

Glucagon-like Peptide-1 Receptor Agonists and Dementia Risk in Type 2 Diabetes: A Systematic Review and Meta-analysis

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KEY TAKEAWAY

In adults with T2DM, GLP-1RA use was associated with 23% lower risk of incident Alzheimer's disease (pooled HR 0.77, 95% CI 0.69–0.87) and 40% lower risk of dementia/ADRD (pooled HR 0.60, 95% CI 0.55–0.66) versus active antidiabetic comparators — findings that are associative and support prioritization of dedicated long-term RCTs.

BACKGROUND

- ▶ T2DM increases risk of AD and ADRD
- ▶ GLP-1RAs may exert neuroprotective effects via anti-inflammatory, anti-oxidative, and anti-amyloid/tau mechanisms
- ▶ Real-world evidence remains heterogeneous across cohorts and comparator groups

OBJECTIVE

Synthesize comparative evidence on GLP-1RAs vs active antidiabetics for incident AD and dementia/ADRD in T2DM

METHODS

Design: Systematic review & meta-analysis (PRISMA 2020)

Search: PubMed & Europe PMC through Oct 10, 2025

Population: Adults with T2DM, free of dementia at baseline

Comparators: Active antidiabetics (DPP-4i or other)

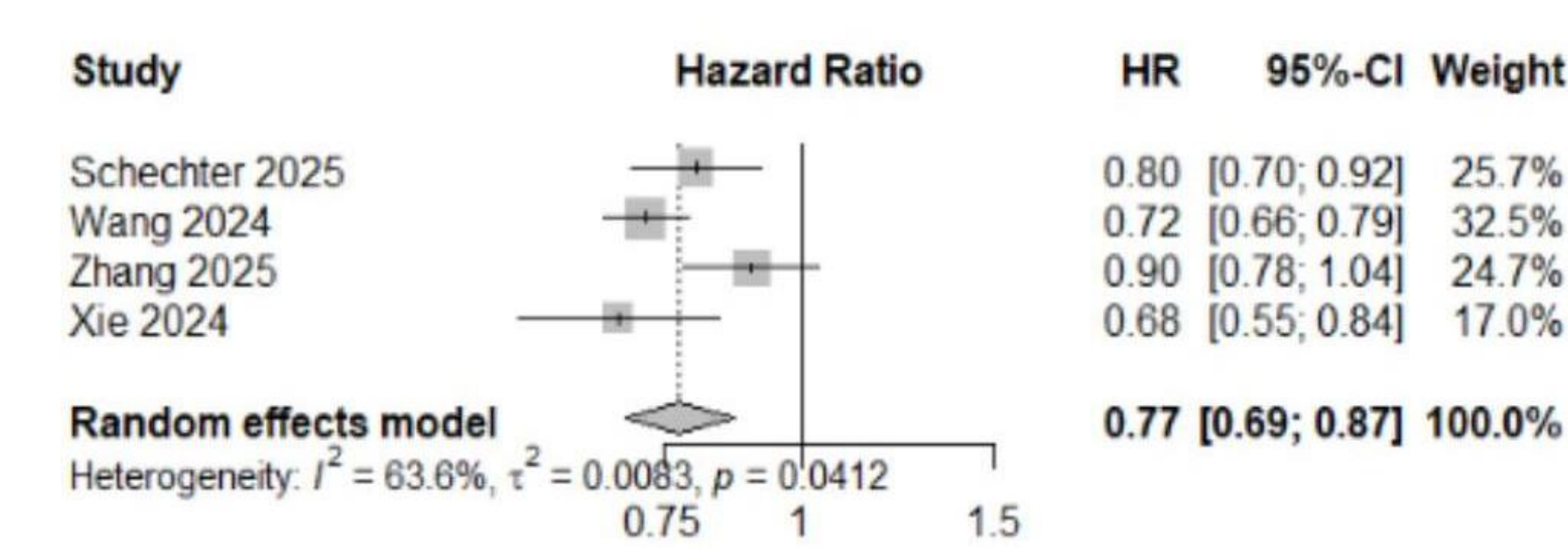
Statistics: Random-effects REML; I² for heterogeneity

Risk of bias: ROBINS-I (observational) / RoB 2 (RCTs)

4,663 records identified
90 full-texts reviewed → 7 studies included
4 studies → AD meta-analysis | 3 studies → Dementia/ADRD

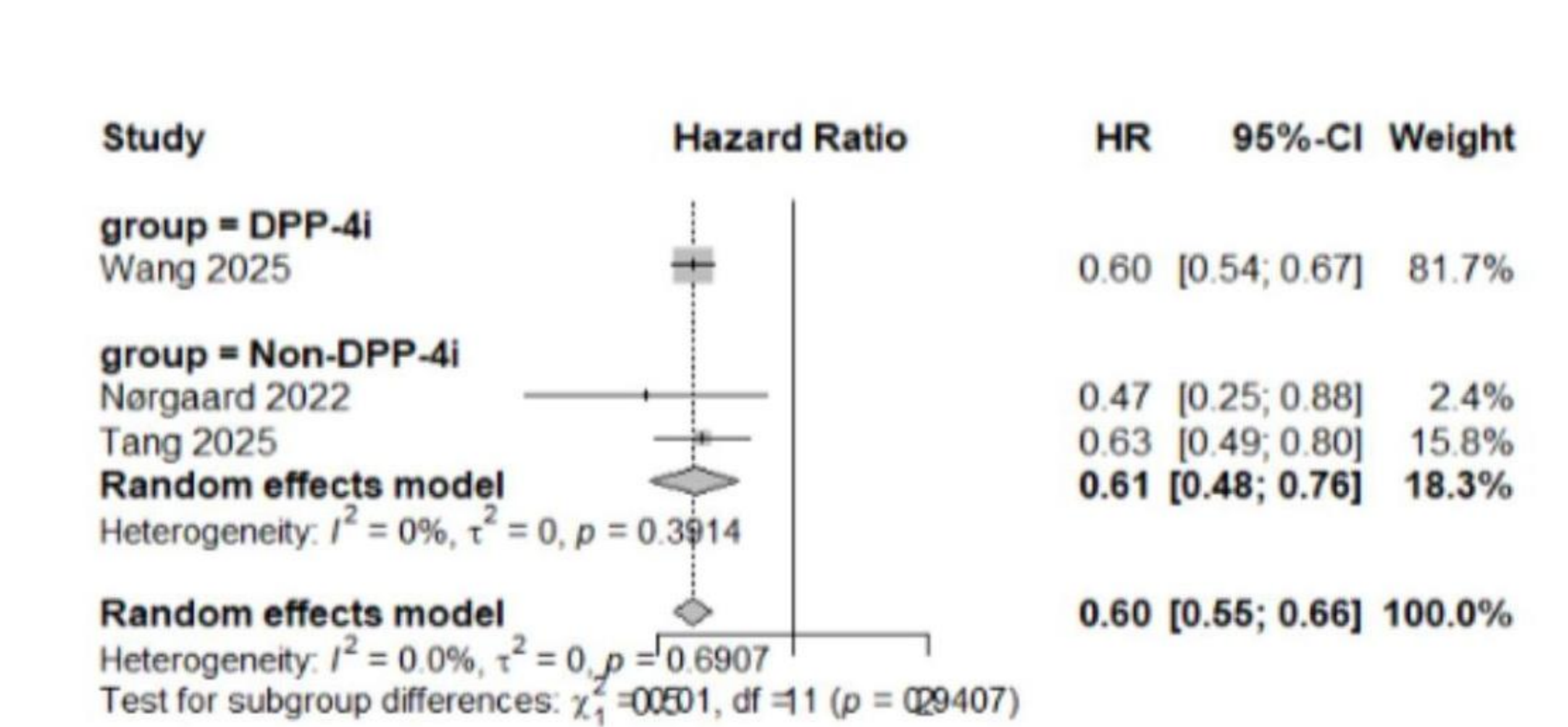
RESULTS

Incident Alzheimer's Disease (AD)



Pooled HR 0.77 (95% CI 0.69–0.87) | 4 studies | I² = 63.6%
GLP-1RAs associated with 23% lower risk of incident AD vs active comparators

Incident Dementia / ADRD



Pooled HR 0.60 (95% CI 0.55–0.66) | 3 studies | I² = 0%
40% lower risk; stable across all sensitivity analyses including exclusion of pooled CVOT evidence

CONCLUSIONS

- ▶ GLP-1RAs associated with 23% lower risk of incident AD
HR 0.77 (95% CI 0.69–0.87)
- ▶ GLP-1RAs associated with 40% lower risk of dementia/ADRD
HR 0.60 (95% CI 0.55–0.66)
- ▶ Effect consistent across DPP-4i and non-DPP-4i comparator subgroups
- ▶ Findings are associative — dedicated long-term RCTs with prespecified, adjudicated cognitive endpoints are needed to establish causality

LIMITATIONS

- ▶ Observational designs — residual confounding cannot be excluded
- ▶ ICD-based outcome ascertainment without clinical adjudication
- ▶ Heterogeneity across GLP-1RA molecules, comparators, and databases
- ▶ Too few studies for formal publication bias assessment

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