# Newer Glucose-Lowering Drugs and Risk of Depression: A Meta-Analysis of Randomized Outcomes Trials

**Huilin Tang[1], Ying Lu[1], Pareeta Kotecha[1], William Donahoo[2], Jiang Bian[3], Jingchuan Guo[1]**

[1]Department of Pharmaceutical Outcomes and Policy, [2]Division of Endocrinology, Diabetes and Metabolism, [3]Department of Health Outcomes and Biomedical Informatics, University of Florida, Gainesville, Florida, USA

## Background

- Preclinical studies have indicated that newer glucose-lowering drugs (GLDs), i.e., dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs), and sodium-glucose co-transporter-2 (SGLT2) inhibitors, may have antidepressant effects.
- However, data from population studies remain limited and controversial.

## Objective

- This meta-analysis of randomized outcome trials aimed to evaluate the effects of DPP-4 inhibitors, GLP-1RAs, and SGLT2 inhibitors on risk of depression among people with or without type 2 diabetes (T2D).

## Methods

- **Electronic databases:** PubMed, Embase, and CENTRAL from inception to November, 2023.
- **Inclusion criteria:** Randomized cardiovascular and renal outcome trials that reported the depression associated with DPP-4 inhibitors, GLP-1RAs, and SGLT2 inhibitors in patients with or without T2D.
- **Outcomes of interest:** Depression identiied using MedDRA "Preferred Term".
- **Risk of bias assessment:** Low, high, or unclear for six domains based on Cochrane risk of bias tool.
- **Statistical analysis:** We calculated the pooled odds ratio (OR) with 95% confidence interval (CI) using Peto's method.

## Results

- Twenty-six randomized outcome trials were included
  - ✓ DPP-4 inhibitors: 5 trials
  - ✓ GLP-1RAs:8 trials
  - ✓ SGLT2 inhibitors:13 trials
- Median follow-up: 2.2 years (range: 0.8 - 5.4) years
- Risk of bias was judged as low except for the selective reporting domain (unclear).

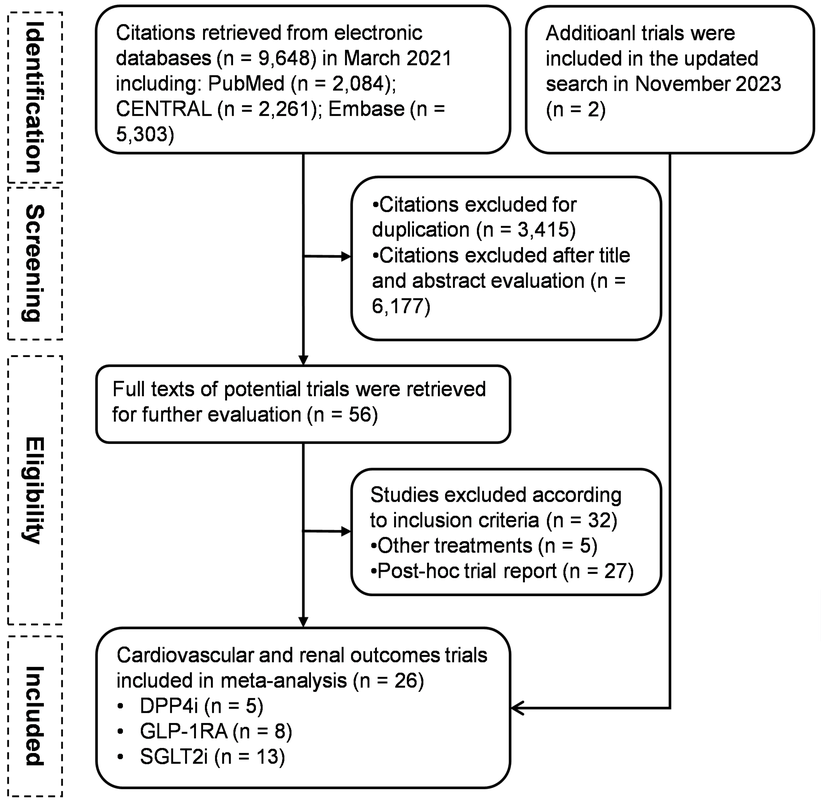


**Fig 1. Flowchart of trial selection**

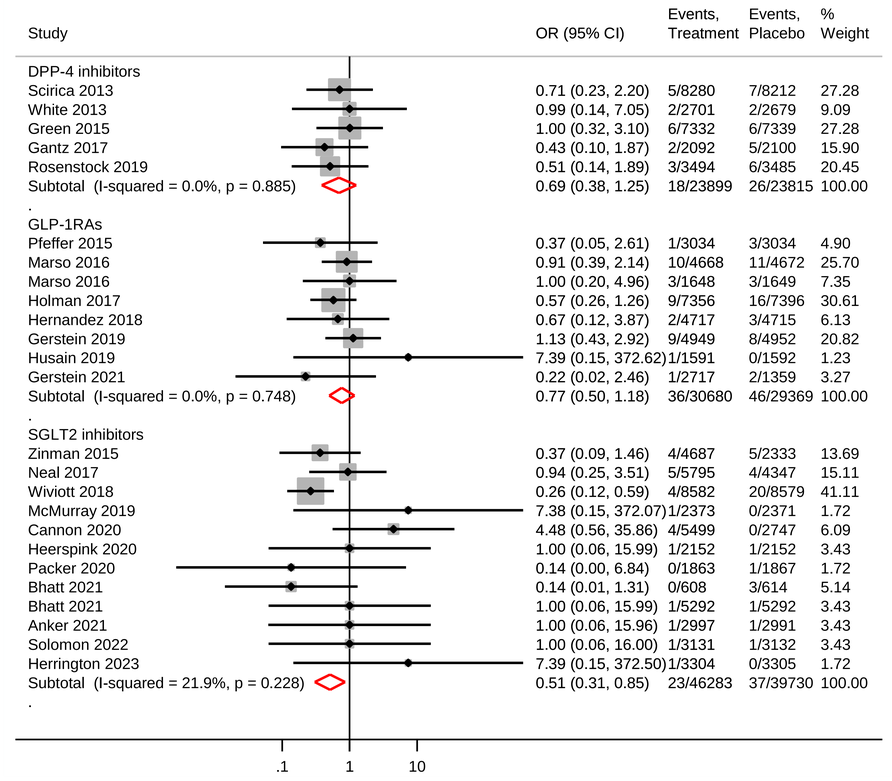


**Fig 2.** Meta-analysis of the association between each class of newer GLD and risk of depression in participants with or without T2D

## Conclusions

- SGLT2 inhibitors may be associated with a lower risk of depression, whereas no significant decrease in the risk was observed for GLP-1RAs and DPP-4 inhibitors.
- Comparative effectiveness studies using real-world data are warranted to confirm our findings.

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