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The protective effects of insulin on the developing of dementia in chronic kidney disease patients with hypertension and diabetes: a population-based nationwide study

Yun-Yi Chen[1,2], Yi-Hsien Chen[3], Yu-Wei Fang[4,5], Jing-Tong Wang[4] and Ming-Hsien Tsai[4,5*]

Abstract

Background Chronic kidney disease (CKD), hypertension, and diabetes are associated with dementia, and insulin resistance promotes vascular dysfunction resulting in dementia. However, the study of insulin use in preventing dementia in CKD patients with diabetes and hypertension is limited. We aim to assess the effects of insulin use on the incidence of dementia in patients with CKD with hypertension and diabetes.

Design, setting and participants A retrospective cohort study using the nationwide database from Taiwan's National Health Insurance Research Database. We selected 11,758 CKD patients with diabetes and hypertension in 2006, including 5,864 insulin users and 5,894 non-insulin users. Moreover, their medication possession ratios (MPR) were calculated.

Main outcomes We used the competing risk model to estimate the hazard ratio (HR) for the incidence of dementia for insulin use in the target population.

Results In a follow-up period of 11 years, 1285 events of dementia were recorded, and the multivariate-adjusted HR for dementia by insulin usage (yes vs. no) and insulin usage per MPR is 0.652 (95% confidence interval [CI]: 0.552 to 0.771) and 0.995 (95% CI: 0.993 to 0.998) respectively. Such a significant negative association was consistent in almost all subgroups. Moreover, a dose-dependent effect of insulin was noted, where patients with higher insulin MPRs were less likely to have dementia.

Conclusion The CKD patients with hypertension and diabetes who received insulin therapy had a 35% decreased risk of dementia.

Keywords Chronic kidney disease, Real-world evidence, Insulin, Insulin resistance, Hypertension, Diabetes, Dementia

*Correspondence:
Ming-Hsien Tsai
chaosmyth.tw@gmail.com
[1]Department of Research, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan
[2]Institute of Hospital and Health Care Administration, National Yang Ming Chiao Tung University, Taipei, Taiwan
[3]Department of Family Medicine, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan
[4]Division of Nephrology, Department of Internal Medicine, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan
[5]Department of Medicine, Fu-Jen Catholic University School of Medicine, Taipei, Taiwan

Background

Chronic Kidney Disease (CKD) is a global health challenge, with an estimated prevalence of 13.4% [1, 2]. Taiwan has reported a higher CKD prevalence of 15.5% (Stage 1–5) [3] and a higher incidence of end-stage renal disease (ESRD) in a comparison of international data from the United States Renal Data System [4]. Moreover, CKD causes a considerable financial burden because it leads to ESRD requiring dialysis and increases the risk of cardiovascular mortality and morbidity as renal function declines [2, 5].

Dementia, a catch-all term for neurodegeneration disease aside from normal brain aging, is a significant health concern for older adults worldwide [6], with a forecasted all-cause dementia report predicting a prevalence of 152 million cases by 2050 [7]. Alzheimer's disease (AD) accounts for 60–80% of cases, with vascular dementia as the second most common cause of dementia [8]. The treatment strategies for dementia include pharmacological and non-pharmacological approaches, but the efficacy of treatments remains limited [8, 9]. According to clinical guidelines, the identification of modifiable risk factors is the primary strategy for preventing dementia [10].

Research has shown CKD to be an independent risk factor for cognitive impairment and the development of dementia [11, 12]. Adequate hypertension control has been shown to lower the risk of dementia [13, 14]. In addition to the effect of lowering blood pressure, Renin-angiotensin-aldosterone system (RAAS) blockades, which are the preferred agents in the CKD population for delaying the CKD progression [15, 16], help prevent the onset of dementia via the modulation of the RAAS in the brain [17–19]. Interestingly, some studies has reported that insulin plays a crucial role in central nervous system (CNS) health aside from the effect of lowering serum glucose level, and insulin dysregulation can contribute to conditions of pathological brain aging, such as AD and vascular cognitive impairment [20–22].

However, results on the relationship between insulin use and cognitive health have been inconsistent in the literature [23–25]. In addition, no data are available on the effects of insulin control on preventing dementia in CKD patients with diabetes and hypertension. Thus, our objective is to utilize the National Health Insurance Research Database (NHIRD), which represents real-world data, to examine the correlation between the administration of insulin and the onset of dementia among the high-risk cohort comprising individuals with diabetes and hypertension who are afflicted with CKD.

Methods

Data source and research samples

This study analyzed CKD data from the NHIRD maintained by the Health and Welfare Data Science Center (HWDC), Ministry of Health and Welfare, Taiwan; this CKD database has been described in a previous publication [17]. NHIRD contains the claims records of health care utilization of 99.9% of Taiwan's 23 million population enrolled in the Taiwan National Health Insurance (NHI) program [26]. The deidentified information retained in the data included date of birth, sex, residency area, diagnostic codes, medical procedures, and drug prescriptions. In the NHIRD, diseases were defined by the codes from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) before 2015 and by the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) after 2015. Before the NHIRD data were released for research, the personal information of all beneficiaries was deidentified and anonymized to ensure privacy, following rigorous secrecy guidelines.

Study design and study population

The study was designed as a retrospective and population-based longitudinal cohort study. The selected population was patients with CKD diagnosed with hypertension (ICD-10: I10–I15) and diabetes (ICD-10: E08–E13) from January 1, 2006, through December 31, 2006. ($n = 18{,}434$). We excluded patients who had previously been diagnosed with malignancy (ICD-10: C00-C96,D45, D47.Z9, E31.22, Z51.12), ESRD (ICD-10: N18.6), dementia (ICD-10: F01.50, F01.51, F03.90, and F03.91), or cerebrovascular diseases (ICD-10: I60- I63, I65-I69, and G45-G46). Patients under regular hemodialysis and peritoneal dialysis and patients who previously underwent renal transplantation were also excluded. We excluded patients younger than 20, older than 80, or with missing information. A total of 11,758 patients with CKD with hypertension and diabetes were chosen for analysis (Fig. 1).

The index date was defined as January 1, 2007. The data were analyzed from the index date to the first instance of the desired outcome, dementia, or to the end of the observation date (December 31, 2017). Therefore, an aggregate follow-up duration of 11 years was implemented for the cohort of patients.

Exposure to study drugs

We used a medication possession ratio (MPR) to estimate the amount of insulin medication that patients had been prescribed. MPR is measured as the sum of days a given drug is featured in the observation period divided by the total number of days in the observation period [27]. Insulin use and non-use were defined by MPR > 0% and MPR = 0%, respectively.

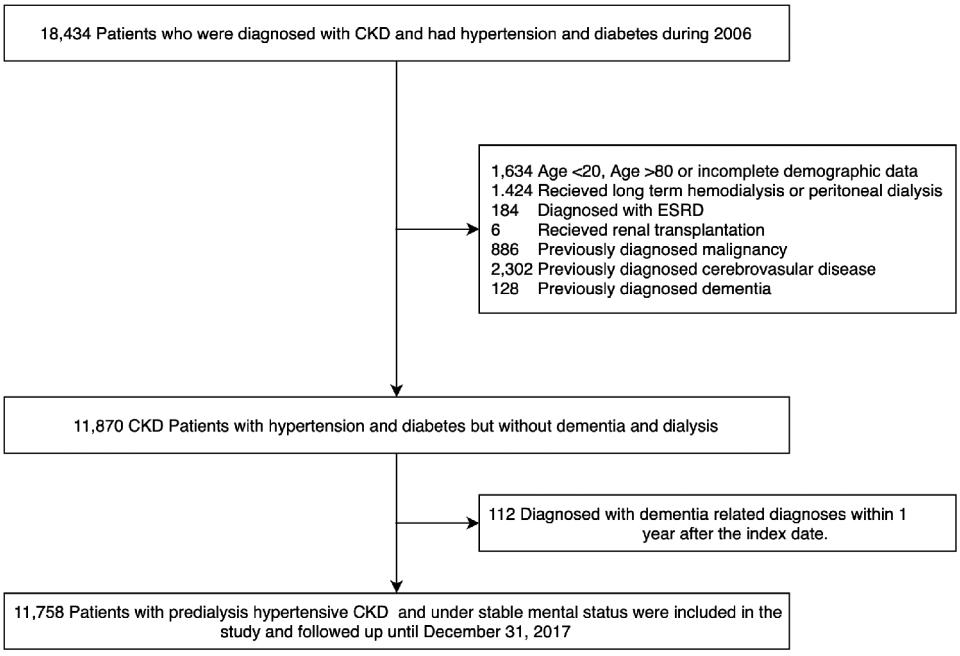

Fig. 1 Flow chart of patient enrollment in the study. Abbreviation: CKD, chronic kidney disease; ESRD, end stage of kidney disease

Covariates

We defined baseline comorbidities as those identified in at least 3 outpatient diagnoses or 1 inpatient diagnosis the year before the index date. ischemic heart disease (ICD-10: I10–I15), hyperlipidemia (ICD-10: E78), atrial fibrillation (ICD-10:I48), chronic heart failure (ICD-10: I50), peripheral artery disease (ICD-10: I70.2–I70.9), asthma (ICD-10: J45), chronic obstructive pulmonary disease (ICD-10: J44), major depression disease (ICD-10: F32–F33), Parkinson's disease (ICD-10: G20–G21), rheumatic arthritis (ICD-10: M05–M06), hyperthyroidism (ICD-10: E05), hypothyroidism (ICD-10: E01.8 and E02–E03), gout (ICD-10: M10), and insomnia (ICD-10: G47.0, and F51.0). The following drugs were considered to be used by the patient if they were used for at least 3 months within the year before the index date: benzodiazepines, anticoagulants, NSAIDs, acetaminophen, statins, calcium channel blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), metformin, beta-blockers, and diuretics.

Outcome measurement

Dementia, the primary outcome in this research, was indicated if the patient was eligible for an NHI card for severe illness issued by the NHI administration for dementia-related diagnoses. The card is issued if the patient fulfills the dementia criteria in ICD-9-CM: 290 (Item 6 – 1) or ICD-10-CM: F01.50, F01.51, F03.90, and F03.91, as diagnosed from a licensed neurologist or psychiatrist.

Statistical analysis

Continuous data of baseline characteristics are expressed as the mean ± standard deviation, whereas categorical data are expressed as the frequency and proportion. Groups (insulin users vs. nonusers) were compared using Chi-squared tests for portions and t-tests for means of continuous variables.

Competing risk regression analyzes were conducted for dementia development (death was considered a competing event) using the method described by Fine and Gray [28]. The stratified proportional sub-distribution hazard ratio (HR) was calculated to estimate the exposure and covariate effects on the cumulative incidence function. All statistical analyses were conducted in version 9.4 of SAS (SAS Institute, Cary, NC, USA) software. A 2-sided p-value < 0.05 indicated statistical significance for all tests.

Sensitivity analysis

A separate multivariable regression model was adopted to assess the reliability of our findings. We model insulin usage (yes vs. no) or MPR of insulin as a function of dementia event using a modified stepwise procedure with 3 modeling steps, in which the variables of demographic data, comorbidities, and medications were added into models at each step.

We also conducted analyses of insulin MPR at the following period to assess the dosing effect of insulin on the prevention of dementia, in which we used a Cochran-Armitage test to test the dose-dependent effect of insulin use. We stratified insulin users by MPR rates into ≤ 20%,

Table 1 Baseline characteristics of CKD patients with hypertension and diabetes

	Total (*n* = 11,758)	Insulin nonusers (*n* = 5,864)	Insulin users (*n* = 5,894)	*p*
Sex				< 0.001
Male (%)	6236 (53)	3205 (54.7)	3031 (51.4)	
Female (%)	5522 (47)	2659 (45.3)	2863 (48.6)	
Age	62.1 ± 10.9	62.6 ± 10.9	61.7 ± 11	< 0.001
20–39 (%)	860 (7.3)	398 (6.8)	462 (7.8)	0.001
40–64 (%)	5794 (49.3)	2829 (48.2)	2965 (50.3)	
65–80 (%)	5104 (43.4)	2637 (45)	2467 (41.9)	
Comorbidities				
Ischemic Heart Disease (%)	2794 (23.8)	1352 (23.1)	1442 (24.5)	0.072
Hyperlipidemia (%)	6186 (52.6)	3075 (52.4)	3111 (52.8)	0.708
Atrial Fibrillation (%)	163 (1.4)	92 (1.6)	71 (1.2)	0.091
CHF (%)	839 (7.1)	357 (6.1)	482 (8.2)	< 0.001
PAD (%)	439 (3.7)	192 (3.3)	247 (4.2)	0.008
Asthma (%)	624 (5.3)	298 (5.1)	326 (5.5)	0.277
COPD (%)	1631 (13.9)	784 (13.4)	847 (14.4)	0.116
Major Depressive Disorder (%)	129 (1.1)	70 (1.2)	59 (1)	0.315
Parkinson's Disease (%)	94 (0.8)	42 (0.7)	52 (0.9)	0.312
Rheumatoid Arthritis (%)	114 (1)	50 (0.9)	64 (1.1)	0.197
Insomnia (%)	1012 (8.6)	500 (8.5)	512 (8.7)	0.756
Hyperthyroidism (%)	102 (0.9)	53 (0.9)	49 (0.8)	0.671
Hypothyroidism (%)	91 (0.8)	54 (0.9)	37 (0.6)	0.069
Gout (%)	2019 (17.2)	1164 (1.9)	855 (14.5)	< 0.001
Drugs				
BZDs (%)	2473 (21)	1233 (21)	1240 (21)	0.987
Anticoagulants (%)	5060 (43)	2465 (42)	2595 (44)	0.029
NSAIDs (%)	4506 (38.3)	2220 (37.9)	2286 (38.8)	0.301
Acetaminophen (%)	4189 (35.6)	1997 (34.1)	2192 (37.2)	< 0.001
Statin (%)	4655 (39.6)	2100 (35.8)	2555 (43.4)	< 0.001
CCB (%)	6483 (55.1)	3143 (53.6)	3340 (56.7)	< 0.001
ACEIs (%)	3463 (29.5)	1662 (28.3)	1801 (30.6)	0.008
ARBs (%)	5340 (45.4)	2465 (42.0)	2875 (48.8)	< 0.001
Metformin (%)	7166 (61)	3411 (58.2)	3755 (63.7)	< 0.001
Beta-Blocker (%)	4106 (34.9)	1997 (34.1)	2109 (35.8)	0.049
Diuretics (%)	4269 (36.3)	1873 (31.9)	2396 (40.7)	< 0.001

Abbreviation: CHF, chronic heart failure; PAD, peripheral artery disease, COPD, chronic obstructive pulmonary disease, NSAID, non-steroid anti-inflammatory drug; BZD, benzodiazepine; CCB, calcium channel blocker ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers

20–40%, 40–60%, 60–80%, and > 80% MPR subgroups. The ≤ 20% MPR subgroup was used as our reference point.

Finally, to test the consistency of the ability of insulin to protect against dementia in CKD patients with diabetes and hypertension, we performed a subgroup analysis by age, sex, comorbidities, and medications. Groups whose number of patients was < 10% of the total sample were excluded from the subgroup analysis.

Results

Patient characteristics

We enrolled 11,758 patients with CKD with hypertension and diabetes in the present study (Table 1). The mean age of the enrolled patients was 62.1 ± 10.9 years, 47% were women, and 52.6% had hyperlipidemia. Among them, 5864 patients had insulin prescriptions, and others (5,894) were insulin nonusers.

Table 1 shows the differences in baseline characteristics between insulin users and nonusers. Patients who were women, were younger, with the comorbidities of congestive heart failure and peripheral artery disease, and without gout were likely to be prescribed insulin (all $p < 0.005$). Moreover, insulin users were more likely to be prescribed anticoagulation agents, acetaminophen, statin, calcium channel blocker, ACEIs, ARBs, metformin, beta-blockers, and diuretics (all $p < 0.005$).

Risk factors for developing dementia in CKD patients with diabetes and hypertension

We identified 1285 events of dementia during an 11-year observation period. Table 2 shows the risk factors that may contribute to the development of dementia. Older adult women, people with atrial fibrillation or insomnia, and users of benzodiazepines and metformin were at significant risk for the development of dementia. Table 2 also shows that comorbidity of chronic heart failure and the usage of insulin, ACEIs, and diuretics were associated with a significantly lower risk of dementia.

However, after several variables were controlled for, the only significant variables were insulin usage; sex; age; chronic heart failure; insomnia; and the usage of benzodiazepines, ACEIs, metformin, and diuretics. Interestingly, the protective effects of ARBs against dementia were significant, whereas they were nonsignificant in the univariate analysis.

The effects of insulin usage on the incidence of dementia

There were 376 events of dementia for insulin users and 909 events of dementia for insulin nonusers in this study. The curves from the Fine and Gray method for the adjusted cumulative hazards of dementia between insulin users and nonusers indicated significance ($\chi^2 = 5.67$, $p = 0.017$) (Fig. 2). Insulin protected against dementia

Table 2 Risk for developing dementia in the CKD population with diabetes and hypertension

	Crude		Multivariable	
	HR (95%CI)	***p***	**aHR (95%CI)**	***p***
Insulin (vs. non)	0.628 (0.0.533–0.741)	< 0.001	0.652 (0.552–0.771)	< 0.001
Male (vs. female)	0.524 (0.444–0.619)	< 0.001	0.571 (0.481–0.677)	< 0.001
Age				
20–39 (reference)	1		1	
40–64	15.608 (3.899–62.485)	< 0.001	14.136 (3.531–56.596)	< 0.001
65–80	33.374 (8.362–133.208)	< 0.001	29.828 (7.473–119.051)	< 0.001
Comorbidities				
Ischemic Heart Disease (vs. non)	1.150 (0.958–1.381)	0.134	1.047 (0.857–1.280)	0.650
Hyperlipidemia (vs. non)	1.074 (0.914–1.262)	0.387	1.133 (0.947–1.356)	0.172
Atrial fibrillation (vs. non)	1.766 (1.036–3.011)	0.036	1.647 (0.972–2.792)	0.063
CHF (vs. non)	0.569 (0.380–0.859)	0.005	0.526 (0.345–0.802)	0.002
PAD (vs. non)	1.341 (0.923–1.948)	0.123	1.203 (0.817–1.772)	0.348
Asthma (vs. non)	1.300 (0.944–1.792)	0.108	1.206 (0.799–1.819)	0.373
COPD (vs. non)	1.220 (0.982–1.516)	0.073	1.038 (0.782–1.379)	0.794
Major depression (vs. non)	1.745 (0.958–3.177)	0.068	1.557 (0.839–2.887)	0.162
Parkinson's disease (vs. non)	0.623 (0.201–1.932)	0.412	0.416 (0.134–1.294)	0.129
Rheumatoid arthritis (vs. non)	1.426 (0.707–2.876)	0.321	1.211 (0.592–2.478)	0.599
Insomnia (vs. non)	1.610 (1.267–2.045)	< 0.001	1.332 (1.030–1.722)	0.028
Hyperthyroidism (vs. non)	1.780 (0.927–3.415)	0.083	1.715 (0.888–3.314)	0.108
Hypothyroidism (vs. non)	0.874 (0.325–2.353)	0.790	0.711 (0.261–1.939)	0.504
Gout (vs. non)	0.998 (0.807–1.235)	0.987	1.026 (0.825–1.277)	0.816
Drugs				
BZDs (vs. non)	1.463 (1.223–1.751)	< 0.001	1.232 (1.005–1.510)	0.045
Anticoagulants (vs. non)	1.163 (0.99–1.367)	0.066	1.101 (0.924–1.312)	0.282
NSAIDs (vs. non)	1.105 (0.938–1.302)	0.232	0.984 (0.825–1.174)	0.860
Acetaminophen (vs. non)	1.091 (0.924–1.288)	0.305	0.963 (0.804–1.153)	0.678
Statins (vs. non)	0.947 (0.802–1.117)	0.518	0.965 (0.802–1.162)	0.707
CCB (vs. non)	1.015 (0.864–1.194)	0.852	0.919 (0.778–1.086)	0.322
ACEI (vs. non)	0.734 (0.608–0.888)	0.001	0.717 (0.588–0.875)	0.001
ARB(vs. non)	0.892 (0.758–1.05)	0.169	0.819 (0.688–0.975)	0.024
Metformin (vs. non)	1.227 (1.036–1.454)	0.018	1.279 (1.075–1.522)	0.005
Beta–blocker (vs. non)	0.900 (0.757–1.068)	0.227	0.883 (0.739–1.053)	0.166
Diuretic (vs. non)	0.791 (0.665–0.942)	0.008	0.792 (0.658–0.954)	0.013

Multivariable model: put all the parameters into analysis

Abbreviation: CHF, chronic heart failure; PAD, peripheral artery disease, COPD, chronic obstructive pulmonary disease, NSAID, non-steroid anti-inflammatory drug; BZD, benzodiazepine; CCB, calcium channel blocker ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blockers

throughout all models and are detailed in Table 3. The effects of insulin usage (yes vs. no) were investigated using 4 stepwise variable-adjusted models; the results were consistent in all the models—the HRs were 0.628 (95% CI: 0.533 to 0.741); 0.631 (95% CI: 0.535 to 0.744); 0.636 (95% CI: 0.539 to 0.751); and 0.652 (95% CI: 0.552 to 0.771), respectively. Moreover, every unit increase in the MPR of insulin was also associated with a significantly lower risk of dementia in the 4 regression models (the HRs were 0.994 [95% CI: 0.992 to 0.996]; 0.995 [95% CI: 0.992 to 0.997]; 0.995 [95% CI: 0.992 to 0.997]; and 0.995 [95% CI: 0.993 to 0.998] respectively).

Dose-dependent effects of insulin usage on the incidence of dementia

Table 4 details the dose-dependent effect of insulin on the incidence of dementia. All groups had significant results relative to the < 20% MPR subgroup. MPR > 80% yielded the best protective effects, with an HR of 0.653 (95% CI: 0.511 to 0.833), and the other subgroups had no significant difference in risk. However, the Cochran-Armitage test indicated a significant dose-dependent effect of insulin usage on decreases in the incidence of dementia ($p < 0.001$).

Subgroup analysis

Figure 3 shows the association between dementia incidence and insulin usage stratified by covariates. The

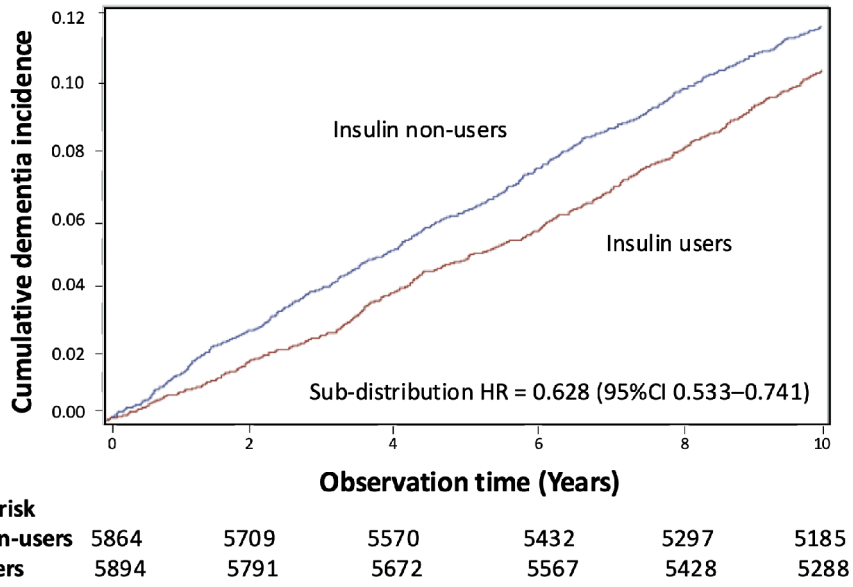

Fig. 2 Comparison of the cumulative incidence of dementia between insulin users and nonusers. The curves display a lower risk of dementia diagnosis in the group of insulin users. The subdistribution hazard ratio was calculated with death taken as a competing risk. The plot was truncated at the 10th year. Abbreviation: HR, hazard ratio; CI, confidence interval

Table 3 Competing risk analysis of insulin usage effects on dementia by Stepwise adjusting confounders

	Insulin (users vs. nonusers)		Every incremental of MPR of insulin	
	HR (95%CI)	*p* value	HR (95%CI)	*p* value
Crude	0.628 (0.533–0.741)	< 0.001	0.994 (0.992–0.996)	< 0.001
Model 1	0.631 (0.535–0.744)	< 0.001	0.995 (0.992–0.997)	< 0.001
Model 2	0.636 (0.539–0.751)	< 0.001	0.995 (0.992–0.997)	< 0.001
Model 3	0.652 (0.552–0.771)	< 0.001	0.995 (0.993–0.998)	< 0.001

Model 1 is adjusted for age and gender. Model 2 comprises model 1 as well as adjustments for comorbidities, including ischemic heart disease, hyperlipidemia, diabetes, atrial fibrillation, congestive heart failure, peripheral artery disease, asthma, chronic obstructive pulmonary disease, major depression, Parkinson's disease, rheumatoid arthritis, insomnia, hyperthyroidism, hypothyroidism, and gout. Model 3 comprises model 2 as well as adjustments for medications of benzodiazepine, anticoagulants, non-steroid anti-inflammatory drug, acetaminophen, statins, calcium channel blocker, angiotensin converting enzyme inhibitors, angiotensin receptor blockades, metformin, beta–blocker, and diuretics

Abbreviation: MPR, medication possession ratio; HR, hazard ratio; CI, confidence interval

Table 4 The dosing effect of insulin prescription on dementia

	Number	aHR (95%CI)	*P* value	Trend test
MPR ≤ 20% (reference)	6990	1		*p* = 0.001
20% < MPR ≤ 40%	481	0.755 (0.491–1.161)	0.201	
40% < MPR ≤ 60%	419	0.880 (0.567–1.344)	0.554	
60% < MPR ≤ 80%	454	0.676 (0.422–1.081)	0.104	
MPR > 80%	2129	0.653 (0.511–0.833)	< 0.001	

Multivariable adjusting model as model 3 in Table 3

Abbreviation: MPR, medication possession ratio; aHR, adjusted hazard ratio; CI, confidence interval

dementia protective effect of insulin use was consistent and significant all subgroups of individuals with hypertensive and diabetic CKD with the exceptions being those aged 40 to 64 years, those with gout disease, and those using ACEIs.

Discussion

The main finding in this nationwide cohort study is that the use of insulin exerted a significant protective effect against dementia in a hypertensive and diabetic CKD cohort. This protective effect was dose dependent. We consistently observed this protective effect of insulin on dementia in almost all subgroups. Our study uses real-world data and indicates that early initiation of insulin therapy in individuals with diabetic CKD protects against dementia.

Insulin has a multifaceted purpose in the CNS in addition to regulating glucose metabolism in peripheral tissues. In normal physiology, insulin crosses the blood-brain barrier through a receptor-mediated transport process, and the rate is modulated by conditions such as obesity and inflammation [29]. Insulin resistance, also known as impaired insulin sensitivity, is defined as the failure of target tissues to have a normal insulin response. Several studies have investigated the relationship between insulin resistance and dementia, including Alzheimer's disease [30, 31] and vascular cognitive impairment [32, 33]. Insulin directly affects Alzheimer's

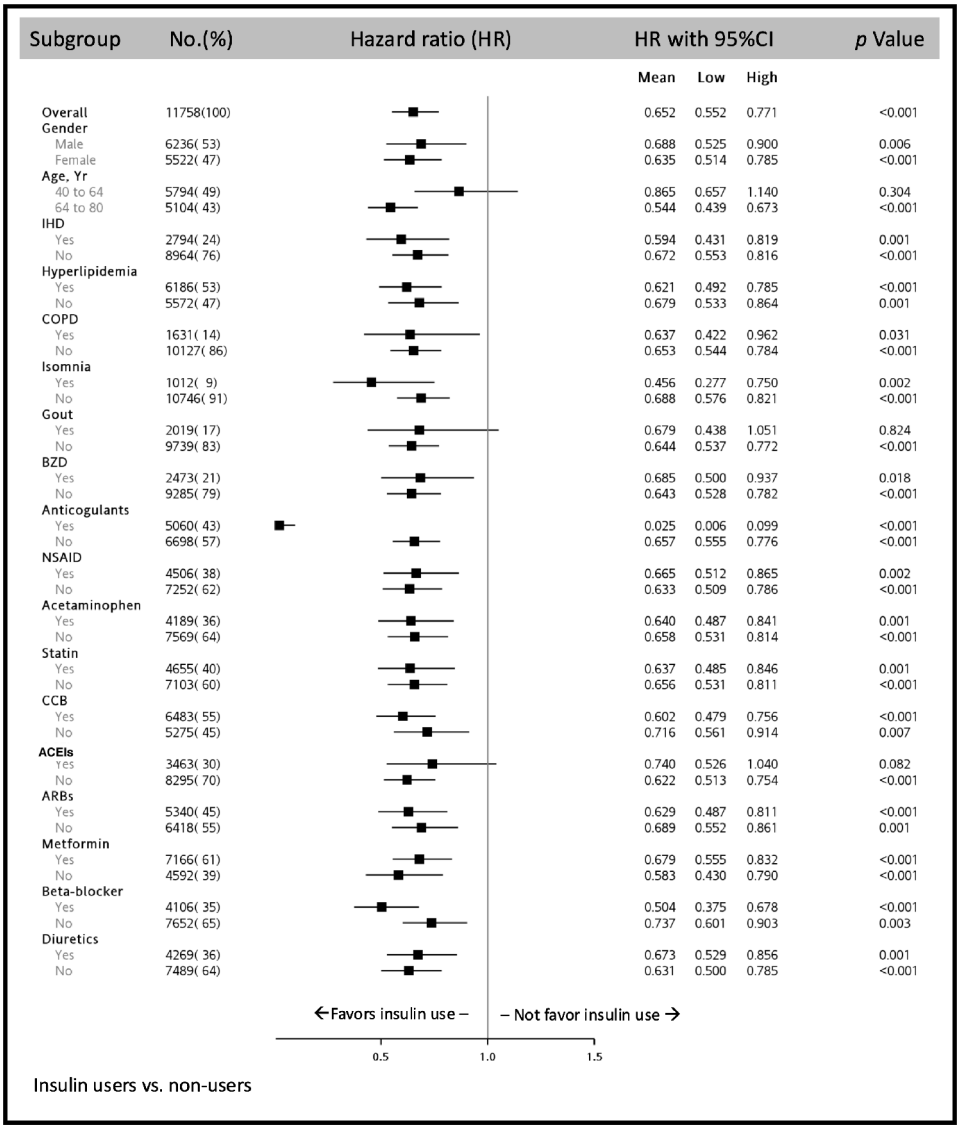

Fig. 3 Subgroup analysis of the effect of insulin use on the incidence of dementia in the multivariable model*. *The full adjusting model was the same as the full adjusting model in Table 2. Abbreviation: IHD, ischemic heart disease; COPD, chronic obstructive pulmonary disease, BZD, benzodiazepine; NSAID, non-steroid anti-inflammatory drug; CCB, calcium channel blocker ACEIs, angiotensin converting enzyme inhibitor; ARBs, angiotensin receptor blockers

disease pathology by protecting against Aβ synaptotoxicity and modulating clearance through its effect. Insulin at normal concentrations protects against cognitive impairment because of its vasoactive effect on cerebral and peripheral blood flow by encouraging endothelial cells to release nitric oxide, which dilates blood vessels [22, 34]. However, insulin at high concentrations can alternatively constrict blood vessels by stimulating the production of endothelin-1 via the mitogen-activated protein kinase pathway. Insulin resistance-associated chronic hyperinsulinemia promotes vasoconstriction, resulting in reduced blood supply to the brain [35].

Intranasal insulin administration is a noninvasive method for delivering insulin to the brain parenchyma and can achieve cerebral concentrations 100 times greater than that in intravenous delivery [36]. A meta-analysis of 7 randomized control trials reported an improvement in verbal memory, particularly story recall, of apoE4 (–) patients with AD or mild cognitive impairment after intranasal insulin administration [37]. Such strong evidence was compatible with our study's findings on the benefit of insulin use on the incidence of dementia. However, one meta-analysis pooling 5 observational cohort studies demonstrated that insulin treatment might be associated with increased adverse cognitive outcomes in diabetic patients [24]. A reason for this discrepancy might be the insulin-induced hypoglycemia or the pitfalls of observational study. Hypoglycemia episodes in diabetic patients are a crucial risk factor for dementia in a systemic review and meta-analysis of 1.4 million patients

[38]. Insulin resistance is greater the longer the patient has DM for; patients who had DM for a long time would be given oral antidiabetic agents (OADs) instead of insulin injection for better blood glucose control. Therefore, diabetic patients with insulin use might indicate high insulin resistance, which is a problem in the observation study.

Managing hyperglycemia in patients with CKD is challenging, requiring the adjustment of OADs and insulin doses [39, 40]. This management is complex because some OADs are contraindicated in CKD, and insulin resistance might therefore increase alongside the decline of renal function due to the accumulation of uremic toxins and inflammatory factors [41]. In Taiwan, the insulin injection rate for DM control was low [42], of which the reason might be the resistance or a fear to the injection therapy. Nevertheless, we found that insulin use has the benefit of preventing dementia in patients with diabetic CKD, indicating that early initiating insulin therapy might be required in such populations to enable better blood glucose control and cognitive health.

Regarding the attenuation of statistical significance within the demographic cohort of individuals aged 40–64 years, as well as the subgroups pertaining to gout pathology and the utilization of ACEIs. The potential hypotheses are delineated as follows. The incidence of dementia is comparatively diminished in individuals within the 40–64 age range [43], thereby mitigating the observable effects of insulin therapy. The inflammatory and metabolic repercussions associated with gout [44] may obscure the advantages conferred by insulin. The neuroprotective attributes of ACEIs [45] in relation to dementia may be confounded with those of insulin, thereby attenuating the observed association. Notwithstanding these deliberations, the neuroprotective impact of insulin on dementia remains evident across a substantial proportion of subcategories, highlighting the necessity for further research into these intricate interactions.

Our study has some strengths. First, the results are representative because our study was a nationwide population-based cohort study. Second, the statistical results for the primary outcome of dementia reflected reality well due to the long follow-up duration of 11 years. Moreover, to ensure that the diagnosis of dementia was reliable and to avoid overcoding (common in a medical claims dataset), we used the approved application for the catastrophic illness certificate of dementia in the NHI, where diagnoses are made according to a strict protocol by a neurologist or psychiatrist. However, our study still has some limitations. First, information regarding potential confounding factors associated with dementia, including body mass index, blood pressure, socioeconomic status, lifestyle and laboratory data, were unavailable in the NHI database. These factors are strongly associated with both insulin use and dementia risk, and their omission might introduce the potential for residual confounding. Second, the extent to which the severity of comorbidities, including but not limited to CKD, hypertension, and hyperlipidemia, as well as the degree of glycemic control, could not be accurately assessed or determined from the NHIRD, which may consequently introduce a degree of bias into our results and lead to potentially misleading interpretations. However, we undertake a comprehensive approach that includes multivariable adjustments, meticulous subgroup analyses, and detailed examinations of dosing effects, all of which could significantly mitigate the potential biases that may arise in our research findings. Finally, it is important to note that the results of the study are confined specifically to the context of Taiwan, indicating that the implications derived from this research may not necessarily be applicable to other regions or populations, thus necessitating further exploration into the generalizability of these findings in broader contexts.

Conclusion

This investigation offers valuable understanding regarding the neuroprotective role of insulin in mitigating dementia in individuals with CKD who also suffer from hypertension and diabetes. We advocate for the prompt initiation of insulin therapy in this patient demographic.

Abbreviations

CKD	Chronic kidney disease
ESKD	End stage of kidney disease
CNS	Central nervous system
MPR	Medication possession ratio
NSAIDs	Non-steroidal anti-inflammatory drugs
ACEIs	Angiotensin converting enzyme inhibitors
ARBs	Angiotensin receptor blockers
SD	Standard deviation
HR	Hazard ratio
CI	Confidence interval
OADs	Oral antidiabetic agents

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Author contributions

Conceptualization: C-YY, F-YW, and C-YH; Data curation: C-YY; Formal analysis: T-MH and C-YY; Funding acquisition: T-MH and C-YY; Investiga-tion: C-YY and F-YW; Methodology: C-YY, T-MH and F-YW; Supervision: C-YY and F-YW; Validation: C-YY; Visualization: T-MH, W-JT; Writing– original draft: T-MH; Writing– review & editing: T-MH and C-YY. All authors discussed the results and contributed to the final manuscript.

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Data availability

The dataset used in this study is held by the Taiwan Ministry of Health and Welfare (MOHW). Any researcher interested in accessing this dataset can apply for access. Please visit the website of the National Health Informatics Project of the MOHW (https:// dep.mohw.gov.tw/dos/np-2497-113.html).

Declarations

Ethics approval and consent to participate
The study protocol adhered to the International Conference on Harmonization Good Clinical Practice guidelines, the Declaration of Helsinki, and applicable laws for noninterventional and observational studies. This study was approved by Shin Kong Wu Ho-Su Memorial Hospital's Ethics Review Board (IRB number: 20200806R) and the informed consent was waived because all personal information was deidentified in this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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