from 33.9 to 43 kg/m^2 and BMI z score from 2.9 to 3.9. Although all studies included children with obesity or severe obesity, only 3 of the studies exclusively included participants with T2D or prediabetes,[18,19,21] although diagnosis of T2D was not an exclusion criterion for the remainder of studies.

Of the 3 trials which explored exenatide, 1 applied a dose of 2 mcg daily for the duration of intervention,[17] and the other 2 commenced at 5 mcg daily and escalated to 10 mcg after 1 month.[14,15] In the other 6 trials, which applied liraglutide, 1 commenced at 0.3 mg daily and escalated gradually up to 1.8 mg,[19] 1 commenced at 0.3 mg daily and escalated up to 3 mg,[13] 1 commenced at 0.6 mg daily and escalated up to 1.2 mg,[18] 1 commenced at 0.6 mg and escalated to 1.8 mg,[21] and 2 commenced at 0.6 mg daily and escalated up to 3 mg.[16,20] Although 82.4% and 92.9% of liraglutide-treated participants reached the maximum daily dosage in Kelly et al[20] and Mastrandrea et al,[13] respectively, just 55.6% of participants reached the maximum dose of 1.8 mg in Tamborlane et al because of the dosing guidelines.[21]

Among the included studies, GLP-1RA use resulted in a modest reduction in body weight (MD 1.50 [-2.50, -0.50] kg, I^2 64%), BMI (MD -1.24 [-1.71, -0.77] kg/m^2, I^2 0%), and BMI z score (MD -0.14 [-0.23, -0.06], I^2 43%) (**Figure 2**). Subsequent subgroup analyses by the specific medication revealed no discernable difference in the body weight reducing effects of exenatide (MD -2.02 [-4.54, 0.49] kg, I^2 72%) when compared with liraglutide (MD -1.51 [-2.85, -0.17] kg, I^2 67%), with a subgroup heterogeneity I^2 of 0%. Similarly, BMI reductions were indistinguishable between exenatide (MD -1.11 [-1.67, -0.55] kg/m^2, I^2 0%) and liraglutide (MD -1.58 [-2.42, -0.70] kg/m^2, I^2 0%), with a subgroup heterogeneity I^2 also of 0%. Finally, BMI z score reduction was similar between exenatide (MD -0.09 [-0.18, 0.00]) and liraglutide (MD -0.17 [-0.28, -0.06], I^2 43%), with a subgroup heterogeneity I^2 of 16.4% (**Figure 2**).

A sensitivity analysis exploring the effect of concurrent lifestyle intervention, provided to both control and intervention arms, on weight and BMI outcomes revealed the adjunctive therapy to be highly complementary to GLP-1RA treatment (**Figure 3**; available at www.jpeds.com). This was true for weight reduction, which improved from an MD of -0.76 kg (-1.43, -0.09; I^2 29%) without lifestyle intervention to -4.25 kg (-6.31, -2.20; I^2 0%) with lifestyle intervention (subgroup heterogeneity I^2 90.1%). Similarly, BMI reduction was improved from an MD of -0.97 kg/m^2 (-1.59, -0.35; I^2 0%) without lifestyle intervention to -1.60 kg/m^2 (-2.32, -0.88; I^2 0%) with lifestyle intervention (subgroup heterogeneity I^2 41.1%). Finally, BMI z score was reduced by an MD of -0.13 (-0.22, -0.03; I^2 45%) without lifestyle intervention, but -0.22 (-0.37, -0.07) with lifestyle MD (subgroup heterogeneity I^2 6.2%). An additional sensitivity analysis exploring the effects separating normoglycemic populations from those with prediabetes or T2D did not reveal a significant effect of population insulin resistance status on GLP-1RA weight, BMI or BMI z score reducing capacity (**Figure 4**; available at www.jpeds.com).

Among the 6 studies that reported HbA1c, GLP-1RA intervention only had an effect on populations which were exclusively composed of children with insulin resistance (ie, T2D or prediabetes: MD -1.05 [-1.93, -0.18] %, I^2 76%), and no

Table III. Included studies baseline population characteristics

Studies Author year	Study population demographics and baseline data								
	n	Mean age y (SD)	Male n (%)	White %	Black %	Other %	Mean weight (kg)	Mean BMI (kg/m^2)	BMI z score
Kelly et al 2012[15]	11	12.7 (2.1)	2 (18.2)	NR	NR	NR	93.8	37	NR
Kelly et al 2013[14]	26	15.2 (1.8)	10 (38.5)	76.9	15.4	7.7	124	43	NR
Klein et al 2014[19]	21	15 (NR)	7 (33.3)	66.7	33.3	0	113	40	3.4
Danne et al 2017[16]	21	14.9 (1.3)	7 (33.3)	NR	NR	NR	105.5	36	3.2
Mastrandrea et al 2019[13]	24	9.9 (1.1)	15 (62.5)	58.3	41.7	37.5	71.5	NR	3.9
Kelly et al 2020[20]	251	14.6 (1.6)	102 (40.6)	83.7	8	8.3	100.8	36	3.17
Weghuber et al 2020[17]	44	14.4 (2.3)	22 (50)	93.2	2.3	4.5	104.4	36	3.2
Tamborlane et al 2019[21]	134	14.6 (1.7)	51 (38.1)	64.9	11.9	23.2	91.5	33.9	2.94
Zhou et al 2017[18]	42	11.16 (2.2)	29 (69)	NR	NR	NR	NR	30.94	NR

NR, not reported.

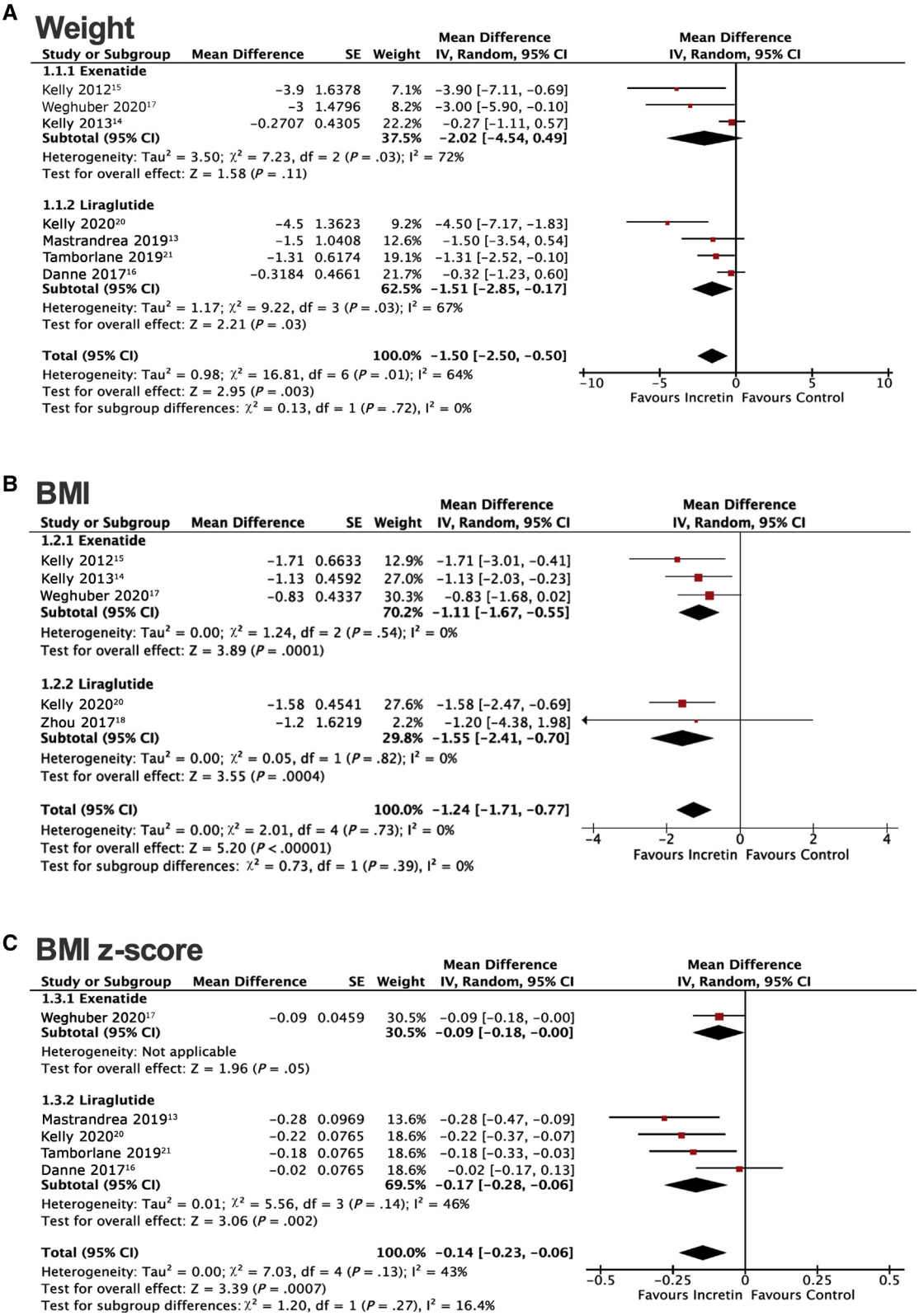


Figure 2. Forrest plot of mean difference change in weight, BMI, and BMI z score following GLP-1 receptor agonist intervention in children with obesity. Studies are subgrouped by the specific intervention.

effect was detected in those which included mixed populations (MD -0.08 [-0.13, 0.02] %, I^2 0%; subgroup heterogeneity I^2 79%) (**Figure 5**). However, no effect on fasting plasma glucose was noted for either population (insulin resistance: MD -16.26 [-41.23, 8.71] mg/dL, I^2 76%; mixed population: MD -1.76 [-3.51, 0.01] mg/dL, I^2 0%). In the 3 studies that explored lipid profile following intervention, no improvements in total cholesterol (MD -4.17 [-11.29, 2.95] mg/dL; I^2 39%), LDL-C (MD -4.63 [-10.25, 0.98] mg/dL; I^2 0%), or triglycerides (MD 1.24 [-10.47, 12.96] mg/dL; I^2 0%) were noted (**Figure 6**). Finally, despite no effect on DBP among the 4 studies reporting blood pressure (MD 0.28 [-1.39, 1.94] mm Hg, I^2 13%), a modest decrease in systolic blood pressure was detected (MD -2.30 [-4.11, -0.49] mm Hg; I^2 0%) (**Figure 6**).

Of the studies where liraglutide was used, the most commonly affected systems for TEAEs were gastrointestinal (GI), skin and subcutaneous tissue (6.3-14.3 per 100 participants), neurologic (18.8-50 per 100 participants), endocrine, and hepatobiliary (**Table IV**; available at www.jpeds.com). The most common endocrine TEAE was hypoglycemia (14.3-25 per 100 participants), and the singular hepatobiliary TEAE was elevated transaminases (0-7.1 per 100 participants). For the 3 studies assessing exenatide, the

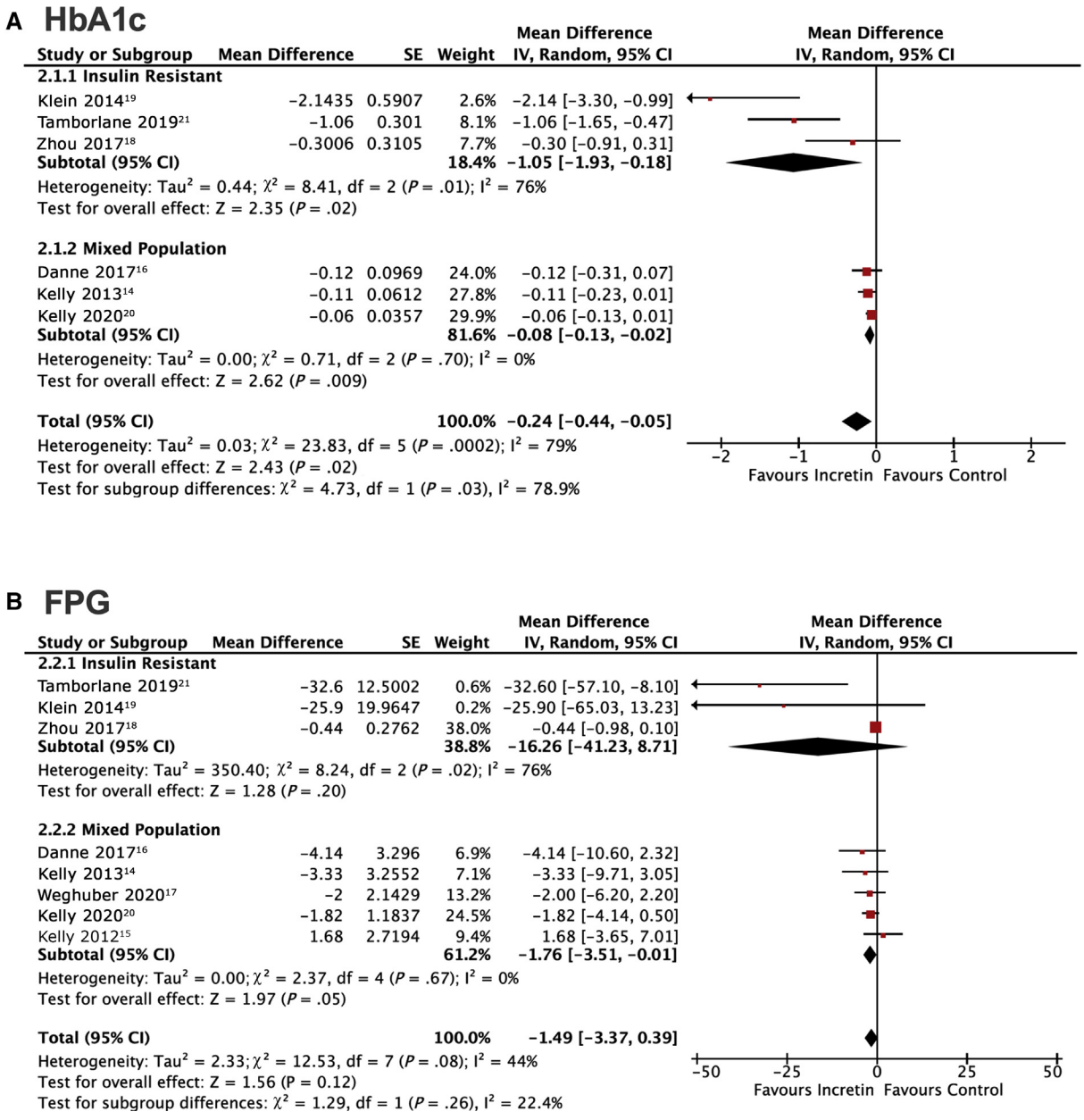


Figure 5. Forrest plot of mean difference change in glycemic control following GLP-1 receptor agonist intervention in children with obesity. Studies are subgrouped according to their exclusive inclusion of children and adolescents with some degree of insulin resistance (ie, T2D or prediabetes) or not (ie, mixed population). *FPG*, fasting plasma glucose.

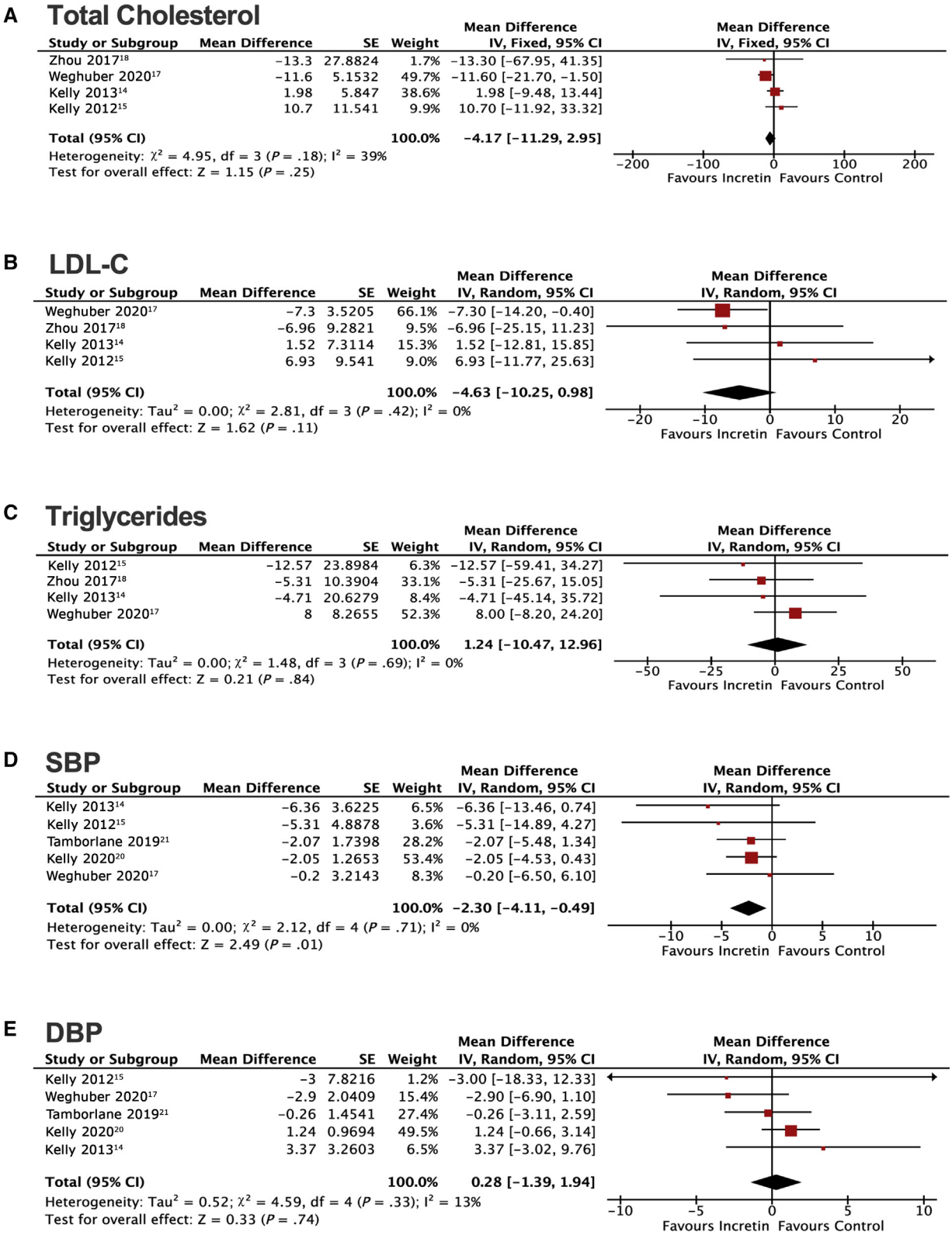


Figure 6. Forrest plot of mean difference change in cardiovascular parameters following GLP-1 receptor agonist intervention in children with obesity. *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure.

primary system implicated in TEAEs was also GI. The most common GI TEAEs were nausea (36.4-62.0 per 100 participants), vomiting (27.3-31 per 100 participants), and abdominal pain (15-18.2 per 100 participants) with diarrhea being reported in a single study (8 per 100 participants).

Of the GI-related TEAEs, a significantly increased risk of nausea (RR 2.11 [1.44, 3.09]; I^2 0%) (**Figure 7**) was described, and although there was a greater risk of diarrhea (RR 1.66 [0.91, 3.04]; I^2 0%), vomiting (RR 1.65 [0.71, 3.85]; I^2 30%), and abdominal pain (RR 1.32 [0.73, 2.39]; I^2 0%) in the GLP-1RAs groups, none of these were found to be statistically significant. No significant difference was noted between the 2 medications for RR of nausea (exenatide RR 2.17 [0.79, 5.95]; I^2 18%; liraglutide RR 2.49 [1.35, 4.59]; I^2 0%) or abdominal pain (exenatide RR 7 [0.40, 121.39]; liraglutide RR 1.22 [0.66, 2.24]; I^2 0%; subgroup heterogeneity I^2 0%).

All studies in liraglutide-treated children reported on pancreatic enzymes,[13,16,19-21] bar 1.[18] Danne et al reported 1 participant who was found to have elevated amylase and lipase, and 1 with isolated elevated lipase following liraglutide initiation. Klein et al noted no effect on amylase, but 3 instances of marginally elevated lipase following liraglutide treatment (all less than twice the upper limit of normal).[19] Similarly, Tamborlane et al found higher levels of lipase in the blood of treated children at both 26 and 52 weeks of intervention (treatment ratio 1.11 [1.01, 1.23]).[21] Although Mastrandrea et al noted increased mean levels of both lipase and amylase in their liraglutide-treated group[13]; however, they deemed these to be clinically inconsequential as all cases were under 3 times the upper limit of normal. A single case of pancreatitis, which was moderate in severity and resolved without intervention, was reported amongst all liraglutide-treated participants.[20] No pancreatic enzyme or pancreatitis data was reported for exenatide.

Calcitonin levels, which may alert investigators to any cases of medullary thyroid cancer, were assessed by 4 of the studies concerning liraglutide and reported as normal.[13,16,19,21] No studies exploring exenatide reported on calcitonin levels.

In general, the studies included in this review were deemed to be at a low risk of performance, detection, and reporting bias; although several were represented as unclear and 2 studies were deemed at high risk of performance bias,[15,18] owing to their open-label designs (**Figure 8**; available at www.jpeds.com). Just 3 of the 9 studies reported specific random sequence generation and allocation concealment methods.[17,20] Concerning attrition rates placed 5 out of the 9 studies at a significant risk of bias,[13-15,17,20] as determined by the predefined cut-off of >13% or overtly uneven losses. Several studies were classed as unclear or high risk of bias due to their modest participant size or sort intervention duration. Because of the relatively low number of studies included in the present meta-analysis, it was not possible to perform the Egger test for the synthesized data; however, visual inspection of funnel plots resulted in low concern for publication bias (**Figure 9**; available at www.jpeds.com).

Discussion

Our systematic review of the literature revealed 8 RCTs and 1 crossover RCT, involving a total of 574 participants with a mean age of ~14 years and baseline BMI ranging from 33.9 to 43.0 kg/m^2. Ultimately, we found that GLP-1RAs confer a modest but clear blood pressure, HbA1c, and weight reducing effect, the latter of which is complimented by concurrent lifestyle intervention, with relatively minor, predominantly GI, side effects.

In the present meta-analysis, GLP-1RAs demonstrated weight-reducing effects; however, in contrast to what has been established in adult populations, there was no difference noted in the efficacy of liraglutide and exenatide in this population.[22] Although these were the only 2 compounds for which pediatric data are available, trials are ongoing with more novel iterations of GLP-1RAs (eg, clinicaltrials.gov ID: NCT04102189). As per the National Institute for Health and Care Excellence guidelines, obesity prevention and lifestyle weight management interventions, including instructive exercise and nutritional education, promotion of healthy options, and behavioral counseling, represent the mainstay of obesity management in children.[23] Although these interventions can be highly effective in certain individuals in the correct setting, they have their clear limitations (eg, patient and carer engagement) and may benefit from adjunctive approaches or therapies. In line with this, we found lifestyle interventions to be complementary in amplifying the weight-reducing effects of GLP-1RAs in children with obesity. Indeed, this has been demonstrated previously in adult populations,[24] and research into the anti-obesity potential of GLP-1RAs appears to be continuing in this direction,[25] for example in the Semaglutide Treatment Effect in People with obesity (STEP) trials.[26,27]

GLP-1RAs were originally designed and distributed for their effects on glycemic control, with reductions in HbA1c of 1.48% and 1.28% in the Diabetes Therapy Utilization: Researching Changes in A1C, Weight and Other Factors Through Intervention with Exenatide Once Weekly (DURATION)-6 trial for liraglutide and exenatide, respectively.[22] In our subgroup analysis which separated studies that exclusively included participants with proven insulin resistance from mixed population studies, we demonstrated a significant effect of GLP-1RA on the HbA1c only in the former group. However, this is to be expected as such therapies are unlikely to display corrective effects in individuals without suboptimal baseline glycemic control. Indeed, the effect size was comparable with adult data, with a reduction of 1.05% in the insulin resistant subgroup.

In a similar manner to weight reduction, the hypocholesterolemic and cardioprotective effects of GLP-1RAs became clear soon after the antihyperglycemic effects were established.[28] Since this point, virtually all of the established and approved GLP-1RA medications have been assessed for

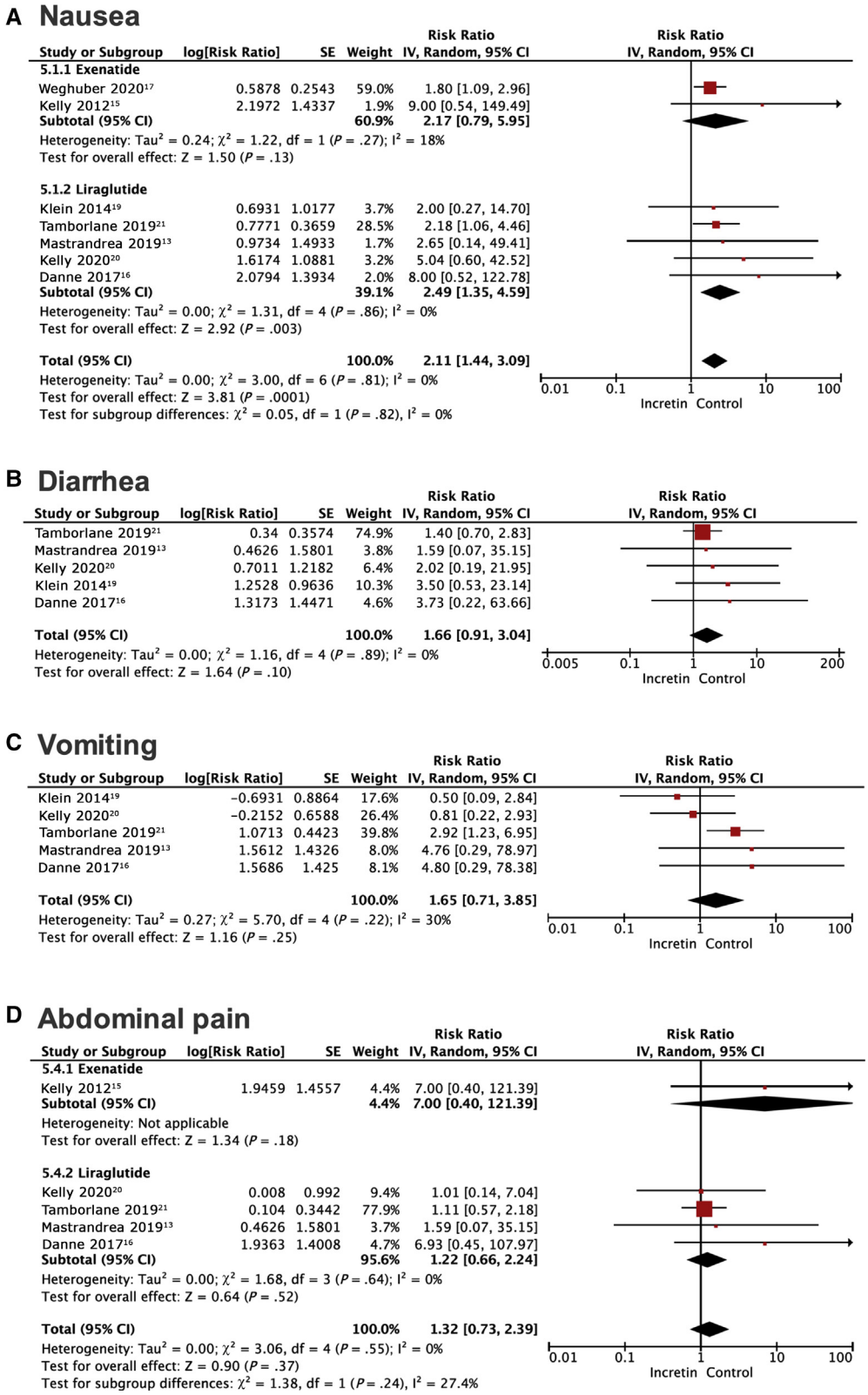


Figure 7. Forrest plot of risk ratios for gastrointestinal treatment emergent adverse events associated with GLP-1 receptor agonist intervention in children with obesity. Studies are subgrouped by the specific intervention.

their cardioprotective capacity in a large phase III RCT,[29-32] with several novel compounds currently under assessment (clinicaltrials.gov ID: NCT03496298). However, all of the above trials have been focused on adults with T2D and significant cardiovascular risk factors or comorbidities. Although the pediatric studies included in this analysis did not set out to explore the effects of such medications on cardiovascular-related outcomes such as lipid profile and blood pressure, these outcomes were reported. Although there were no notable effects on total cholesterol, LDL-C, or triglycerides, these outcomes were generally within normal ranges or at the upper end of normal at baseline, suggesting that there was little scope for reduction. This may explain the absent or minimal effect noted in this study when compared with similar adult studies.[33] Nevertheless, we did note a significant reduction in systolic blood pressure, which may be of clinical importance when considered in the context of life-long hypertension in children with additional cardiovascular risk factors.

One of the major concerns which initially arose around GLP-1RA use was a perceived increased rate of pancreatitis and pancreatic cancer.[34] However, in the 5 liraglutide studies, which examined pancreatic enzymes in the present analysis,[13,16,19-21] lipase and amylase were elevated in only a handful of cases and all but 1 case were deemed to be at clinically inconsequential levels. Ultimately, a single episode of acute pancreatitis was detected amongst all liraglutide-treated participants.[20] This is in keeping with the current knowledge, as several meta-analyses of GLP-1RA trials involving patients with T2D[35-37] and cardiovascular risk factors[35] have repeatedly revealed no increased risk of either pathology. Similarly, an increased risk of medullary thyroid cancer with GLP-1RA use has been theorized as a result of rodent data[38]; however, no such effect was detected in the 4 liraglutide studies that examined calcitonin levels included in this meta-analysis. This is also in keeping with the results of larger adult trials.[39]

Anti-obesity therapies must be tolerable to facilitate compliance and subsequent efficacy.[40,41] This is of particular relevance considering the GI-related TEAEs, which have previously been attributed to the GLP-1RAs. Indeed, several notes of concern were registered with the editor regarding the effects of such TEAEs on nutrient intake[42] and absorption[43] in children following the recent study by Kelly et al.[20] However, although we found an increase RR of nausea events in the present meta-analysis, we observed no such significant increased risk for other potentially concerning GI symptoms such as vomiting, diarrhea, or abdominal pain. In keeping with this, previous reports have shown that liraglutide exerts satiating effects that appear to be entirely uncoupled from the GI-related TEAEs.[44] Together, these data suggest that GLP-1RAs are generally safe to use in children who will be monitored for local and systemic symptoms, as well as GI side effects.

The study is limited by the relatively low number of trials uncovered, as well as the fact that 1 study contributed approximately one-half of the participants for the meta-analysis. In addition, more than one-half of the included trials were of a short duration (ie, <3 months), which may ultimately underestimate the potential effect size of such therapies. Moreover, the relatively large proportion of participants with concomitant T2D may have introduced a degree of heterogeneity in the estimated weight-reducing efficacy, although this was not detected in subgroup analysis. Similarly, the diversity of dosage regimens and the variability in their implementation success may represent a further source of heterogeneity that must be considered. Although no publication bias could be detected, a number of the studies exceeded the predefined acceptable attrition rate and therefore represented a high risk of bias. Nevertheless, confidence in the primary outcome can be gained from the homogeneity displayed within the meta-analyses.

This meta-analysis revealed GLP-1RAs to be effective in reducing weight, HbA1c, and blood pressure in children and adolescents with obesity or severe obesity. In addition, this weight-reducing effect appears to be bolstered by concurrent lifestyle intervention. A modest decrease in systolic blood pressure was also identified. Finally, apart from increased rates of minor GI-related symptoms such as nausea, no serious TEAEs were noted. Ultimately, this meta-analysis indicates that GLP-1RAs are safe, tolerable, and effective in improving cardiometabolic profile in children with obesity. ■

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50 Years Ago in *The Journal of Pediatrics*

Parenteral Nutrition of the Small Premature Infant

Benda G, Babson S. Peripheral intravenous alimentation of the small premature infant. J Pediatr 1971;79:494-98.

Parenteral nutrition refers to intravenous nourishment to provide the main energy and total nutrition source for an infant that cannot be fed (for any clinical condition) or as a complementary therapy to enteral feeding.

In *The Journal* 50 years ago, Benda and Babson described the indications, features, and advantages in the concern of parenteral nutrition for small premature infants. They highlighted the importance of establishing a source of nutritional support for premature infants to provide them enough nutrients for appropriate growth and development, optimal weight gain, and survival improvement.

Since the publication of this report, we have seen a continual increase in scientific evidence about the nutritional role that parenteral nutrition plays and the estimated energy requirements to satisfy healthy growth and development in these infants.[1] This specifically includes studies that evaluated the optimal infusion rate, the best route of administration, the advantages, risks, and more importantly, a detailed assessment of each of the nutritional components. This data has allowed the development of standardized nutritional formulas based on scientific recommendations. In the ensuring 50 years, valuable information, based on scientific evidence, validates its use and efficacy (enhancing growth rates, reducing mortality, and optimizing neurocognitive development).

In future studies, it will be important to continually reassess the guidelines that determine the way most practitioners administer parenteral nutrition. This will be aided by additional information about the optimal composition of neonatal intravenous nutrition, the adverse effects, the safety of providing early and aggressive intravenous components (lipids, proteins, carbohydrates, and trace elements), as well as the optimal time to initiate their supplementation.

Since publication of this review, 2 particular statements remain true: the early initiation of nutritional support is an important step in achieving appropriate growth and this manner can reduce the mortality rate in premature infants.

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Reference

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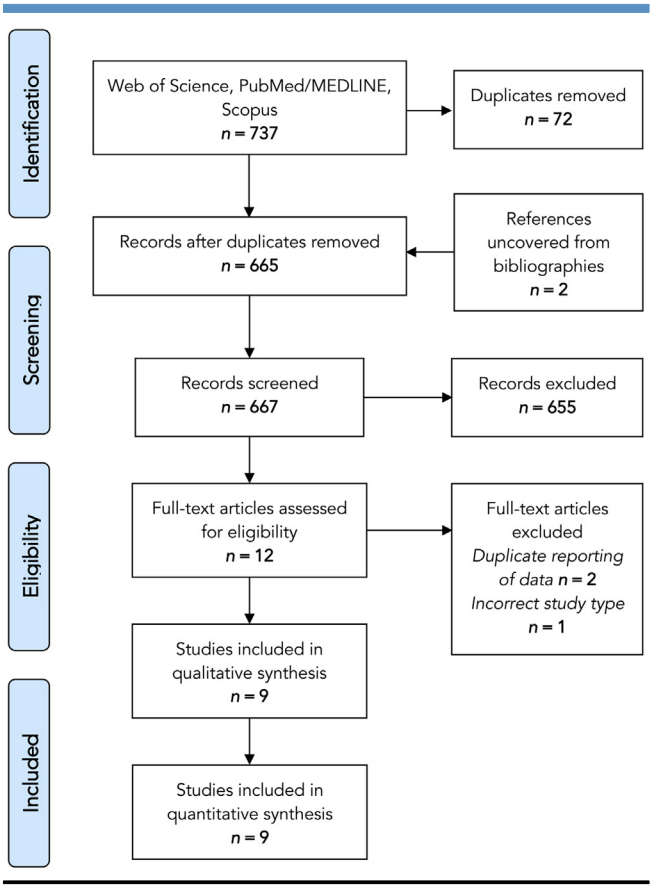


Figure 1. PRISMA flowchart of study search, screening, inclusion, and synthesis counts.

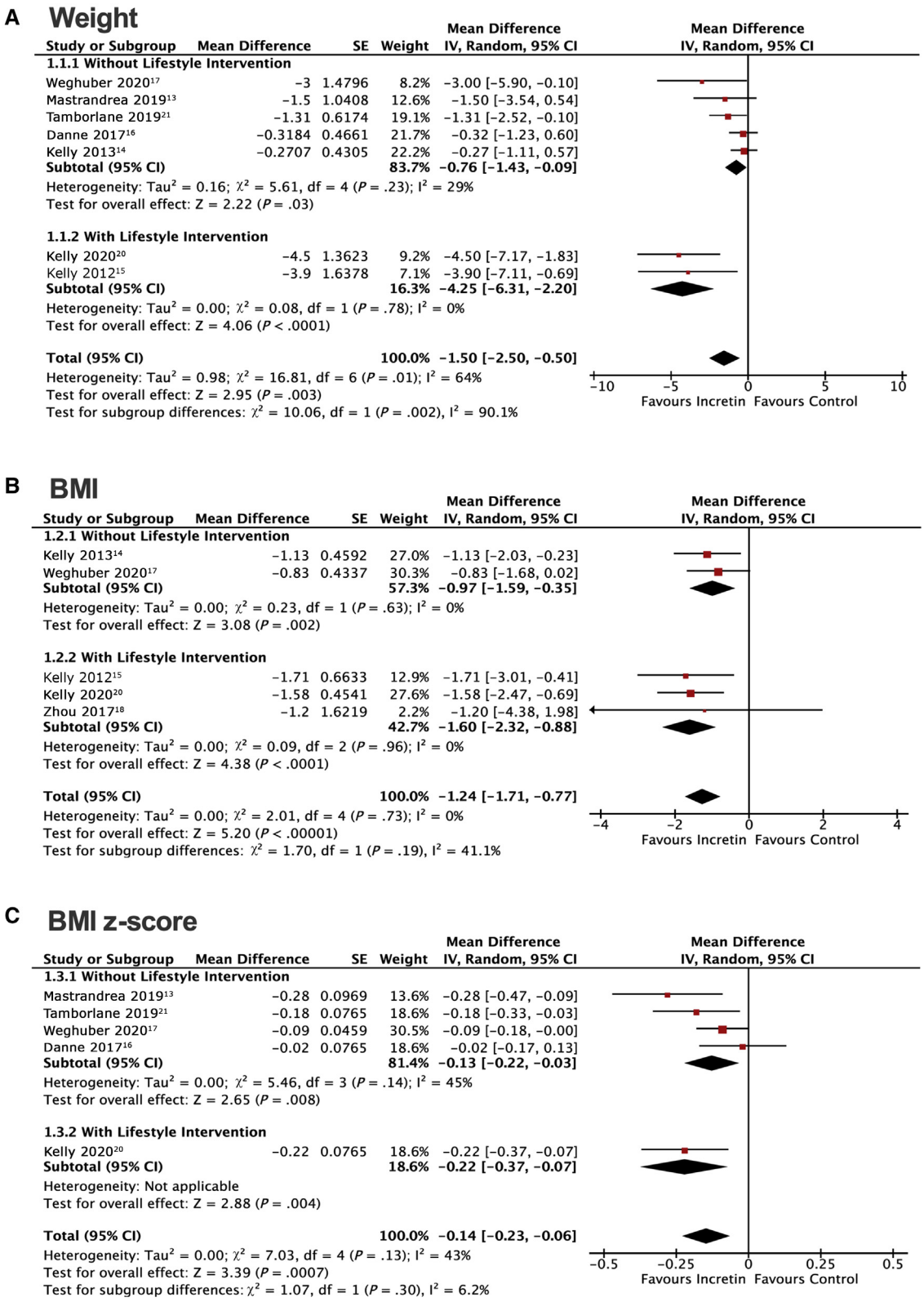


Figure 3. Sensitivity analysis exploring the effects of adjunctive lifestyle interventions on the weight, BMI, and BMI z score reducing efficacy of GLP-1 receptor agonist intervention in children with obesity.

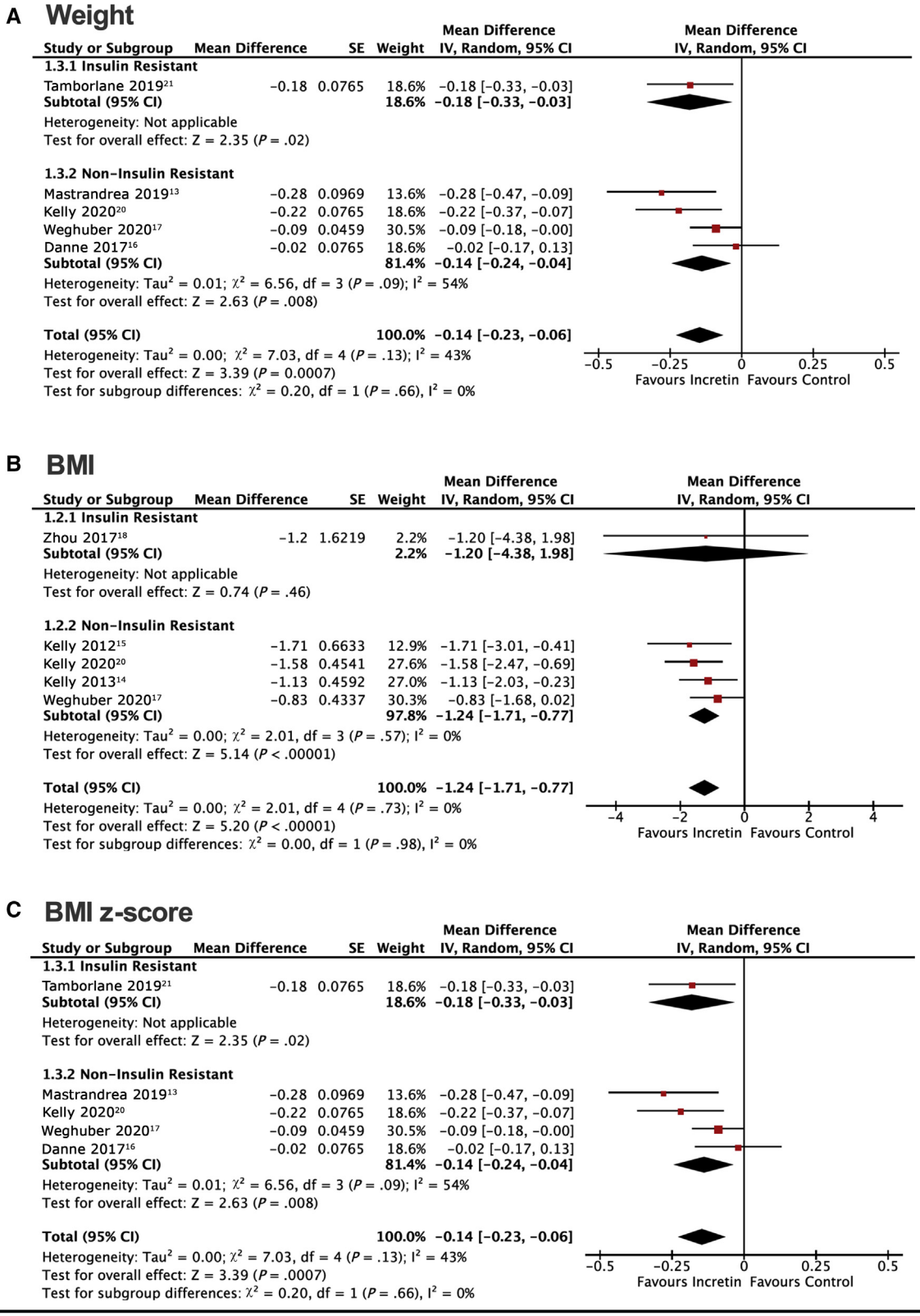


Figure 4. Subgroup analysis exploring the effects of insulin resistance on the weight, BMI, and BMI z score reducing Efficacy of GLP-1 receptor agonist intervention in children with obesity.

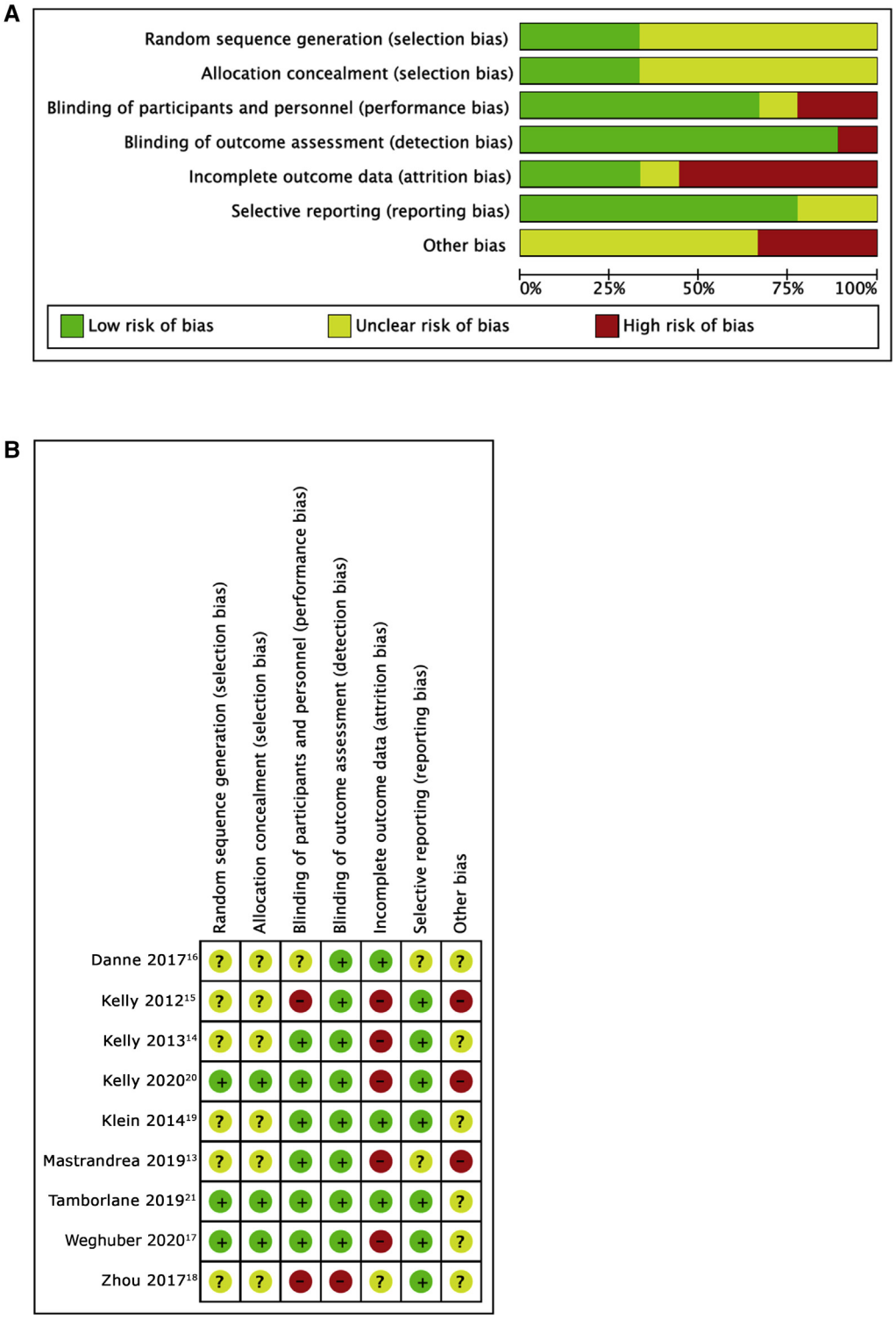


Figure 8. Risk of bias assessment. **A,** Summary of risk of bias scores across categories; **B,** Breakdown of risk of bias assessment across individual studies.

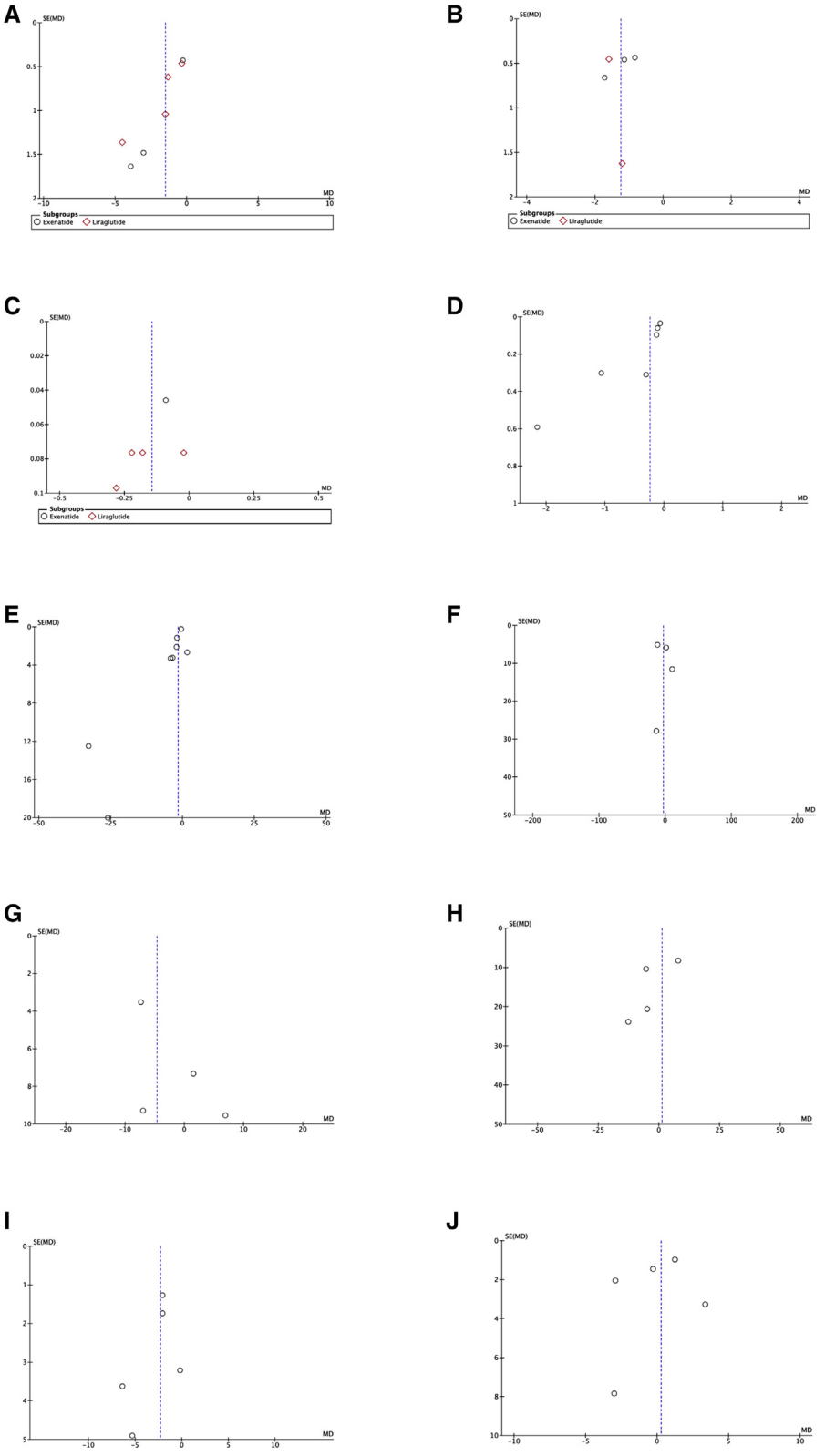


Figure 9. Detection of publication bias. Funnel plots of synthesized studies for parameters including **A,** weight, **B,** BMI, **C,** BMI z score, **D,** HbA1c, **E,** fasting plasma glucose, **F,** total cholesterol, **G,** LDL-C, **H,** triglycerides, **I,** SBP, and J, DBP. *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure.

Table I. Database search strategies and results

Databases	Strategy	Result
SCOPUS	(TITLE-ABS-KEY ("Obesity" OR "Obese" OR "Overweight") AND TITLE-ABS-KEY ("Children" OR "Child" OR "Pa*diatric" OR "Boy" OR "Girl" OR "Adolescent" OR "Teen") AND TITLE-ABS-KEY ("glucagon-like peptide-1 receptor agonists" OR "GLP-1RA" OR "Exenatide" OR "Lixisenatide" OR "Dulaglutide" OR "Liraglutide" OR "dipeptidyl peptidase-4 inhibitors" OR "DPP-4i" OR "Sitagliptin" OR "Vildagliptin" OR "Saxagliptin" OR "Linagliptin") AND TITLE-ABS-KEY ("Intervention Studies" OR "intervention" OR "controlled trial" OR "randomized" OR "randomised" OR "random" OR "randomly" OR "placebo" OR "assignment" OR "trial")) AND PUBYEAR > 1994	312
WEB OF SCIENCE	("Obesity" OR "Obese" OR "Overweight") AND TOPIC: ("Children" OR "Child" OR "Pa*diatric" OR "Boy" OR "Girl" OR "Adolescent" OR "Teen") AND TOPIC: ("glucagon-like peptide-1 receptor agonists" OR "GLP-1RA" OR "Exenatide" OR "Lixisenatide" OR "Dulaglutide" OR "Liraglutide" OR "dipeptidyl peptidase-4 inhibitors" OR "DPP-4i" OR "Sitagliptin" OR "Vildagliptin" OR "Saxagliptin" OR "Linagliptin") AND TOPIC: ("Intervention Studies" OR "intervention" OR "controlled trial" OR "randomized" OR "randomised" OR "random" OR "randomly" OR "placebo" OR "assignment" OR "trial")	51
MEDLINE	AB ("Obesity" OR "Obese" OR "Overweight") AND AB ("Children" OR "Child" OR "Pa*diatric" OR "Boy" OR "Girl" OR "Adolescent" OR "Teen") AND AB ("glucagon-like peptide-1 receptor agonists" OR "GLP-1RA" OR "Exenatide" OR "Lixisenatide" OR "Dulaglutide" OR "Liraglutide" OR "dipeptidyl peptidase-4 inhibitors" OR "DPP-4i" OR "Sitagliptin" OR "Vildagliptin" OR "Saxagliptin" OR "Linagliptin") AND AB ("Intervention Studies" OR "intervention" OR "controlled trial" OR "randomized" OR "randomised" OR "random" OR "randomly" OR "placebo" OR "assignment" OR "trial")	374

Table II. Included study design, interventions, and funding sources

Studies Author year	Study details						
	Intervention	Control	Dose regimen	Country	Setting	Design	Sponsorship source
Kelly et al 2012[15]	13 wk Exenatide + Lifestyle intervention	Volume-matched placebo pen + Lifestyle intervention	Offered lifestyle modification and initiated at a dose of 5 mcg twice daily subcutaneously. Up titrated to 10 mcg twice daily after 1 mo for the remainder of the trial. If the 10 mcg dose was not tolerated, the dose was reduced to 5 mcg.	US	Pediatric obesity/ endocrinology outpatient clinics	Crossover RCT	Minnesota Obesity Center (NIH grant P30DK050456 NORC) and GCRC (M01-RR00400, General Clinical Research Center Program, NCRR/NIH). Glucose meters donated by Bayer HealthCare.
Kelly et al 2013[14]	13 wk Exenatide	Volume-matched placebo pen	Initiated at 5 mcg twice daily. After 1 mo, up titrated to 10 mcg twice daily for the remaining 2 mo	US	Pediatric obesity/ endocrinology outpatient clinic	RCT	Community Health Collaborative grant from the University of Minnesota Clinical and Translational Science Institute, by award 1UL1RR033183 from the National Center for Research Resources, and by grant 8UL1TR000114-02 from the National Center for Advancing Translational Sciences of the National Institutes of Health.
Klein et al 2014[19]	5 wk Liraglutide	Volume-matched placebo pen	Initiated at 0.3 mg daily for first wk and increased weekly thereafter to 0.6 mg, 0.9 mg, 1.2 mg, and 1.8 mg.	Belgium Slovenia United Kingdom US	Pediatric obesity/ endocrinology outpatient clinics	RCT	Novo Nordisk
Danne et al 2017[16]	5 wk Liraglutide	Volume-matched placebo pen	Initiated at 0.6 mg daily, and the dose was increased by 0.6 mg/ wk to a maximum of 3.0 mg daily.	Germany	Novo Nordisk investigational site	RCT	Novo Nordisk
Mastrandrea et al 2019[13]	8 wk Liraglutide	Volume-matched placebo pen	Initiated at 0.3 mg daily. Dose was escalated from 0.3 to 1.2 mg in weekly increments of 0.3 mg and then followed with 0.6 mg weekly increments to a maximum dose of 3.0 mg or maximum tolerated dose.	US	Not specified	RCT	Novo Nordisk

(*continued*)

Table II. Continued

Studies Author year	Study details						
	Intervention	Control	Dose regimen	Country	Setting	Design	Sponsorship source
Kelly et al 2020[20]	56 wk Liraglutide + Lifestyle intervention	Volume-matched placebo pen + Lifestyle intervention	12-wk run-in period where all participants received lifestyle therapy (counselling about healthy nutrition and physical activity for weight loss). Treatment was initiated at a dose of 0.6 mg daily for 1 wk, increased weekly thereafter until the maximum tolerated dose or 3.0 mg daily.	Belgium Mexico Russia Sweden US	Pediatric obesity/ endocrinology outpatient Clinics	RCT	Novo Nordisk
Weghuber et al 2020[17]	26 wk Exenatide	Volume-matched placebo pen	Weekly subcutaneous injections of the Bydureon (exenatide) 2 mg.	Sweden Austria	Not specified	RCT	Regional Research Council in Uppsala-Orebro, Sweden, the Swedish Diabetes Foundation, the Swedish Society for Diabetology, Swedish Research Council (2016-01040), and AstraZeneca
Tamborlane et al 2019[21]	26 wk double blind + 26-wk open-label extension Liraglutide + Metformin	Volume-matched placebo pen + Metformin	Initiated at a dose of 0.6 mg per d. The dose was increased in 0.6-mg increments to a maximum dose of 1.8 mg per d.	25 countries	Not specified	RCT	Novo Nordisk
Zhou et al 2017[18]	3 mo Liraglutide + Lifestyle intervention	Lifestyle intervention	Initial dose was 0.6 mg daily. After 1 wk, adjusted to 1.2 mg/ daily for 3 mo	China	Pediatric obesity/ endocrinology outpatient clinics	RCT	Not stated

Table IV. Treatment emergent adverse events and potential side-effect of GLP-1RAs in children with obesity

Studies Author year	TEAE	Group/dose (mg)	Number of participants (*n*)	Proportion of participants (%)	Total events (*n*)
Klein et al 2014[19]	Hypoglycemia	0.6	3	25	4
Liraglutide	Hypoglycemia	Placebo	0	0	0
	Diarrhea	0.3	3	21.4	3
	Diarrhea	0.6	3	25	3
	Diarrhea	0.9	0	0	0
	Diarrhea	1.2	0	0	0
	Diarrhea	1.8	1	11.1	1
	Diarrhea	Placebo	1	14.3	1
	Nausea	0.3	3	21.4	3
	Nausea	0.6	0	0	0
	Nausea	0.9	0	0	0
	Nausea	1.2	0	0	0
	Nausea	1.8	1	11.1	1
	Nausea	Placebo	1	14.3	1
	Vomiting	0.3	0	0	0
	Vomiting	0.6	1	8.3	1
	Vomiting	0.9	1	11.1	1
	Vomiting	1.2	0	0	0
	Vomiting	1.8	0	0	0
	Vomiting	Placebo	2	26.3	3
Kelly et al 2012[15]	Nausea	10 mcg	4	36.36	
Exenatide	Vomiting		3	27.27	
	Headache		3	27.27	
	Abdominal pain – mild		2	18.18	
	Abdominal pain – moderate		1	9.09	
	Injection site bruising		1	9.09	
Danne et al 2017[16]	Nausea	0.6-3 mg	7	50	11
Liraglutide	Nausea	Placebo	0	0	0
	Vomiting	0.6-3 mg	4	28.6	4
	Vomiting	Placebo	0	0	0
	Diarrhea	0.6-3 mg	3	21.4	3
	Diarrhea	Placebo	0	0	0
	Abdominal pain	0.6-3 mg	4	28.6	12
	Abdominal pain	Placebo	0	0	0
	Upper abdominal pain	0.6-3 mg	2	14.3	2
	Upper abdominal pain	Placebo	0	0	0
	Distension	0.6-3 mg	1	7.1	1
	Distension	Placebo	0	0	0
	Abdominal wall hematoma	0.6-3 mg	1	7.1	1
	Abdominal wall hematoma	Placebo	0	0	0
	Injection site pain	0.6-3 mg	3	21.4	5
	Injection site pain	Placebo	0	0	0
	Injection site pruritus	0.6-3 mg	1	7.1	1
	Injection site pruritus	Placebo	0	0	0
	Transaminase elevation	0.6-3 mg	1	7.1	1
	Transaminase elevation	Placebo	0	0	0
	Alopecia	0.6-3 mg	1	7.1	1
	Alopecia	Placebo	0	0	0
	Hematoma	0.6-3 mg	1	7.1	1
	Hematoma	Placebo	0	0	0
	Hypoglycemic episodes	0.6-3 mg	2	14.3	3
	Hypoglycemic episodes	Placebo	0	0	0
	Nervous system disorders	0.6-3 mg	7	50	13
	Nervous system disorders	Placebo	1	14.3	1
	Infection	0.6-3 mg	6	42.9	6
	Infection	Placebo	2	28.6	2
	MSK	0.6-3 mg	3	21.4	3
	MSK	Placebo	0	0	0
	Reproductive system/breast disorders	0.6-3 mg	3	21.4	3
	Reproductive system/breast disorders	Placebo	0	0	0
	Respiratory and mediastinal	0.6-3 mg	2	14.3	5
	Respiratory and mediastinal	Placebo	1	14.3	1
	Skin and subcutaneous	0.6-3 mg	2	14.3	2
	Skin and subcutaneous	Placebo	0	0	0
	Injury and procedural complications	0.6-3 mg	1	7.1	1
	Injury and procedural complications	Placebo	0	0	0
	Vascular disorders	0.6-3 mg	1	7.1	2
	Vascular disorders	Placebo	0	0	0
Mastrandrea et al 2019[13]	GI	0.3-3 mg	6	37.5	19

(*continued*)

Table IV. Continued

Studies Author year	TEAE	Group/dose (mg)	Number of participants (*n*)	Proportion of participants (%)	Total events (*n*)
Liraglutide	GI	Placebo	1	12.5	1
	Nausea	0.3-3 mg	2	12.5	2
	Nausea	Placebo	0	0	0
	Vomiting	0.3-3 mg	4	25	5
	Vomiting	Placebo	0	0	0
	Diarrhea	0.3-3 mg	1	6.3	1
	Diarrhea	Placebo	0	0	0
	Abdominal pain upper	0.3-3 mg	1	6.3	5
	Abdominal pain upper	Placebo	0	0	0
	Dyspepsia	0.3-3 mg	0	0	0
	Dyspepsia	Placebo	1	12.5	1
	Salivary hypersecretion	0.3-3 mg	1	6.3	1
	Salivary hypersecretion	Placebo	0	0	0
	Headache	0.3-3 mg	2	12.5	2
	Headache	Placebo	0	0	0
	Dizziness	0.3-3 mg	1	6.3	1
	Dizziness	Placebo	0	0	0
	Injection site induration	0.3-3 mg	2	12.5	2
	Injection site induration	Placebo	0	0	0
	Injection site reaction	0.3-3 mg	1	6.3	1
	Injection site reaction	Placebo	0	0	0
	Orbital edema	0.3-3 mg	1	6.3	1
	Orbital edema	Placebo	0	0	0
	Increased ALT	0.3-3 mg	0	0	0
	Increased ALT	Placebo	1	12.5	1
	Nervous system disorders	0.3-3 mg	3	18.8	4
	Nervous system disorders	Placebo	4	50	5
	General and site conditions	0.3-3 mg	3	18.8	4
	General and site conditions	Placebo	1	12.5	1
	Infection	0.3-3 mg	2	12.5	2
	Infection	Placebo	1	12.5	1
	MSK	0.3-3 mg	1	6.3	1
	MSK	Placebo	1	12.5	2
	Respiratory and mediastinal	0.3-3 mg	2	12.5	4
	Respiratory and mediastinal	Placebo	0	0	0
	Ear	0.3-3 mg	1	6.3	1
	Ear	Placebo	0	0	0
	Eye	0.3-3 mg	1	6.3	1
	Eye	Placebo	0	0	0
	Injury and procedural complications	0.3-3 mg	0	0	0
	Injury and procedural complications	Placebo	1	12.5	1
	Skin and subcutaneous	0.3-3 mg	1	6.3	1
	Skin and subcutaneous	Placebo	0	0	0
	Hypoglycemic episodes	0.3-3 mg	4	25	5
	Hypoglycemic episodes	Placebo	1	12.5	1
Weghuber et al 2020[17]	GI	2 mg			

(*continued*)

Table IV. Continued

Studies Author year	TEAE	Group/dose (mg)	Number of participants (*n*)	Proportion of participants (%)	Total events (*n*)
Exenatide	GI	Placebo			
	Nervous system disorders	2 mg	1	72.7	
	Nervous system disorders	Placebo	1	59.1	
	General and site conditions	2 mg	1	50	
	General and site conditions	Placebo	9	40.9	
	Infection	2 mg	1	81.8	
	Infection	Placebo	2	90.9	
	MSK	2 mg	5	22.7	
	MSK	Placebo	6	27.3	
	Respiratory and mediastinal	2 mg	8	36.4	
	Respiratory and mediastinal	Placebo	8	36.4	
	Ear	2 mg	2	9.1	
	Ear	Placebo	0	0	
	Eye	2 mg	1	4.6	
	Eye	Placebo	1	4.6	
	Injury and procedural complications	2 mg	5	22.7	
	Injury and procedural complications	Placebo	3	13.6	
	Skin and subcutaneous	2 mg	5	22.7	
	Skin and subcutaneous	Placebo	1	4.6	
	Hypoglycemic episodes	2 mg	0	0	
	Hypoglycemic episodes	Placebo	0	0	
	Blood and lymph	2 mg	0	0	
	Blood and lymph	Placebo	2	9.1	
	Endocrine disorders	2 mg	1	4.6	
	Endocrine disorders	Placebo	0	0	
	Immune system disorders	2 mg	1	4.6	
	Immune system disorders	Placebo	0	0	
	Metabolism and nutrition	2 mg	2	9.1	
	Metabolism and nutrition	Placebo	2	9.1	
	Psychiatric disorders	2 mg	1	4.6	
	Psychiatric disorders	Placebo	2	9.1	
	Renal and urinary disorders	2 mg	2	9.1	
	Renal and urinary disorders	Placebo	0	0	
	Reproductive system and breast	2 mg	5	22.7	
	Reproductive system and breast	Placebo	1	4.6	
	Social	2 mg	1	4.6	
	Social	Placebo	0	0	
Kelly et al 2020[20]	Nausea	0.6-3 mg	5	42.4	101

(*continued*)

Table IV. Continued

Studies Author year	TEAE	Group/dose (mg)	Number of participants (*n*)	Proportion of participants (%)	Total events (*n*)
Liraglutide	Nausea	Placebo	1	14.3	25
	Vomiting	0.6-3 mg	4	34.4	85
	Vomiting	Placebo	5	4	8
	Diarrhea	0.6-3 mg	2	22.4	44
	Diarrhea	Placebo	1	14.3	29
	Abdominal pain upper	0.6-3 mg	1	13.6	25
	Abdominal pain upper	Placebo	1	13.5	23
	Abdominal pain	0.6-3 mg	1	8	15
	Abdominal pain	Placebo	1	8.7	15
	URTI	0.6-3 mg	1	8.8	14
	URTI	Placebo	1	8.7	16
	Nasopharyngitis	0.6-3 mg	3	27.2	68
	Nasopharyngitis	Placebo	3	30.2	80
	Headache	0.6-3 mg	2	23.2	43
	Headache	Placebo	3	27.8	53
	Oropharyngeal pain	0.6-3 mg	1	8.8	11
	Oropharyngeal pain	Placebo	1	11.9	18
	Influenza	0.6-3 mg	1	8.8	11
	Influenza	Placebo	1	9.5	12
	Gastroenteritis	0.6-3 mg	1	12.8	22
	Gastroenteritis	Placebo	6	4.8	9
	Pyrexia	0.6-3 mg	1	8	11
	Pyrexia	Placebo	9	7.1	11
	Dizziness	0.6-3 mg	1	10.4	15
	Dizziness	Placebo	4	3.2	5
	Dysmenorrhea	0.6-3 mg	4	3.2	5
	Dysmenorrhea	Placebo	8	6.3	16
	Arthralgia	0.6-3 mg	3	2.4	3
	Arthralgia	Placebo	8	6.3	8
	Pharyngitis	0.6-3 mg	4	3.2	5
	Pharyngitis	Placebo	7	5.6	7
	Hypoglycemia	0.6-3 mg	2	0	0
	Hypoglycemia	Placebo	1	0	0
Kelly et al 2013[14]	Nausea	10-20 mcg		62	
Exenatide	Nausea	Placebo		31	
	Abdominal pain	10-20 mcg		15	
	Abdominal pain	Placebo		23	
	Diarrhea	10-20 mcg		8	
	Diarrhea	Placebo		31	
	Headache	10-20 mcg		23	
	Headache	Placebo		46	
	Vomiting	10-20 mcg		31	
	Vomiting	Placebo		8	
	Hypoglycemia	10-20 mcg		0	
	Hypoglycemia	Placebo		0	
Tamborlane et al 2019[21]	Nausea	0.6-1.8 mg	19	28.8	25

(*continued*)

Table IV. Continued

Studies Author year	TEAE	Group/dose (mg)	Number of participants (*n*)	Proportion of participants (%)	Total events (*n*)
Liraglutide	Nausea	Placebo	9	13.2	12
	Vomiting	0.6-1.8 mg	17	25.8	46
	Vomiting	Placebo	6	8.8	8
	Diarrhea	0.6-1.8 mg	15	22.7	22
	Diarrhea	Placebo	11	16.2	13
	Headache	0.6-1.8 mg	14	21.2	27
	Headache	Placebo	13	19.1	39
	Abdominal pain	0.6-1.8 mg	12	18.2	23
	Abdominal pain	Placebo	5	7.4	6
	Nasopaharyngitis	0.6-1.8 mg	11	16.7	16
	Nasopaharyngitis	Placebo	19	27.9	28
	Dizziness	0.6-1.8 mg	8	12.1	10
	Dizziness	Placebo	2	2.9	4
	Gastroenteritis	0.6-1.8 mg	7	10.6	8
	Gastroenteritis	Placebo	2	2.9	2
	URTI	0.6-1.8 mg	6	9.1	10
	URTI	Placebo	5	7.4	8
	Dyspepsia	0.6-1.8 mg	5	7.6	6
	Dyspepsia	Placebo	1	1.5	1
	Rash	0.6-1.8 mg	4	6.1	5
	Rash	Placebo	1	1.5	1
	Pyrexia	0.6-1.8 mg	4	6.1	5
	Pyrexia	Placebo	5	7.4	5
	Decreased appetite	0.6-1.8 mg	4	6.1	4
	Decreased appetite	Placebo	3	4.4	3
	Constipation	0.6-1.8 mg	4	6.1	4
	Constipation	Placebo	1	1.5	1
	Dysmenorrhea	0.6-1.8 mg	3	4.5	10
	Dysmenorrhea	Placebo	6	8.8	11
	Upper abdominal pain	0.6-1.8 mg	2	3	3
	Upper abdominal pain	Placebo	8	11.8	9
	Increased alanine aminotransferase	0.6-1.8 mg	0	0	0
	Increased alanine aminotransferase	Placebo	4	5.9	5
	Hypoglycemia	0.6-1.8 mg	30	45.5	160
	Hypoglycemia	Placebo	17	25	63

ALT, alanine aminotransferase; *URTI*, upper respiratory tract infection; *MSK*, musculoskeletal.