The Journal of Prevention of Alzheimer's Disease 13 (2026) 100645

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

Original Article

Risk of Dementia after initiation of GLP-1 RA versus long-acting insulin in patients with type 2 Diabetes mellitus

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ARTICLE INFO

Keywords:
Glucagon-like peptide-1 receptor agonist
Dementia
Basal insulin
Diabetes mellitus
Retrospective cohort study
Propensity score–matching

ABSTRACT

Background: Recent studies suggest a decreased risk of dementia in patients treated with glucagon-like peptide-1 receptor agonist (GLP-1 RA). In this study, we compare the risk of dementia associated with GLP-1 RA versus long-acting insulin in adults aged over 50 years with type 2 diabetes (T2DM) using real-world administrative data from a large Taiwan cohort
Design: A population-based retrospective cohort study
Setting: We analyzed 10,783 propensity score-matched pairs of adults with T2DM who initiated either GLP-1 RA or long-acting insulin from Taiwan's National Health Insurance Research Database (2011-2021).
Measurements: Primary outcome was new-onset dementia; secondary outcomes included dementia requiring treatment and specific dementia subtypes (Alzheimer's disease, vascular dementia, and unspecified dementia). Hazard ratios (HRs) were estimated using Cox models. *Results*: Analysis of matched pairs identified 375 cases of newly diagnosed dementia. The incidence rate was 4.86 per 1,000 person-years in GLP-1 RA users versus 7.56 in insulin users. GLP-1 RA use was associated with significantly lower risk of overall dementia (HR 0.64, 95% CI 0.46-0.89, P=0.0072) and unspecified dementia (HR 0.41, 95% CI 0.24-0.68, P=0.0006), but not for Alzheimer's disease (HR 1.48, 95% CI 0.61-3.63, P=0.3867) or vascular dementia (HR 1.66, 95% CI 0.21-13.03, P=0.6324). Among GLP-1 RAs, both liraglutide (HR 0.40, 95% CI 0.20-0.80, P=0.0091) and dulaglutide (HR 0.42, 95% CI 0.19-0.92, P=0.0311) showed significant protective effects against unspecified dementia.
Conclusions: GLP-1 RA use was associated with lower dementia risk versus long-acting insulin in T2DM patients, especially with liraglutide and dulaglutide. As observational, causality requires confirmation from randomized controlled trials.

1. Background

Dementia, as assessed in this study, refers to clinically diagnosed dementia syndromes, which could be generally categorized as Alzheimer's disease (AD), vascular dementia (VaD), and other neurodegenerative dementias, including dementia with Lewy bodies, frontotemporal dementia, Parkinson's dementia, and dementia of unknown etiology etc., according to specific causes and pathological changes [1].

Abbreviations: GLP-1 RA, Glucagon-like peptide-1 receptor agonist; T2DM, Type 2 diabetes mellitus; NHRI, National health research institute; HR, Hazard ratio.

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https://doi.org/10.1016/j.tjpad.2026.100645
Received 29 December 2025; Received in revised form 24 June 2026; Accepted 3 July 2026
Available online 8 August 2026

T2DM is associated with a 60% greater risk of dementia [2], predisposing such people to different subgroups of dementia [3,4], such as AD, VaD and other neurodegenerative dementias, which defined as unspecified dementia (UnD) in our study. While the mechanistic link between the disorders remains to be fully elucidated, diabetes appears to share common pathological mechanisms with AD, VaD and UnD, including overaccumulation of amyloid-β and tau phosphorylation; vascular damage and associated pathways; and chronic neuroinflammation, insulin resistance, and blood-brain barrier damage that result from hyperglycemia and hyperinsulinemia, which may explain the increased risk observed in patients with T2DM [5–7]. Diabetes may also lead to cognitive dysfunction through pathways involving CKD [8] and vision loss, such as that resulting from diabetic retinopathy [9]. Due to the various effects of antidiabetic agents in the reduction of blood glucose, provoking hypoglycemia, as well as regulation of insulin resistance, it is essential to clarify the influence of antidiabetic agents on the risk of dementia in diabetic individuals [10].

Although findings from small randomized controlled trials (RCTs) have shown that local (eg, intranasal) administration of insulin improves cognitive function in people without diabetes who are cognitively intact or who have dementia [11,12], the effect of systemic administration with long-acting insulin on cognitive decline only has a neutral effect [13]. Recent studies suggest that glucagon-like peptide-1 receptor agonists (GLP-1RAs) may reduce the risk of dementia in patients with T2DM compare with placebo [14,15]. GLP-1 RAs have shown promise in protecting against cognitive decline by improving synaptic plasticity, cell survival, and brain markers such as cerebral glucose metabolism and cerebral perfusion [16]. The potential neuroprotective effects of GLP-1RAs are attributed to their ability to address common pathophysiological mechanisms shared between T2DM and cognitive disorders, such as insulin resistance, inflammation, and oxidative stress [17]. GLP-1 RA have been shown to reduce the rates of major adverse cardiovascular events and slow CKD deterioration, both mechanisms could contribute to normal brain functioning. However, there is no clear evidence that GLP-1RAs offers an advantage over long-acting insulin for reducing the risk of dementia. In addition, the effects of GLP-1RAs on specific types of dementia (eg, AD, VaD and UnD) were not examined before. Our study uses real-world administrative data from a large Taiwan cohort to assess these associations across broader clinical settings.

Dementia in T2DM often occurs with a younger age of onset compared with community-based residents without diabetes [18], and it has been demonstrated that T2DM confers the equivalent of a 2–3 year acceleration of cognitive aging [19]. Furthermore, it is unclear whether different patient characteristics such as concomitant treatment or comorbidity status would modify such drug effects. We therefore compared the risk of dementia among adults with diabetes older than 50 years who initiated an GLP-1 RA or long-acting insulin using the nationally representative Taiwan National Health Insurance Service database.

2. Methods

2.1. Study design and participants

We conducted a nationwide retrospective cohort study from 2000 through 2021 using de-identified data from the National Health Insurance Research Database (NHIRD) in Taiwan. The NHIRD is derived from a single-payer system covering approximately 99% of Taiwan's population, providing administrative claims data with near-complete population coverage. The database contains longitudinal records of diagnoses, treatments, procedures, and demographics.

In NHIRD, confirmed T2DM was defined as having at least three outpatient visits within one year or one hospitalization, a criterion validated in a previous study [20]. Disease diagnoses were determined based on diagnostic codes from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD-10-CM. We identified 287,863 T2DM patients who initiated GLP-1RAs or insulin between January 2011 and December 2021, excluding those with any prescriptions of GLP-1RAs or insulin within 12 months prior to cohort entry. The index date was defined as the date of the first visit during which a GLP-1RA or insulin was prescribed during the study period. After excluding patients aged under 50, those with concurrent use of GLP-1RAs and insulin, and those with type 1 diabetes mellitus or dementia, 10,783 GLP-1RA users and 184,156 insulin users remained for analysis. To mitigate baseline comorbidity and prescription medication confounding effects, we conducted a 1:1 propensity score matching based on age, gender, comorbidities, and other medication use, resulting in 10,783 matched pairs (Fig. 1).

2.2. Standard protocol approvals, registrations, and patient consents

This retrospective cohort study was reviewed and approved by the Institutional Review Board of China Medical University Hospital (CRREC-109-018). The requirement for informed consent was waived due to the retrospective nature of the study using de-identified data from Taiwan's National Health Insurance Research Database. Research complied with the Helsinki Declaration of 1975, as revised in 2013. Our study followed the guidelines set forward in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

2.3. Medications

The study focused on two medications: GLP-1RAs (exenatide, liraglutide, dulaglutide, and semaglutide) and basal insulin analogs, such as regular human insulin, insulin glargine, detemir, and degludec. Comprehensive details, including specific drug types and prescription dates, were collected.

2.4. Outcome of dementia

The outcome of interest was the incidence of dementia. Dementia was further classified into Alzheimer's disease (331.0, G30), vascular dementia (290.4, F01.5), and unspecified dementia, such as frontotemporal dementia, Parkinson's dementia, and dementia with Lewy body or dementia of unknown etiology (290.0- 290.4, 294.1, 294.2, F03.90, F01.5, F02.8, F05) [21]. Dementia was identified by at least three outpatient claims or one hospitalization with a dementia diagnosis within 12 months, based on validated NHIRD definitions. Cases diagnosed before or within 30 days of cohort entry were considered prevalent and excluded. All participants were followed up from index date to death, loss to follow-up due to other reasons, or dementia, whichever came first.

2.5. Covariates

We compared baseline comorbidities and medication histories between the GLP-1RAs and insulin groups. Comorbidities encompassed conditions such as obesity, hypertension, dyslipidemia, CKD, chronic obstructive pulmonary disease (COPD), and depression that occurred in the year preceding the index date. Our model also considered other medications used, including meglitinides, thiazolidinedione, DPP-4 inhibitors, Alpha-glucosidase inhibitors, angiotensin-converting enzyme inhibitors (ACEIs)/ angiotensin receptor blockers (ARBs), Beta-blockers, Calcium-channel blockers, diuretics (except thiazides), statins, and aspirin. Comorbidities and medication use were identified from ICD diagnosis codes ($\geq$1 inpatient or $\geq$3 outpatient claims) and prescription records ($\geq$1 prescription), respectively, during the 12 months preceding the index date, using standard claims-based ascertainment criteria commonly applied in NHIRD research [22].

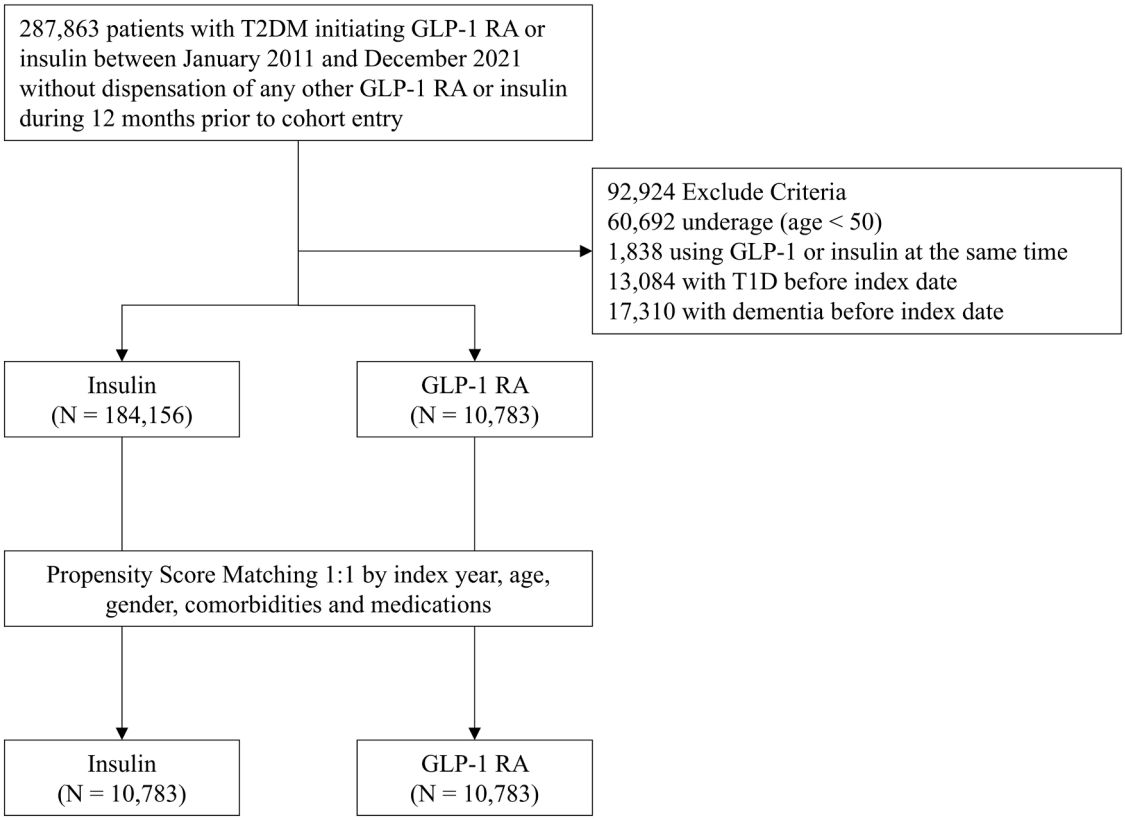


Fig. 1. Flow diagram of recruiting the study subjects.

2.6. Statistical analysis

Propensity score (PS) matching was used to establish a comparison group for GLP-1RAs users. The PS score was calculated for the probability of observing the covariate vector among patients using GLP-1RAs. We conducted logistic regression analysis to estimate the PS, adjusting for index year, age, gender, comorbidities, and relevant clinical medications all listed in Table 1. Greedy nearest neighbor matching was employed to construct a 1:1 PS-matched group with a minimum caliper width of within 0.2. Furthermore, the suitability of covariate comparisons between the propensity score-matched groups was assessed using standardized mean differences (SMD) with a cutoff of 0.10 [23,24]. Continuous variables were expressed as means and standard deviations, while categorical variables were presented as frequencies and percentages. Age was categorized into 10-year groups: 50-59 years, 60-69 years, 70-79 years, and so on. Cumulative incidences of dementia between two groups of patients receiving GLP-1RAs or insulin were estimated and visualized using Kaplan-Meier survival curves and were compared using the log-rank test. All Cox proportional hazard models incorporated competing risks of death, using the cause-specific hazard function to assess the associated risks. The fully adjusted Cox model included diabetes duration, age, sex, and all comorbidities and concurrent medications listed in Table 1. The proportional hazards assumption was assessed by means of scaled Schoenfeld residuals. Because the proportional hazards assumption was violated, conditional and time-varying Cox proportional hazard regression with yearly time intervals was used to determine the crude and adjusted hazard ratios (HR) and 95% confidence intervals (CI) for the risks of dementia or dementia subtypes. Subgroup analyses were conducted among study participants with comorbidities and prescription medications to quantify the association between receiving GLP-1RAs use or not with dementia incidence. All hypothesis tests were two-tailed, with significance defined as α=0.05. Statistical analysis was performed using SAS statistical software version 9.4 (SAS Institute).

3. Results

3.1. Characteristics of study participants

After propensity score matching, we compared 10,783 pairs of GLP-1RAs or insulin users from the Taiwan's NHIRD (Table 1). All standardized mean differences between groups were less than 0.1, indicating well-balanced covariate distributions. All study participants were about 62.59 ± 8.61 years-old of age, about 1: 1 of sex ratios, and higher prevalence of hypertension, as well as dyslipidemia. They also used more DPP-4 inhibitors, ACEI/ARB, and statin. Hypertension and dyslipidemia were the most common comorbidities with prevalence rate of 83.0% and 90.7 %, respectively. The median duration from initiation of GLP-1RAs or insulin to the occurrence of dementia was 2.5 years (interquartile range: 2.7 years).

3.2. GLP-1RAs use and dementia risk

A total of 150 GLP-1RAs users and 225 insulin users were diagnosed with dementia (Table 2) during the study periods. Log-rank tests indicated that GLP-1RAs users had a lower cumulative incidence of dementia compared to insulin users with 4.86 vs. 7.56 cases per 1000 patient-years (P < 0.0001), respectively (Fig. 2). After adjusting for age, gender, diabetes duration, comorbidities, and medications, the GLP-1RAs group had an adjusted hazard ratio (HR) of 0.64 (95% CI, 0.46-0.89; P =0.0072) for dementia, especially for unspecified dementia of 0.41 (95% CI 0.24-0.68, P=0.0006) (Supplementary Table 1).

Among GLP-1RAs users, dulaglutide was the most commonly used medication in both cohorts (about 60%), followed by liraglutide (34%). In NHIRD, only dulaglutide users exhibited significantly reduce risks of dementia (adjusted HRs =0.55, P =0.015) (Table 2). In addition, the

Table 1
Baseline characteristics comparisons at propensity score matched populations in Taiwan NHIRD.

	Overall (N = 21,566)	GLP-1 RA (N = 10,783)	Insulin (N = 10,783)	SMD
Index year, Freq (%)				
2011	18 (0.08%)	11 (0.10%)	7 (0.06%)	0.00
2012	101 (0.47%)	54 (0.50%)	47 (0.44%)	0.00
2013	447 (2.07%)	217 (2.01%)	230 (2.13%)	0.01
2014	679 (3.15%)	326 (3.02%)	353 (3.27%)	0.01
2015	822 (3.81%)	405 (3.76%)	417 (3.87%)	0.00
2016	1,179 (5.47%)	595 (5.52%)	584 (5.42%)	0.00
2017	2,279 (10.57%)	1,144 (10.61%)	1,135 (10.53%)	0.00
2018	3,811 (17.67%)	1,912 (17.73%)	1,899 (17.61%)	0.00
2019	4,209 (19.52%)	2,083 (19.32%)	2,126 (19.72%)	0.01
2020	3,822 (17.72%)	1,918 (17.79%)	1,904 (17.66%)	0.00
2021	4,199 (19.47%)	2,118 (19.64%)	2,081 (19.30%)	-0.01
Age, Mean ± Std	62.59 ± 8.61	62.70 ± 8.64	62.48 ± 8.58	0.02
Age (10 years old a group), Freq (%)				
50 to 59	9,010 (41.78%)	4,443 (41.20%)	4,567 (42.35%)	
60 to 69	8,058 (37.36%)	4,045 (37.51%)	4,013 (37.22%)	
70 to 79	3,564 (16.53%)	1,818 (16.86%)	1,746 (16.19%)	
80+	934 (4.33%)	477 (4.42%)	457 (4.24%)	
Gender (Female), Freq (%)	11,208 (51.97%)	5,610 (52.03%)	5,598 (51.92%)	0.00
Comorbidity, Freq (%)				
Obesity	2,154 (9.99%)	1,166 (10.81%)	988 (9.16%)	-0.07
Hypertension	17,898 (82.99%)	8,924 (82.76%)	8,974 (83.22%)	0.01
Dyslipidemia	19,557 (90.68%)	9,696 (89.92%)	9,861 (91.45%)	0.04
CKD	5,336 (24.74%)	2,693 (24.97%)	2,643 (24.51%)	-0.01
COPD	2,749 (12.75%)	1,435 (13.31%)	1,314 (12.19%)	-0.03
Depression	1,384 (6.42%)	714 (6.62%)	670 (6.21%)	-0.02
Medication, Freq (%)				
Meglitinides	2,245 (10.41%)	1,164 (10.79%)	1,081 (10.03%)	-0.03
Thiazolidinedione	6,977 (32.35%)	3,490 (32.37%)	3,487 (32.34%)	0.00
DPP-4 inhibitors	14,632 (67.85%)	7,295 (67.65%)	7,337 (68.04%)	0.01
Alpha-glucosidase inhibitors	6,208 (28.79%)	3,117 (28.91%)	3,091 (28.67%)	-0.01
ACEI/ARBs	14,171 (65.71%)	7,070 (65.57%)	7,101 (65.85%)	0.01
Beta-blockers	8,155 (37.81%)	4,098 (38.00%)	4,057 (37.62%)	-0.01
Calcium-channel blockers	7,108 (32.96%)	3,582 (33.22%)	3,526 (32.70%)	-0.01
Diuretics	7,064 (32.76%)	3,535 (32.78%)	3,529 (32.73%)	0.00
Statin	17,419 (80.77%)	8,659 (80.30%)	8,760 (81.24%)	0.02
Aspirin	9,699 (44.97%)	4,894 (45.39%)	4,805 (44.56%)	-0.02

adjusted HRs for the UnD with medications of GLP-1 RA were 0.40 (95% CI, 0.20-0.80; P=0.0091) for liraglutide, and 0.42 (95% CI, 0.19 -0.92; P=0.0311) for dulaglutide. (Supplementary Table 1).

3.3. Subgroup analyses

Due to the small numbers of patients with a given dementia subtypes, we only assessed the relationships between GLP-1RAs use and any type of dementia under different stratifications of comorbidities and prescription medications in the propensity score-matched population (Fig. 3). Protective associations with GLP-1RAs use against dementia were significantly observed in T2DM patients with no obesity, hypertension, no CKD, no COPD, no depression, Statin users, and no use of Diuretics (detail information was added in Supplementary Table 2).

4. Discussion

Our study reveals that GLP-1 RAs appear more effective than long-acting insulin in lowering this risk of dementia in adults with T2DM. The results demonstrate that GLP-1 RAs, particularly liraglutide or dulaglutide, are significantly effective against unspecified dementia. However, they did not show the same efficacy for AD or VaD. Among patients with a history of CKD, GLP1-RAs initiation is not associated with a decreased risk for subsequent dementia compared with long-acting insulin initiation (Fig. 3). Because we don't have details on CKD severity, it is likely that patients with more severe CKD received insulin instead of GLP-1 RAs.

People with long-standing diabetes and with poor glycemic control may be more likely to require injectable insulin therapy, and also more likely to develop dementia [25], such as the risk of hypoglycemia and weight gain, which by themselves can impair cognitive functions. However, in a substudy of the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial, the rate of change of cognitive test scores and the incidence of probable cognitive impairment did not differ between the insulin glargine and standard care groups after a median follow-up of 6 years [13]. Indeed, multiple meta-analysis studies assessed the comparisons between GLP-1 RA and insulin treatment confirms a relatively favorable influence of GLP-1 RAs on body weight, systolic blood pressure and triacylglycerol concentrations, as well as the proportion of patients experiencing episodes of hypoglycaemia [26–28]. Favorable effects on cardiovascular risk factors/markers for GLP-1 RAs may translate into a favorable cardiovascular risk overall. Unfortunately, most publications did not report details with dementia in that respect. Thus, we examine the association between insulin and GLP-1 RA use and the risk of dementia.

We observed a significantly lower risk of all-cause dementia for adults with T2DM who were prescribed GLP-1 RAs, consistent with previous observational studies and meta-analysis [14,29]. To our knowledge, there have been no directly comparable studies of the association between GLP-1 RAs and long-acting insulin for predicting the risk of dementia, but our findings are consistent with several other related studies. With regard to our control group by using systemic long-acting insulin, some recent reports showed no significant association was observed between systemic long-acting insulin use and all-cause dementia among patients with T2DM [13,30]. There are several potential mechanisms of action. For example, it is plausible that the effect of GLP-1 RAs on dementia could be related to amelioration of dementia-related risk factors, such as body weight, systolic blood pressure, glycated hemoglobin and cardiovascular disease observed in the included randomized control trials (RCTs) [31,32]. It has been shown that both liraglutide and semaglutide specifically attenuate development of atherosclerotic plaques in *APOE*–/– and *LDLr*–/– mice through an anti-inflammatory mechanism [33], and that semaglutide also can decrease markers of systemic inflammation in patients [34,35]. In humans, it was recently demonstrated that treatment with GLP-1 RAs was associated with a reduced incidence of dementia in patients with T2DM in three pooled RCTs and in a nationwide cohort [14]. Thus, in addition to its glucose lowering effect, GLP-1 RAs may have specific properties for preventing dementia. Nevertheless, additional investigation is still needed to comprehensively understand their underlying

Table 2
Risk for Dementia between GLP-1 RA users and insulin users at propensity score matched populations in Taiwan NHIRD.

	Event	Person Year	Incidence Rate	Crude HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Insulin (N = 10,783)	225	29762.67	7.56	Reference		Reference	
GLP-1 (N = 10,783)	150	30895.45	4.86	0.69 (0.53 - 0.88)	0.0032	0.64 (0.46 - 0.89)	0.0072
Exenatide (N = 133)	4	1101.40	3.63	0.80 (0.22 - 2.98)	0.7394	1.03 (0.22 - 4.80)	0.9678
Liraglutide (N = 3,648)	70	14788.83	4.73	0.69 (0.48 - 1.00)	0.0476	0.73 (0.46 - 1.15)	0.1762
Dulaglutide (N = 6,502)	75	14775.18	5.08	0.67 (0.46 - 0.97)	0.0347	0.55 (0.34 - 0.89)	0.015
Semaglutide (N = 500)	1	230.03	4.35	0.50 (0.05 - 5.51)	0.5715	0.24 (0.01 - 5.70)	0.3765

Incidence rate were calculated as events of dementia per 1,000 person-years.
Adjusted DM duration, age, gender, comorbidities and medications

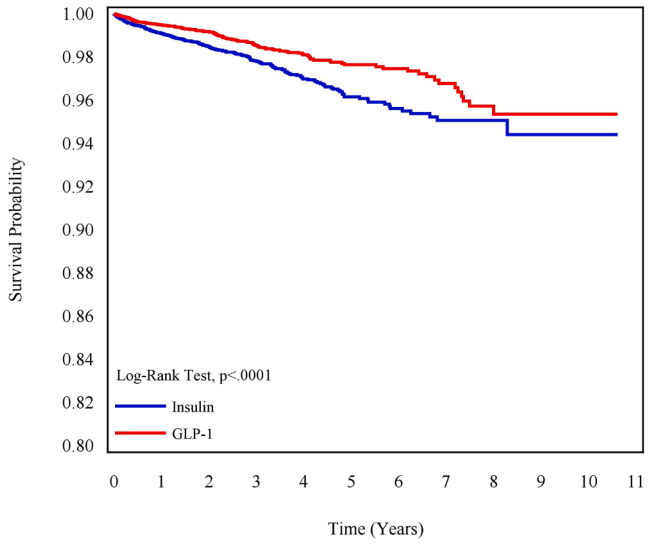


Fig. 2. Survival probability of dementia among patients with type 2 diabetes mellitus treated with GLP-1 RA or basal insulin.

mechanisms.

Crane PK et al. has examined the observational association between plasma glucose concentrations and risk of dementia, and reported an increased risk of UnD and AD combined [36]. Besides, a previous study has showed that observational and genetically high plasma glucose are causally related to the risk of UnD, but not to AD or VaD [37]. In our study, the statistically significant decreased risk was observed specifically for UnD, while such an association was not observed in AD, or VaD. This is supported by a previous study, which observed that individuals with UnD, compared with individuals with AD and VaD, may have higher plasma glucose concentrations as Benn M et al reported [37] and, in the presence of T2DM, were less effectively treated with GLP-1 RAs, suggesting that poor glycaemic control might have contributed to disease risk in these individuals and that improved diabetes management may reduce this risk. Additionally, the reduce risk of VaD development was not statistically significant. This is because the cases and controls were matched using several important risk factors for VaD, such as obesity, hypertension, dyslipidemia, CKD and depression [38].

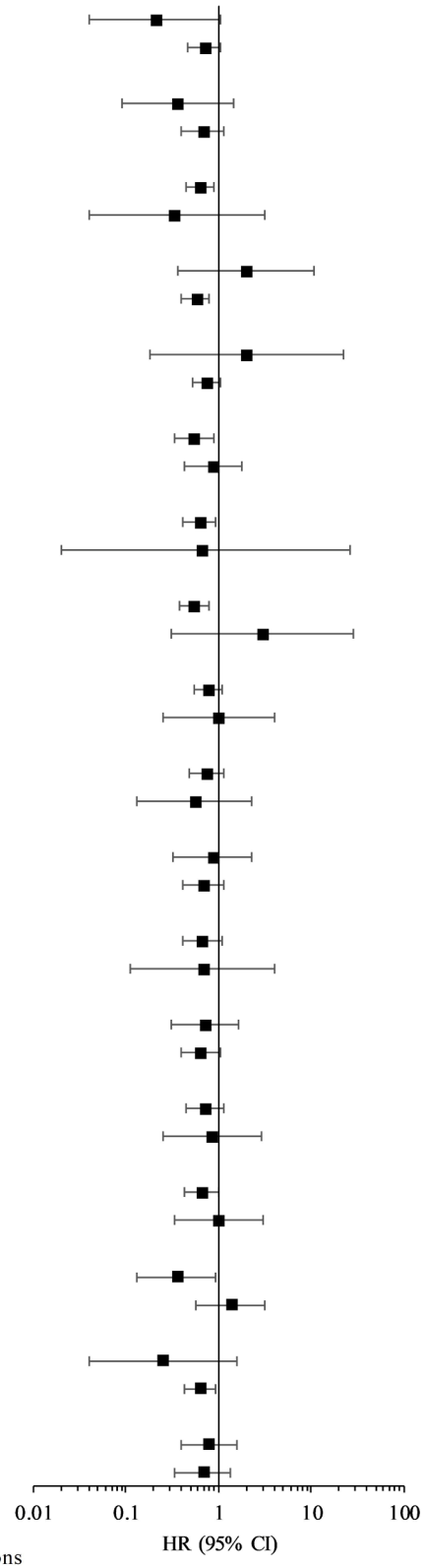
In our follow-up cohort, 59.7% of patients with UnD, 27.2% of patients with AD, and 13.1% of patients with VaD, were treated with GLP-1 RA or insulin (Supplementary Table 1). A study from Australia of community-dwelling people with T2DM found a slight difference, that UnD (40.6%) and AD (39.9%) were the two most frequent subtypes, and VaD was least common (9.1%) [18]. Dementia were mutually exclusive, and we only used the first coded dementia subtype: AD, VaD and UnD, the latter comprising the majority of dementia diagnoses (for ICD codes). As about one-third of cases with other dementia without specification may be attributable to AD [39], we could also include a combined outcome of AD and UnD. Moreover, as dementia increases with age, patients with T2DM may not survive long enough to develop dementia. GLP-1 RAs likely show a stronger association with UnD because UnD may be more influenced by metabolic risk factors (e.g., obesity, insulin resistance), whereas AD and VaD have more distinct pathological mechanisms (amyloid plaques, tau tangles, and cerebrovascular damage) that GLP-1 RAs may not effectively target. However, an alternative explanation relates to diagnostic classification. Many cases of early-stage AD or VaD may initially be classified as UnD. These findings suggest a possible misclassification bias for dementia subtypes as clinicians may be more likely to diagnose UnD, and less likely AD. This pattern of diagnostic coding behavior may thus attenuate the apparent effect of GLP-1 RAs on AD specifically, while overestimating the magnitude of association observed for UnD. Future studies including biomarker-confirmed or clinically adjudicated dementia diagnoses would be better suited to evaluate subtype-specific treatment effects.

The null finding in the CKD subgroup likely reflects residual confounding by renal disease severity, as the NHIRD does not include CKD staging or eGFR data, and long-acting insulin tends to be prescribed preferentially in advanced CKD. Given the limited number of events in this subgroup, this finding should be interpreted with caution.

Confounding by indication is a critical challenge in non-randomized comparisons of GLP-1 RAs and insulin. In clinical practice, GLP-1 RAs are often prescribed to patients with obesity or cardiovascular risk prior to insulin intensification, whereas long-acting insulin is typically reserved for more advanced or poorly controlled diabetes. Although propensity score matching achieved well-balanced baseline covariates, unmeasured confounders such as HbA1c, body mass index, and smoking status could not be accounted for. This residual confounding likely favors GLP-1 RA users, and the observed protective association may therefore be somewhat overestimated. However, our trial has several limitations. The main limitation of the present study was the use of health administrative data to detect individuals with dementia. We explored dementia subtypes and included these data for interest, but they should be interpreted with caution. Although all cases required a diagnosis of dementia to be recorded by a medical practitioner, the diagnostic criteria and accuracy cannot be determined given the broad-based source of the diagnostic information. Notably, relying solely on administrative ICD codes without clinical, neuroimaging, or pathological confirmation introduces potential subtype misclassification. This particularly affects early-stage cases and the UnD category, which dominated our cohort. The non-significant findings for AD and VaD may represent a true lack of effect, but could also stem from limited statistical power and diagnostic shifting into the unspecified category. Second, the NHIRD does not capture HbA1c values or detailed diabetes duration, limiting our ability to adjust directly for glycemic severity. To partially address this, we adjusted for database-recorded disease duration, concomitant antidiabetic medication use, and relevant comorbidities including CKD, hypertension, and dyslipidemia—all of which may serve as proxies for diabetes severity and disease burden. Nevertheless, residual confounding by unmeasured glycemic severity cannot be fully excluded. Third, the median follow-up of 2.5 years may be too short to fully assess dementia risk, given the long prodromal phase of neurodegenerative diseases. Longer-term studies are needed to confirm whether the observed association persists. In addition, the small number of subtype-specific dementia events, particularly for AD and VaD, limited

Table3. Forest plots of stratified analysis on the risk for Dementia between GLP-1 RA Users and Insulin Users at Propensity Score Matched Populations in Taiwan NHIRD

	Event	HR (95% CI)
Age		
50 to 64	26 / 37	0.21 (0.04 - 1.06)
65+	124 / 188	0.70 (0.47 - 1.06)
Gender		
Male	61 / 77	0.36 (0.09 - 1.44)
Female	89 / 148	0.68 (0.40 - 1.14)
Obesity		
No	137 / 206	0.64 (0.45 - 0.90)**
Yes	13 / 19	0.33 (0.04 - 3.21)
Hypertension		
No	15 / 7	2.00 (0.37 - 10.92)
Yes	135 / 218	0.57 (0.40 - 0.80)**
Dyslipidemia		
No	10 / 25	2.00 (0.18 - 22.05)
Yes	140 / 200	0.73 (0.52 - 1.04)
CKD		
No	96 / 161	0.54 (0.33 - 0.90)*
Yes	54 / 64	0.88 (0.43 - 1.79)
COPD		
No	115 / 185	0.62 (0.41 - 0.92)*
Yes	35 / 40	0.66 (0.02 - 26.15)
Depression		
No	131 / 208	0.54 (0.38 - 0.78)**
Yes	19 / 17	3.00 (0.31 - 28.84)
Meglitinides		
No	130 / 195	0.77 (0.55 - 1.10)
Yes	20 / 30	1.00 (0.25 - 4.00)
Thiazolidinedione		
No	113 / 157	0.74 (0.49 - 1.13)
Yes	37 / 68	0.55 (0.13 - 2.29)
DPP-4 inhibitors		
No	37 / 80	0.86 (0.32 - 2.32)
Yes	113 / 145	0.68 (0.41 - 1.13)
Alpha-glucosidase inhibitors		
No	111 / 160	0.66 (0.41 - 1.08)
Yes	39 / 65	0.67 (0.11 - 4.05)
ACEI/ARBs		
No	52 / 61	0.71 (0.31 - 1.62)
Yes	98 / 164	0.64 (0.39 - 1.07)
Beta-blockers		
No	96 / 133	0.71 (0.44 - 1.14)
Yes	54 / 92	0.85 (0.25 - 2.93)
Calcium-channel blockers		
No	94 / 133	0.65 (0.42 - 1.00)
Yes	56 / 92	1.00 (0.33 - 3.07)
Diuretics		
No	79 / 122	0.35 (0.13 - 0.91)*
Yes	71 / 103	1.34 (0.56 - 3.19)
Statin		
No	29 / 42	0.25 (0.04 - 1.58)
Yes	121 / 183	0.62 (0.42 - 0.93)*
Aspirin		
No	66 / 93	0.78 (0.39 - 1.55)
Yes	84 / 132	0.68 (0.34 - 1.36)



Event of GLP-1 RA and Insulin
p value < 0.05 : *; p value < 0.01 : **; p value < 0.0001 : ***
Adjusted DM duration, age, gender, comorbidities and medications

Fig. 3. Subgroup analysis of dementia incidence in T2DM patients taking GLP-1 RA or basal insulin using baseline comorbidities and other medications in the propensity score matched population.

statistical power; therefore, these findings should be interpreted as exploratory. Finally, only those patients seeking medical help will receive a diagnosis of dementia. We adjusted for mental health clinic visits to reduce the information bias. In addition, the under diagnosis of dementia needs to be considered in the association between treatment with GLP-1 RA and dementia risk.

5. Conclusions

This large-scale study demonstrated that, relative to using long-acting insulin, using GLP-1 RAs is associated with a lower risk of incident dementia in adults with T2DM, especially UnD. Further prospective studies and randomized controlled trials should examine the potential role of GLP-1 RAs in preventing cognitive decline in people with or without diabetes.

Declaration of the use of generative AI and AI-assisted technologies in scientific writing and in figures, images and artwork

During the preparation of this work, the authors used Claude (Opus 4.8; Anthropic, San Francisco, CA, USA) to assist with editing for concision and language clarity. All AI-assisted content was reviewed and revised by the authors, who take full responsibility for the published article.

CRediT authorship contribution statement

Chien-Hung Lin: Writing – review & editing, Writing – original draft, Validation, Supervision, Investigation, Conceptualization. **Peir-Haur Hung:** Writing – review & editing, Writing – original draft, Validation, Supervision, Investigation, Conceptualization. **Mu-Chi Chung:** Supervision, Investigation, Conceptualization. **Laing-You Wu:** Methodology, Investigation, Formal analysis. **Chi-Jung Chung:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

Funding: This study is supported in part by Ditmanson Medical Foundation Chiayi Christian Hospital (R113-010), and China Medical University (DMR-114-110, and CMU114-MF-62). The funders performed no role in the study design, data collection and analysis, decision to publish, or manuscript preparation.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2026.100645.

Data availability

The data that support the findings of this study are available from the Taiwan National Health Insurance Research Database but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

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