

# EFFICACY AND TOLERABILITY OF GLP-1 RECEPTOR AGONISTS IN CHILDREN AND ADOLESCENTS WITH OBESITY: A META-ANALYSIS

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## INTRODUCTION

- Prevalence of **pediatric obesity** is approaching **1 in 5** children and adolescents aged 2-19 years in the US.
- For these children, and particularly those with severe obesity, pediatricians have a **paucity of safe, effective and durable weight-reducing pharmaceutical interventions** with high-grade evidence.
- While **GLP-1 receptor agonists have proven to be effective** in reducing weight and improving glucose control in adults, their effects in children and adolescents with obesity is less clear.

## AIM

This meta-analysis study aimed to determine the:

- Weight effects
- BMI/BMI z-score effects
- Cardiometabolic effects
- Gastrointestinal side-effects of GLP-1 receptor agonists in children with obesity.

## METHOD

### Databases & Searching

Web of Science, PubMed/MEDLINE, and Scopus databases were searched 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 Abstraction

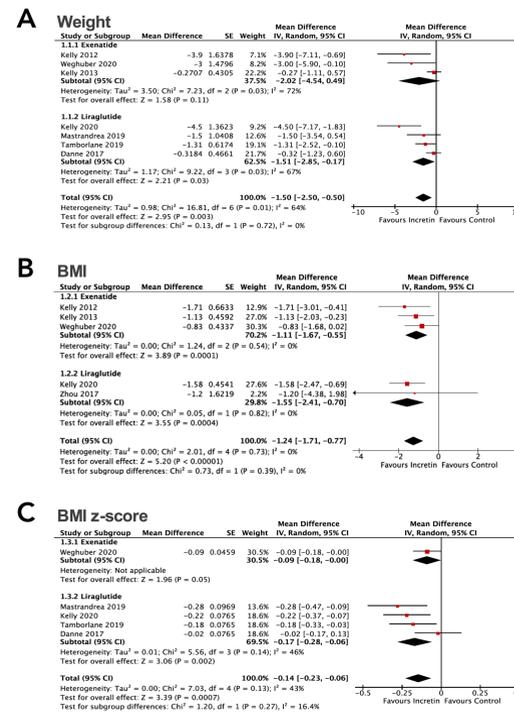
Data were extracted by two independent surveyors and a random effects model was applied to meta-analyze generic inverse variance outcomes.

### Primary Outcomes

Related to weight and cardiometabolic profile, while secondary outcomes of interest were gastrointestinal-related treatment-emergent adverse events.

## RESULTS

- 9 studies with 574 participants were identified, of which 3 involved exenatide and 6 involved liraglutide.
- Figure 1 | GLP-1 receptor agonists use caused a modest reduction in body weight (mean difference [MD] -1.50 [-2.50,-0.50] kg, I<sup>2</sup> 64%), BMI (MD -1.24 [-1.71,-0.77] kg/m<sup>2</sup>, I<sup>2</sup> 0%), and BMI z-score (MD -0.14 [-0.23,-0.06], I<sup>2</sup> 43%).**
- Figure 2 | Glycemic control was improved in children with proven insulin resistance (HbA1c MD -1.05 [-1.93,-0.18] %, I<sup>2</sup> 76%).**
- Figure 3 | Although no lipid profile improvements were noted, a modest decrease in systolic blood pressure was detected (MD -2.30 [-4.11,-0.49] mmHg; I<sup>2</sup> 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<sup>2</sup> 0%), without significant increases in other gastrointestinal symptoms.



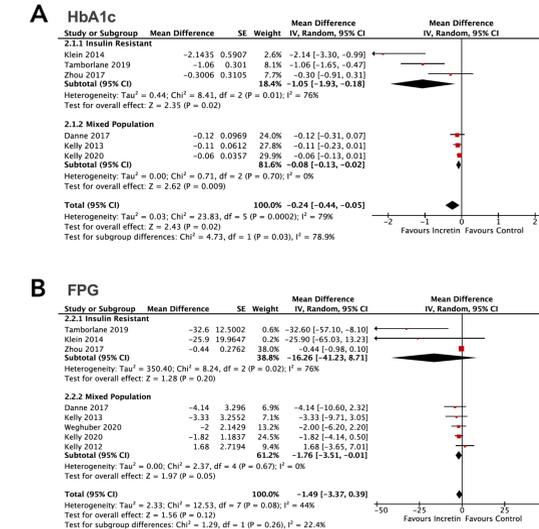
**Figure 1 | Forrest Plot of Mean Difference Change in Weight BMI, and BMI z-score Following GLP-1 Receptor Agonist Intervention in Children with Obesity.** Studies are subgrouped by the specific intervention. BMI, body mass index.

## CONCLUSIONS

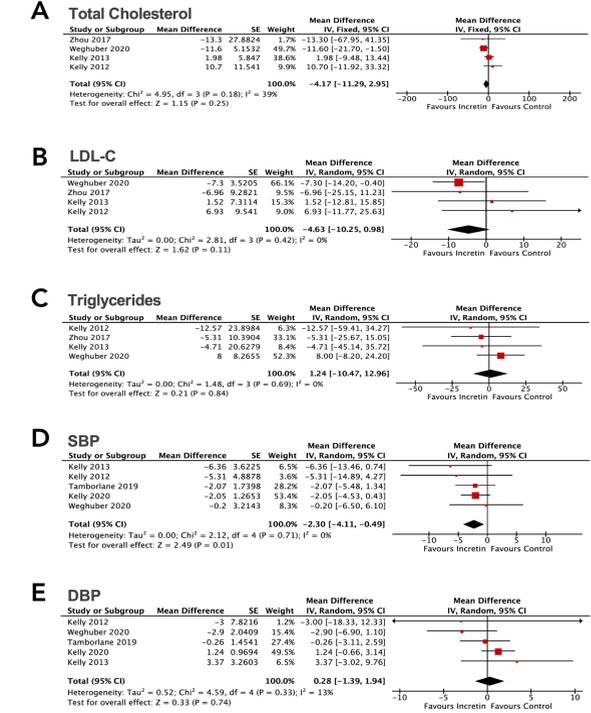
- The two GLP-1RAs uncovered in the paediatric obesity literature were exenatide and liraglutide.
- In children and adolescents with obesity, GLP-1RAs:
  - Were effective in modestly reducing weight
  - Improved glycaemic control
  - Reduced systolic blood pressure
  - Are well tolerated despite increased nausea
  - Do not commonly cause pancreatitis or MTC
- This SRMA is limited by the fact that roughly half of the synthesised data arose from a single RCT.

## INCLUDED RCTS

- Kelly et al.** Exenatide as a weight-loss therapy in extreme pediatric obesity: a randomized, controlled pilot study. Obesity (Silver Spring). 2012;20:364-70.
- Kelly et al.** The effect of glucagon-like peptide-1 receptor agonist therapy on body mass index in adolescents with severe obesity: a randomized, placebo-controlled, clinical trial. JAMA Pediatr. 2013;167:355-60.
- Klein et al.** Liraglutide's safety, tolerability, pharmacokinetics, and pharmacodynamics in pediatric type 2 diabetes: a randomized, double-blind, placebo-controlled trial. Diabetes Technol Ther. 2014;16:679-87.
- Danne, et al.** Liraglutide in an Adolescent Population with Obesity: A Randomized, Double-Blind, Placebo-Controlled 5-Week Trial to Assess Safety, Tolerability, and Pharmacokinetics of Liraglutide in Adolescents Aged 12-17 Years. J Pediatr. 2017;181:146-53 e3.
- Zhou et al.** The effects of GLP-1 analogues on pre-diabetes of the children. Exp Ther Med. 2017;13:1426-30.
- Tamborlane et al.** Liraglutide in Children and Adolescents with Type 2 Diabetes. The New England journal of medicine. 2019;381:637-46.
- Mastrandrea et al.** Liraglutide effects in a paediatric (7-11 y) population with obesity: A randomized, double-blind, placebo-controlled, short-term trial to assess safety, tolerability, pharmacokinetics, and pharmacodynamics. Pediatr Obes. 2019;14:e12495.
- Kelly et al.** A Randomized, Controlled Trial of Liraglutide for Adolescents with Obesity. The New England journal of medicine. 2020;382:2117-28.
- Weghuber et al.** A 6-month randomized, double-blind, placebo-controlled trial of weekly exenatide in adolescents with obesity. Pediatr Obes. 2020;15:e12624.



**Figure 2 | 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 (i.e., type-2 diabetes or prediabetes) or not (i.e., mixed population). HbA1c, glycated hemoglobin; FPG, fasting plasma glucose.



**Figure 3 | Forrest Plot of Mean Difference Change in Cardiovascular Parameters Following GLP-1 Receptor Agonist Intervention in Children with Obesity.** LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure.

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