

Comparative Risk of Dementia for GLP-1 Agonists vs Other Diabetes Treatments in Older Adults With Type 2 Diabetes: A Target Trial Emulation



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Use of tirzepatide or semaglutide was associated with a lower risk of dementia compared with other diabetes treatments in patients over 60 years with type 2 diabetes and overweight or obesity.

INTRODUCTION

- 6 million adults in the US lived with dementia in 2020 and expect 1 million incident cases by 2060¹
- Limited pharmacological treatments, but **modifiable risk factors** including diabetes, obesity, and cardiovascular diseases²
- Semaglutide** (GLP-1 agonist) and **tirzepatide** (dual GLP-1/GIP agonist) approved for diabetes and weight management and shown to be superior to older-generation drugs³⁻⁶
- Evoke trials found no benefit of oral semaglutide in early disease, but potential of more potent formulations for primary prevention remains unclear
- Given recent approval, need for evidence on potential of these drugs for dementia prevention using recent data

Objective: Compare the risk of incident all-cause dementia in new users of GLP-1 agonists (semaglutide or tirzepatide) vs SGLT2 inhibitors, DPP4 inhibitors, and sulfonylureas

METHODS

Data source: Komodo Health, a US national claims data source containing longitudinal information on medical encounters, pharmaceutical fills, and socio-demographic information

Study period: May 1st, 2022, to December 31st, 2025

Component	Target Trial	Emulation
Eligibility	- Type 2 diabetes - BMI$\geq$25 - Age $\geq$60 years - No prior dementia - No type 1 diabetes - No prior use of study drugs - No contraindication for treatment	- Same, with medical conditions identified using ICD-10 codes associated with claims - Additionally require 12 months of prior continuous insurance coverage
Treatment strategies	3 emulated trials: a) Initiate GLP-1* vs SGLT2 b) Initiate GLP-1* vs DPP4 c) Initiate GLP-1* vs sulfonylureas *GLP1s include semaglutide and tirzepatide	Same, using date of first fill as date of treatment start (index date)
Treatment assignment	Random assignment	Inverse probability of treatment weighting (IPTW)
Outcome	All-cause dementia diagnosis	Same
Follow-up	From assignment until outcome, death, loss to follow-up, study end, or 2 years after baseline	Same, but follow-up starts 90 days after treatment start to reduce reverse causality
Causal contrast	Intention-to-treat Per-protocol	Observational analog of intention-to-treat and of per-protocol using inverse probability of censoring weighting (IPCW)
Statistical Analysis	- Kaplan-Meier cumulative incidence curves - Cox proportional hazards model for hazard ratio	- Weighted Kaplan-Meier curves - Weighted Cox proportional hazards model with robust variance

Table 1. Target Trial Emulation Components.

RESULTS

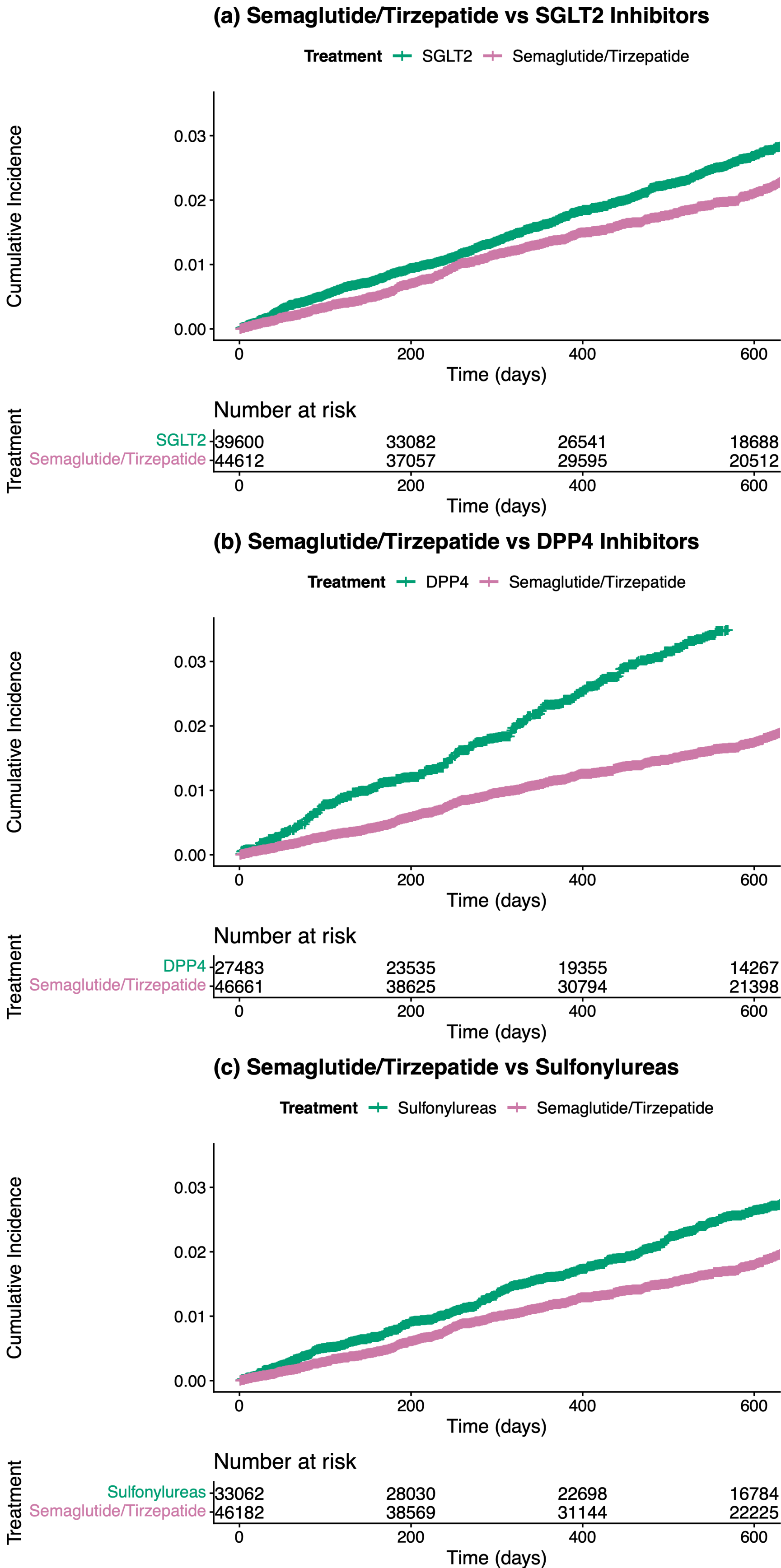


Figure 1. IPTW-Weighted Kaplan-Meier Survival Curves for All-Cause Dementia.

RESULTS

Variable	GLP-1 Agonists (N=58,828)	SGLT2 Inhibitors (N=46,797)	DPP4 Inhibitors (N=8,583)	Sulfonylureas (N=22,183)
Age (years), Mean (SD)	68.6 (5.81)	71.7 (6.93)	71.9 (7.09)	71.2 (6.67)
Male	23,453 (39.9%)	25,750 (55.0%)	3,814 (44.4%)	11,476 (51.7%)
Insurance plan type				
Medicare	16,144 (27.4%)	15,331 (32.8%)	2,852 (33.2%)	6,156 (27.8%)
Commercial	15,123 (25.7%)	7,311 (15.6%)	1,223 (14.2%)	3,078 (13.9%)
Medicaid	554 (0.9%)	700 (1.5%)	163 (1.9%)	297 (1.3%)
Missing	27,007 (45.9%)	23,455 (50.1%)	4,345 (50.6%)	12,652 (57.0%)
BMI category				
25-29.9	6,421 (10.9%)	12,957 (27.7%)	2,732 (31.8%)	6,656 (30.0%)
30-34.9	19,179 (32.6%)	17,558 (37.5%)	3,294 (38.4%)	8,446 (38.1%)
35-39.9	16,699 (28.4%)	9,392 (20.1%)	1,543 (18.0%)	4,280 (19.3%)
40+	16,529 (28.1%)	6,890 (14.7%)	1,014 (11.8%)	2,801 (12.6%)

Table 2. Key Patient Characteristics by Group.

- Semaglutide and tirzepatide** users tend to be **younger, female, White, on commercial insurance**, and have **higher BMI at baseline**
- Semaglutide and tirzepatide found to be **protective for dementia** compared with SGLT2, DPP4, and sulfonylureas (results consistent in sensitivity analyses)
- Strongest compared with DPP4, but residual confounding after IPTW for that group

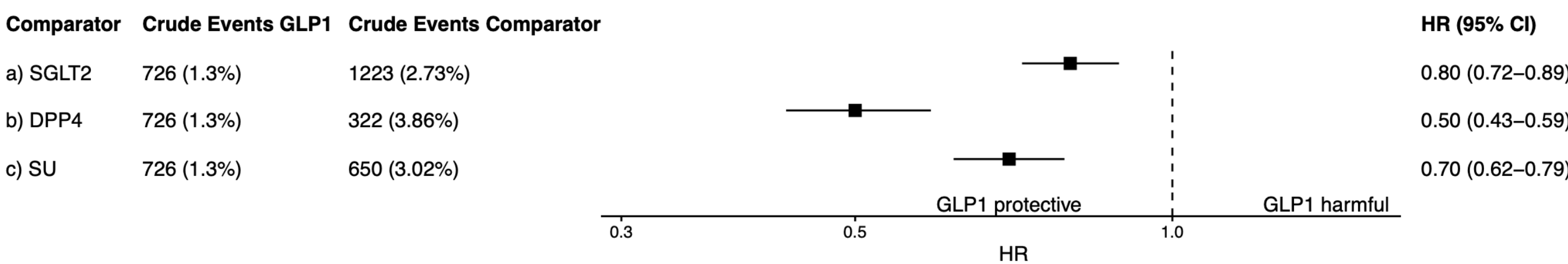


Figure 1. Forest Plot for IPTW-Weighted Hazard Ratio for All-Cause Dementia.

CONCLUSIONS

- Protective association between use of semaglutide/tirzepatide compared with other diabetes treatments in patients over 60 with T2D and overweight or obesity
- Results support the potential of these medications for primary prevention of dementia in patients with modifiable risk factors

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