Comparative Risks of Dementia and Parkinson's Disease with GLP-1 RAs versus Other Oral Glucose-Lowering Medications in Obese Patients with Type 2 Diabetes: A Large Real-World Cohort Study

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Background

- Type 2 diabetes raises dementia risk by ~59% and Parkinson's disease (PD) risk by ~27%; midlife obesity adds further dementia risk.
- GLP-1 receptor agonists (GLP-1 RAs) act on brain GLP-1 receptors and are neuroprotective in preclinical studies: less neuroinflammation, better neuronal insulin signalling, improved neuronal survival.
- Large real-world comparisons with other glucose-lowering drugs are limited.

Objective

To compare the risks of dementia and Parkinson's disease in adults with type 2 diabetes and obesity initiating GLP-1 RAs versus other oral glucose-lowering medications.

Methods

- **Design:** historical prospective, active-comparator new-user cohort using Clalit Health Services electronic health records (4.7 million members, 53% of Israel's population).
- **Population:** adults ≥40 y with T2D and BMI ≥30 kg/m² initiating non-insulin glucose-lowering drugs, 2008–2021.
- **Matching:** 1:1 nearest-neighbor on age, sex, BMI category, diabetes duration and calendar year of initiation.
- **Outcomes:** incident all-cause dementia and PD (validated diagnosis codes); follow-up to November 2023.
- **Analysis:** multivariable Cox models; secondary comparisons by drug class (sulfonylureas, DPP-4 and SGLT2 inhibitors); subgroups by sex and age.

Study population

46,962 matched adults with T2D and obesity · median follow-up ~7 years

90,061 CHS members with T2D initiating non-insulin glucose-lowering drugs, 2008–2021 (age ≥40, BMI ≥30 kg/m²)

↓ 14,842 excluded*

75,219 potentially eligible patients

↓ 1:1 nearest-neighbor matching

23,481 GLP-1 RA initiators	**23,481** initiators of other oral agents

*Active cancer or end-stage renal disease (prior 2 y), pregnancy, ischemic stroke, prior dementia or PD, insulin therapy.

Baseline characteristics after matching

Characteristic	GLP-1 RA	Other agents
Age, y, mean (SD)	61.2 (9.8)	64.3 (10.2)
Women	58.6%	46.6%
BMI, kg/m², mean (SD)	35.9 (5.1)	33.7 (3.5)
HbA1c, %, mean (SD)	8.9 (1.6)	8.1 (1.6)
Diabetes duration, y, mean (SD)	14.0 (8.9)	4.4 (3.4)
Hypertension	74.7%	70.2%

Incidence per 10,000 person-months

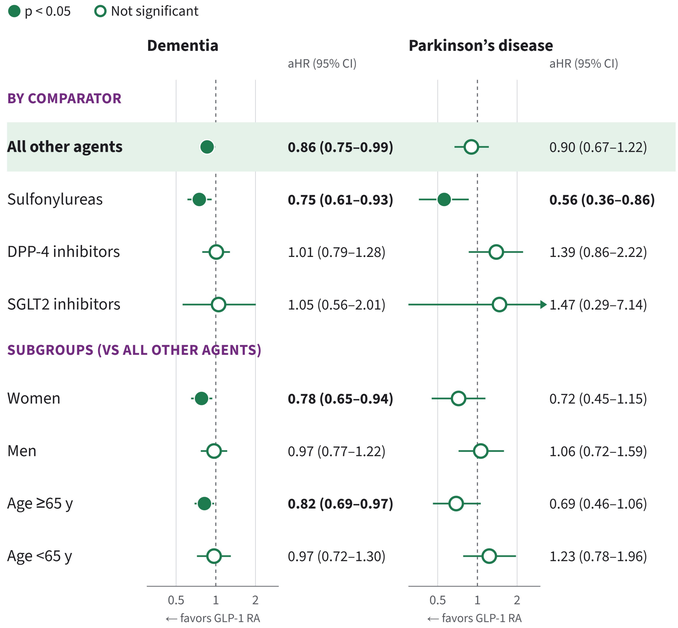
Dementia · 1,125 (4.8%) vs 1,822 (7.8%) cases



Parkinson's disease · 231 (1.0%) vs 338 (1.4%) cases



GLP-1 RA vs comparators: adjusted hazard ratios



Multivariable Cox models. Drug-class comparisons keep the original 1:1 matched pairs. Arrow: CI extends beyond axis (upper limit 7.14).

Statistical power

>99% power for the primary dementia comparison, but <30% for Parkinson's disease (569 events). PD findings should be interpreted cautiously.

Key findings

14%

lower dementia risk vs all other oral agents

aHR 0.86 (0.75–0.99)

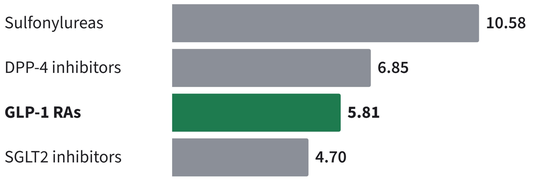
0.90

Parkinson's disease: no significant difference overall

aHR (0.67–1.22)

Dementia incidence by drug class

Cases per 10,000 person-months



Conclusions

- GLP-1 RA initiation was associated with **lower dementia risk** than other oral glucose-lowering drugs, most clearly versus sulfonylureas.
- Associations were stronger in **women** and adults **≥65 years**.
- Brain health should be considered when choosing diabetes therapy; randomized trials are needed to confirm causality.

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