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Diabetes status, duration, and risk of dementia among ischemic stroke patients

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Abstract

Background The influence of duration of type 2 diabetes mellitus (T2DM) on the likelihood of developing new-onset dementia in post-stroke population is not well understood. Therefore, we aimed to clarify the relationship between the duration of T2DM and the risk of developing dementia in the post-stroke population.

Methods Leveraging the Korean National Health Insurance Database, this study included 118,790 individuals with a history of stroke but no previous dementia diagnosis. We classified diabetes status into five categories: normoglycemia, impaired fasting glucose (IFG), newly diagnosed T2DM, and established T2DM with durations of less than 5 years and 5 years or more. The primary endpoint was the incidence of all-cause dementia.

Results Among 118,790 participants (average age 64.26 ± 9.95 years, 48% male), 16.7% developed dementia during an average follow-up of 7.3 ± 2.3 years. Participants with a history of T2DM for less than five years at cohort entry had a 26.7% higher risk of developing all-cause dementia compared to those with normoglycemia. Those with T2DM for five years or longer had a 46.7% increased risk, with an adjusted hazard ratio (aHR) of 1.466 (95% confidence interval [CI], 1.408–1.527). Specifically, the risk of developing Alzheimer's disease (AD) and vascular dementia (VaD) rose by 43.4% and 51.4%, respectively, for individuals with T2DM lasting more than five years (aHR 1.434, 95% CI 1.366–1.505; aHR 1.514, 95% CI 1.365–1.679, respectively).

Conclusions Our findings demonstrated a significant association between an extended duration of T2DM and an increased risk of developing all-cause dementia, including AD and VaD in post-stroke population. These results emphasize proactive dementia prevention approaches in stroke survivors, particularly those with longstanding T2DM.

Keywords Stroke, Dementia, Diabetes mellitus, Duration, Cognition

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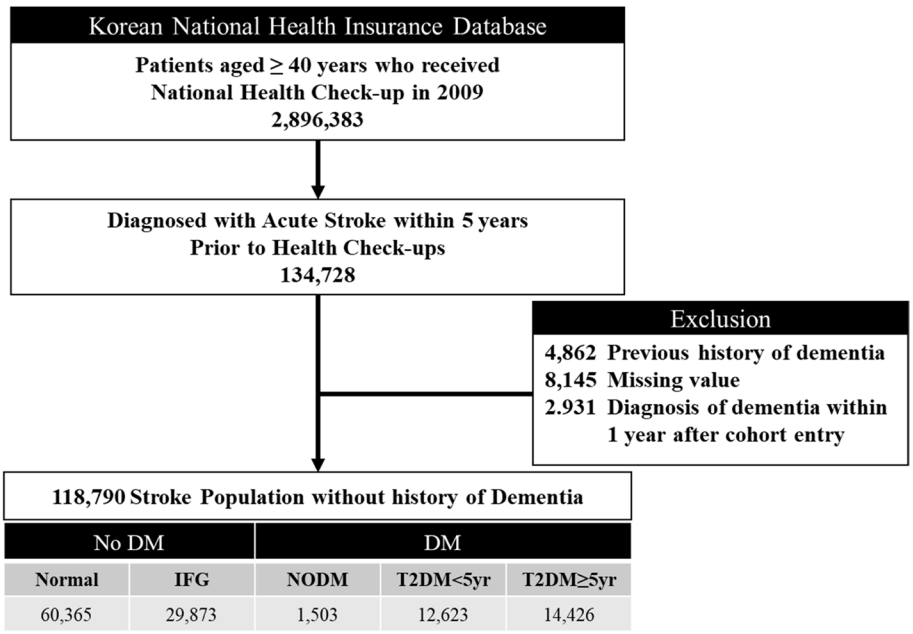

Fig. 1 Study flow chart. Abbreviation: DM, diabetes mellitus; IFG, Impaired fasting glucose; NODM, new-onset DM

Introduction

The incidence of cognitive impairments following a stroke, notably Post-Stroke Cognitive Impairment and Post-Stroke Dementia (PSD), significantly contributes to the disability burden observed in post-stroke survivors [1–4]. This issue is increasingly prevalent in developed nations, where an aging population and healthcare advancements have led to reduced mortality but an elevated incidence of PSD [3]. Notably, PSD can develop independently of functional impairments poststroke, leading to considerable decreases in independence for daily activities [5]. Such conditions not only increase healthcare costs but also profoundly affect the quality of life for patients and their caregivers.

Given the clinical significance of PSD, identifying and modifying its risk factors is crucial, especially since direct preventive treatments are scarce. Therefore, the focus shifts to the understanding and addressing of risk factors [4, 6]. Known risk factors for PSD include age, educational level, stroke severity, post-stroke functional status, stroke lesion location, visible neuroimaging markers, vascular risks, and lifestyle factors [1, 3, 7–9]. Among these, type 2 diabetes mellitus (T2DM) has emerged as a key risk factor, increasing the risk of both stroke recurrence and PSD [1, 10, 11]. However, the nuanced relationship between prediabetes and PSD, as well as the role of T2DM duration in PSD risk, remains inadequately explored [10, 11]. As a vascular risk factor, T2DM may play a greater role in the development of vascular dementia, however, the differential impact of duration of T2DM on each type of dementia has not been fully understood [12].

Therefore, our study aimed to investigate the association between the duration of T2DM and the risk of developing dementia in individuals who have experienced acute stroke. To achieve this goal, we utilized data from the Korean National Health Insurance Service (K-NHIS) database, which encompasses the vast majority of the Korean population.

Methods

Ethical approval

Authorization to utilize the K-NHIS data was obtained following the study's endorsement by the official review committee of the Korean government. The Dongtan Sacred Heart Hospital's institutional review board (IRB HDT: 2023–12-005) also approved the study. Individuals who participated in the national health examinations provided written consent for the use of their data in this research. This investigation was carried out in alignment with the principles of the Declaration of Helsinki and adhered to the STROBE guidelines.

Data source and study population

For this study, data were sourced from the K-NHIS [13]. Figure 1 illustrates the population enrollment flow. From the 2,896,383 individuals aged 40 years and older who underwent a national health examination in 2009, we selected those who had experienced an acute stroke within 5 years prior to their examination (n = 134,728).

Acute stroke was determined using International Classification of Disease, 10th Revision (ICD-10) codes I63 and I64, specifically for individuals who underwent brain imaging through computed tomography (CT) or magnetic resonance imaging (MRI) upon hospital admission. This methodology, corroborated by several studies, is recognized as a reliable technique for identifying acute stroke incidents [14–17]. We excluded individuals with a prior dementia diagnosis ($n=4,862$), those with missing values for key variables used as covariates in the multivariable analysis ($n=8,145$, listed below), and anyone diagnosed with dementia within 1 year after cohort entry ($n=2,931$), to mitigate the risk of immortal time bias and reverse causation. Participants were followed from the index date until the earliest occurrence of the primary outcome, death, or December 31, 2018.

K-NHIS operates as a universal single-payer healthcare system, encompassing more than 97% of South Korea's population. The K-NHIS database, established in 2002 from medical billing records, provides comprehensive data on drug prescriptions, healthcare utilization, demographic characteristics, and diagnoses classified under the ICD-10 system. To promote preventive healthcare, the K-NHIS recommends biennial health examinations for all residents aged 40 years and above, offering these assessments free of charge. These routine checkups include reviewing the individual's medical history, lifestyle surveys, laboratory blood tests, and physical evaluations. The program recorded a high engagement rate, with a 74.8% participation level in 2014 [13].

Diabetic status and duration

The principal exposure variable examined was diabetes status, which was classified into the following categories: nondiabetic, impaired fasting glucose (IFG), newly diagnosed type 2 diabetes mellitus (NODM), established type 2 diabetes mellitus (T2DM) of less than 5 years, and T2DM of 5 years or more at baseline [18]. Fasting plasma glucose(FPG) is measured every 1 to 2 years as part of Korean National Health Screening Program [19], and the IFG was determined by an FPG between 100 and 125 mg/dL [20]. NODM was defined when there was no previous recorded disease code or history of antidiabetic drug prescription, but with a FPG level $\geq$ 126mg/dL at health examination. T2DM was identified using ICD-10 codes E11–E14, recorded either as the primary diagnosis or within the first four supplementary diagnoses. For a consistent diagnosis, we included only individuals meeting additional criteria: a prescription of at least one antidiabetic medication or a fasting blood glucose (FBG) level of $\geq$ 126 mg/dL. The duration of T2DM was calculated from the first recorded date of diabetes-related ICD-10 codes with the associated antidiabetic medication prescriptions before the index date.

Study outcome and covariates

The primary outcome of interest was the incidence of all-cause dementia, encompassing Alzheimer's disease (AD), vascular dementia (VaD), and other dementia types. This was identified through the ICD-10 codes F00, F01, F02, F03, G30, or G31, along with the prescription of dementia-specific medications such as donepezil, galantamine, rivastigmine, or memantine. Secondary outcomes included the incidence of AD (as F00.x and G30.x) and VaD (as F01.x), which were defined using ICD-10 codes solely. If both codes for AD and VaD were present simultaneously for an individual, then the main diagnosis code was extracted for the final diagnosis in this study. Other dementia subtypes were not analyzed due to their rarity and the challenges in accurate subtyping.

The covariates collected included demographic data, body measurements (weight, height, waist circumference), and other variables related to vascular and cognitive health risks. Covariates were defined operationally using different combinations of ICD-10 codes, prescription information, and health check-up data depending on the variables: hypertension, taking anti-hypertensive drugs or SBP > 140 mmHg or DBP > 90 mmHg along with I10-I13, I15; dyslipidemia, lipid-lowering agent or total cholesterol $\geq$ 240 mg/dL with E78; atrial fibrillation, I48; chronic kidney disease, estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^{2}or undergoing dialysis with N18, N19, and depression, F32-34 [21].

Lifestyle factors, such as information on physical activity, alcohol consumption, and income level, were collected via health checkup questionnaires. Laboratory values, including FPG, cholesterol, triglyceride levels, eGFR based on the Modification of Diet in Renal Disease formula, and systolic and diastolic blood pressure, were also documented. Proteinuria was defined as more than 1 + result in dipstick urine test. Income was stratified into quartiles for analysis. Body mass index (BMI) was categorized as underweight (BMI $\leq$ 18.5 kg/m^2), normal weight (BMI 18.25–22.9 kg/m^2), overweight (BMI 23–24.9 kg/m^2), obese (BMI 25–29.9 kg/m^2), or severely obese (BMI > 30 kg/m^2) [22]. Regular physical activity was classified as engaging in moderate exercise for $\geq$ 5 days a week or vigorous exercise for $\geq$ 3 days a week. Alcohol consumption was noted for individuals reporting any intake level.

Statistical analysis

Complete case analysis was performed after excluding individuals with missing data for the examined variables. Participants were categorized into five distinct

groups based on their diabetes status. We then compared baseline characteristics, the prevalence of risk factors, lifestyle behaviors, and laboratory results across these groups. Categorical variables were compared using the chi-square (χ^2) test, while continuous variables were analyzed using one-way ANOVA to assess differences between groups. The cumulative incidence probability of dementia was estimated using the Kaplan–Meier method and the log-rank test was performed for the comparisons between the group. The annual incidence rate of dementia was calculated as the number of new dementia cases per 1000 person-years.

To assess the impact of diabetes status, specifically the duration of T2DM, on the risk of dementia, we conducted comparisons with the nondiabetic group using multivariable Cox proportional hazard regression models, incorporating adjustments for known stroke and dementia risk factors identified in prior research. The analysis was structured progressively across three models: Model 1 was a crude analysis, Model 2 was adjusted for age, sex, income levels, BMI levels, hypertension, dyslipidemia, and atrial fibrillation, and Model 3 was additionally adjusted for smoking, regular physical activity, HDL-cholesterol levels, gamma-glutamyl transferase (GTP) levels, proteinuria, CKD, and depression. The proportional hazards assumption for the Cox models was assessed using Schoenfeld residuals and confirmed to be met, indicating that the model was appropriate for the analysis.

The potential effect modification by age and sex was evaluated in the subgroup analysis, as these factors are well-established modifiers of dementia risk in stroke patients through their influence on both vascular and neurodegenerative pathways [23]. To formally assess effect modification, interaction terms were included in the fully adjusted Cox proportional hazards model. The significance of these interactions was tested using a likelihood ratio test, with corresponding p-for-interaction values reported.

To account for the possibility that death may compete with the risk of developing dementia in a post-stroke population, we performed competing risk analyses with death as a competing event. This approach was used to provide a more accurate assessment of dementia and its subtypes by considering the elevated mortality risk associated with both stroke and advanced age in our cohort. Competing risk analysis was conducted as secondary analysis, allowing us to evaluate dementia risks independently of mortality outcomes. We employed the Fine-Gray subdistribution hazard model to estimate subdistribution hazard ratios with 95% confidence intervals (CIs), for the primary and secondary endpoints.

Results

Demographics and clinical characteristics of the study population

The final study cohort consisted of 118,790 eligible participants, with a mean age of 64.26 ± 9.95 years and 48.0% male (Fig. 1). Participants were divided into five categories according to their diabetes status: 50.82% were nondiabetic, 25.15% had IFG, 1.27% were newly diagnosed with T2DM, 10.63% had T2DM for less than 5 years, and 12.14% had T2DM for 5 years or more. The baseline characteristics of each group are detailed in Table 1. For participants excluded due to missing values in critical covariates, a comparison between the final analysis cohort and the excluded patients showed no clinically significant differences (Supplemental Table 1).

Association between diabetes status and risk of dementia

Participants were followed for an average of 7.3 ± 2.3 years from the index date. Table 2 presents the crude and adjusted hazard ratios (aHRs) for the risk of all-cause dementia and secondary outcomes within the study cohort. Out of the total, 19,844 cases (16.71%) of all-cause dementia were recorded, with AD accounting for 14,415 cases (72.64%) and VaD accounting for 3,005 cases (15.14%). The incidence of all-cause dementia cases across diabetic status groups included 9,250 (10.35%) in the nondiabetic group, 4,616 (15.45%) in the IFG group, 266 (17.70%) in the NODM group, 2,387 (18.91%) in the T2DM group with a duration of less than 5 years, and 3,325 (23.05%) in the T2DM group with a duration of 5 years or more. The incidence rates per 1,000 person-years (PY) and 95% confidence intervals for all-cause dementia were 20.61 [20.35, 20.87], 20.93 [20.63, 21.23], 26.24 [23.62, 28.86], 26.53 [25.10, 27.96], and 34.09 [32.95, 35.23] for each group.

Multivariable Cox proportional hazards analysis showed no significant increase in all-cause dementia risk for the IFG group compared to the nondiabetic group. Although the NODM group showed an increased risk of all-cause dementia in the crude analysis compared to the nondiabetics, this difference was not significant after adjustment. Additionally, NODM was not significantly associated with an increased risk of AD or VaD. A significantly increased risk of all-cause dementia was associated with both a T2DM of less than 5 years (aHR 1.267, 95% CI 1.210–1.327) and a T2DM of 5 years or more (aHR 1.466, 95% CI 1.408–1.527), even after adjustments. This heightened risk was also noted for both AD and VaD.

Kaplan–Meier curves demonstrated that the cumulative incidence probability of all-cause dementia was significantly different between the groups, with the highest cumulative incidence probability observed in the group

Table 1 Demographic and clinical characteristics of the study population according to the diabetes status group

	Total (*n* = 118,790)	Non-diabetic (*n* = 60,365, 50.82%)	IFG (*n* = 29,873, 25.15%)	NODM (*n* = 1,503, 1.27%)	DM < 5 years (*n* = 12,623, 10.63%)	DM ≥ 5 years (*n* = 14,426, 12.14%)	*P*-value
Age	64.26 ± 9.95	63.58 ± 10.31	64.27 ± 10.02	66.23 ± 11.14	64.76 ± 9.2	66.46 ± 8.26	< 0.0001
≥ 65 years	61,710 (51.95)	29,773 (49.32)	15,439 (51.68)	870(57.88)	6,797 (53.85)	8,831 (61.22)	< 0.0001
Sex, male	57,018 (48)	26,680 (44.20)	15,239 (51.01)	865(57.55)	6,793 (53.81)	7,441 (51.58)	< 0.0001
Low income	22,202 (18.69)	11,346 (18.8)	5,411 (18.11)	318(21.16)	2,578 (20.42)	2,549 (17.67)	< 0.0001
Obesity, BMI ≥ 25	49,516 (41.69)	22,210 (36.79)	13,562 (45.40)	581 (38.65)	6,685 (52.96)	6,478 (44.90)	< 0.0001
BMI, kg/m2	24.45 ± 3.15	24.08 ± 3.08	24.7 ± 3.12	24.15 ± 3.18	25.31 ± 3.24	24.76 ± 3.17	< 0.0001
Waist circumference, cm	83.89 ± 8.48	82.42 ± 8.33	84.52 ± 8.29	84.27 ± 8.71	86.75 ± 8.31	86.22 ± 8.28	< 0.0001
Smoking	16,127 (13.58)	7,717 (12.78)	4,036 (13.51)	273(18.16)	2,088 (16.54)	2,013 (13.95)	< 0.0001
Ex-	20,484 (17.24)	9,513 (15.76)	5,679 (19.01)	288(19.16)	2,372 (18.79)	2,632 (18.24)	< 0.0001
Alcohol	31,971 (30.82)	15,245 (25.25)	9,292 (31.10)	526 (34.99)	3,574 (28.31)	3,334 (23.11)	< 0.0001
Regular physical activity	23,823 (20.05)	11,766 (19.49)	6,035 (20.2)	282(18.76)	2,620 (20.76)	3,120 (21.63)	< 0.0001
Hypertension	77,961 (65.63)	35,501 (58.82)	20,249 (67.78)	1,097 (72.99)	9,769 (77.39)	11,345 (78.64)	< 0.0001
Dyslipidemia	47,339 (39.85)	20,382 (33.76)	15,084 (40.45)	573 (38.13)	6,624 (52.48)	7,676 (53.21)	< 0.0001
Chronic kidney disease	20,576 (17.32)	8,824 (14.62)	5,077 (17)	347 (23.09)	2,388 (18.92)	3,940 (27.31)	< 0.0001
Proteinuria	5,973 (5.03)	1,975 (3.27)	1,316 (4.41)	88 (5.85)	908 (7.19)	1,686 (11.69)	< 0.0001
Depression	15,080 (12.69)	7,601 (12.59)	3,680 (12.32)	189 (12.57)	1,609 (12.75)	2,001 (13.87)	0.0002
Atrial fibrillation	3,402 (2.86)	1,596 (2.64)	876 (2.93)	68 (4.52)	427 (3.38)	435 (3.02)	< 0.0001
SBP, mmHg	128.77 ± 16.05	127.31 ± 15.9	129.8 ± 15.84	130.85 ± 16.7	130.82 ± 16.18	130.68 ± 16.35	< 0.0001
DBP, mmHg	78.45 ± 10.22	78.09 ± 10.14	79.19 ± 10.22	79.77 ± 10.3	79.24 ± 10.22	77.56 ± 10.36	< 0.0001
Fasting plasma glucose, mg/dL	105.5 ± 31.53	88.73 ± 7.45	108.51 ± 6.77	143.12 ± 24.19	132.61 ± 43.89	141.81 ± 53.01	< 0.0001
Total Cholesterol, mg/dL	194.43 ± 39.55	195.06 ± 37.98	199.3 ± 39.31	197.81 ± 43.06	192.06 ± 42.23	183.46 ± 41.43	< 0.0001
HDL, mg/dL	54.01 ± 32.65	54.84 ± 32.46	54.84 ± 34.54	53.66 ± 23.92	51.53 ± 30.66	51.04 ± 31.55	< 0.0001
LDL, mg/dL	113.46 ± 41.05	115.32 ± 40.27	116.74 ± 40.28	113.86 ± 47.93	108.63 ± 42.66	103.03 ± 41.64	< 0.0001
*Triglyceride, mg/dL	126.39 (126.02–126.77)	118.21 (117.73–118.69)	130.72 (129.96–131.49)	136.73 (133.02–140.54)	146.19 (144.82–147.57)	136.24 (135.05–137.43)	< 0.0001
GFR, mL/min/1.73m2	79.14 ± 32.95	80.55 ± 33.84	78.88 ± 31.94	76.96 ± 39.03	78.32 ± 29.27	74.73 ± 33.15	< 0.0001
*rGTP, IU/L	27.62 (27.51–27.72)	25.06 (24.93–25.19)	29.9 (29.66–30.14)	32.61 (31.34–33.93)	34.93 (34.48–35.39)	28.13 (27.83–28.44)	< 0.0001
T2DM duration, years	-	-	-	-	1.91 (0.23–3.62)	7.08 (6.23–7.46)	

Abbreviation: *BMI* body mass index, *DM* diabetes mellitus, *GFR* glomerular filtration rate, *GTP* Gamma-glutamyl transpeptidase, *IFG* impaired fasting glucose, *T2DM* type 2 diabetes mellitus

* Geometric mean and 95% confidence interval

with a T2DM duration of 5 years or more. This was followed by similar levels in the groups with a T2DM of less than 5 years and in the NODM group, with the IFG group not showing a significant increase compared to the nondiabetic group (Fig. 2).

Subgroup analyses

Subgroup analyses were performed to examine the risk of dementia by diabetes status across different demographic segments. While the general pattern persisted across groups, a notable finding was that younger population displayed a more pronounced association between dementia risk and T2DM, both < 5 years and ≥ 5 years, compared to their older counterparts. Specifically, in the 40–64 age group, the aHR for all-cause dementia was 1.345 for DM < 5 years and 1.836 for DM ≥ 5 years, compared to 1.248 and 1.399, respectively, in those aged ≥ 65 (P for interaction < 0.001). Regarding sex differences, initial crude analyses suggested a greater risk of dementia associated with diabetes in females. However, this

Table 2 Hazard ratios and 95% confidence intervals of any dementia, Alzheimer's disease and vascular dementia by diabetes status in stroke patients

	N	Event	IR, per 1000 PY	HR (95% CI)		
				Model1	Model2	Model3
All-cause Dementia						
Normal	60,365	9,250	20.61	1 (Ref.)	1 (Ref.)	1 (Ref.)
IFG	29,873	4,616	20.93	1.016 (0.981,1.053)	0.983 (0.949,1.019)	0.979 (0.945,1.014)
New onset	1,503	266	26.24	1.286 (1.139,1.453)	1.007 (0.891,1.137)	0.992 (0.878,1.121)
< 5 years	12,623	2,387	26.53	1.294 (1.237,1.353)	1.288 (1.230,1.348)	1.267 (1.210,1.327)
≥ 5 years	14,426	3,325	34.09	1.676 (1.611,1.744)	1.502 (1.442,1.564)	1.466 (1.408,1.527)
Alzheimer's Disease						
Normal	60,365	6,810	15.18	1 (Ref.)	1 (Ref.)	1 (Ref.)
IFG	29,873	3,382	15.33	1.012 (0.971,1.054)	0.984 (0.944,1.026)	0.980 (0.940,1.022)
New onset	1,503	180	17.76	1.187 (1.024,1.377)	0.929 (0.801,1.078)	0.918 (0.791,1.065)
< 5 years	12,623	1,694	18.83	1.250 (1.185,1.319)	1.260 (1.194,1.330)	1.243 (1.177,1.312)
≥ 5 years	14,426	2,349	24.09	1.618 (1.544,1.696)	1.464 (1.395,1.535)	1.434 (1.366,1.505)
Vascular Dementia						
Normal	60,365	1,359	3.03	1 (Ref.)	1 (Ref.)	1 (Ref.)
IFG	29,873	681	3.09	1.020 (0.931,1.119)	0.962 (0.877,1.055)	0.957 (0.872,1.050)
New onset	1,503	45	4.44	1.477 (1.097,1.988)	1.179 (0.875,1.587)	1.158 (0.860,1.560)
< 5 years	12,623	388	4.31	1.429 (1.277,1.600)	1.340 (1.194,1.503)	1.310 (1.167,1.471)
≥ 5 years	14,426	532	5.46	1.817 (1.644,2.009)	1.557 (1.405,1.725)	1.514 (1.365,1.679)

Model1: crude analysis; Model2: adjustment with age, sex, income, BMI, hypertension, dyslipidemia, and atrial fibrillation; Model3: additional adjustment with smoking, drinking, exercise, HDL, rGTP, proteinuria, chronic kidney disease and depression

Abbreviation: *HR* hazard ratio, *IFG* impaired fasting glucose, *IR* incidence rate

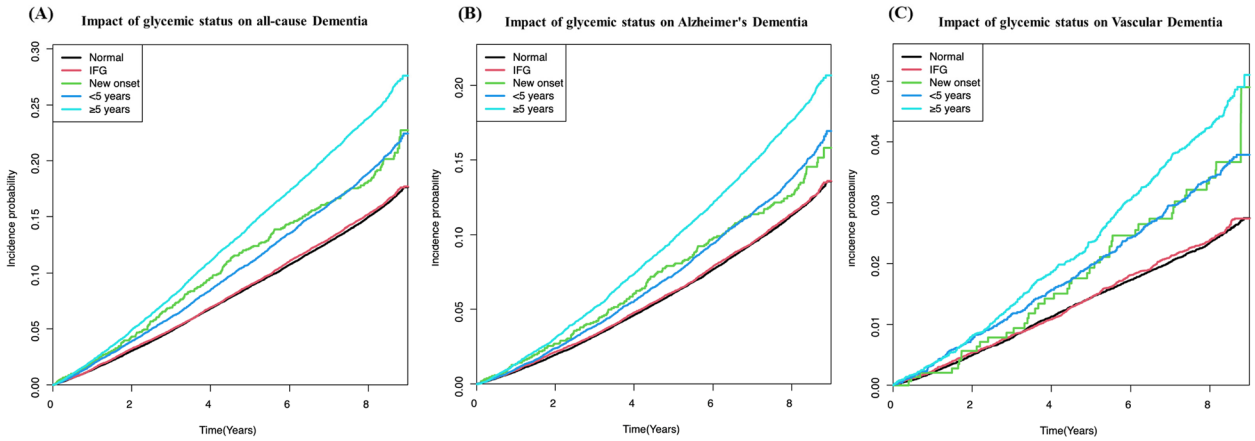

Fig. 2 Incidence probability of **A** all-cause dementia, **B** Alzheimer's disease dementia, and **C** Vascular Dementia after stroke according to the diabetic status. Abbreviation: IFG, impaired fasting glucose

difference became nonsignificant upon applying adjustments in the multivariable analyses (Table 3).

Competing risk analysis

Competing risk analyses, treating death as a competing event, yielded results consistent with those of the primary analysis. The association between T2DM duration and dementia risk remained robust, with aHRs comparable to those observed in the primary Cox regression model. The results are demonstrated in the Supplemental Table 2.

Table 3 Hazard ratios and 95% confidence intervals of all-cause dementia by diabetes status in stroke patient according to the prespecified subgroup

Subgroup		Glycemic Status	N	All-cause Dementia	IR, per 1000 PY	HR (95% CI)		
						Model1	Model2	Model3
Age	40–64	Normal	30,592	1,365	5.51	1 (Ref.)	1 (Ref.)	1 (Ref.)
		IFG	14,434	624	5.36	0.974 (0.886,1.071)	0.962 (0.875,1.058)	0.960 (0.873,1.056)
		NODM	633	31	6.23	1.135 (0.795,1.621)	1.172 (0.821,1.673)	1.148 (0.804,1.639)
		< 5 years	5,826	366	7.96	1.452 (1.294,1.630)	1.375 (1.225,1.544)	1.345 (1.197,1.511)
		≥ 5 years	5,595	523	12.21	2.238 (2.024,2.476)	1.893 (1.710,2.095)	1.836 (1.658,2.033)
	≥ 65	Normal	29,773	7,885	39.25	1 (Ref.)	1 (Ref.)	1 (Ref.)
		IFG	15,439	3,992	38.34	0.977 (0.940,1.015)	0.988 (0.951,1.026)	0.983 (0.946,1.021)
		NODM	870	235	45.58	1.182 (1.038,1.346)	1.006 (0.884,1.146)	0.992 (0.871,1.130)
		< 5 years	6,797	2,021	45.92	1.178 (1.122,1.237)	1.267 (1.206,1.332)	1.248 (1.188,1.312)
		≥ 5 years	8,831	2,802	51.23	1.326 (1.270,1.385)	1.430 (1.369,1.494)	1.399 (1.338,1.462)
	p for interaction					< 0.0001	< 0.0001	< 0.0001
Sex	Male	Normal	26,680	3,588	18.43	1 (Ref.)	1 (Ref.)	1 (Ref.)
		IFG	15,239	1,927	17.23	0.934 (0.884,0.988)	0.968 (0.915,1.023)	0.973 (0.921,1.029)
		NODM	865	112	19.02	1.039 (0.861,1.254)	0.980 (0.812,1.183)	0.967 (0.801,1.168)
		< 5 years	6,793	1,029	21.34	1.162 (1.084,1.245)	1.295 (1.207,1.388)	1.276 (1.190,1.369)
		≥ 5 years	7,441	1,363	27.16	1.490 (1.400,1.586)	1.438 (1.351,1.532)	1.410 (1.323,1.502)
	Female	Normal	33,685	5,662	22.29	1 (Ref.)	1 (Ref.)	1 (Ref.)
		IFG	14,634	2,689	24.74	1.112 (1.062,1.164)	0.994 (0.949,1.041)	0.982 (0.938,1.029)
		NODM	638	154	36.26	1.648 (1.404,1.934)	1.026 (0.874,1.204)	1.011 (0.861,1.187)
		< 5 years	5,830	1,358	32.52	1.468 (1.384,1.558)	1.281 (1.207,1.360)	1.260 (1.186,1.338)
		≥ 5 years	6,985	1,962	41.45	1.887 (1.793,1.987)	1.547 (1.469,1.630)	1.507 (1.430,1.588)
	p for interaction					< 0.0001	0.4422	0.5317

Model1: crude analysis; Model2: adjustment with age, sex, income, BMI, hypertension, dyslipidemia, and atrial fibrillation; Model3: additional adjustment with smoking, drinking, exercise, HDL, rGTP, proteinuria, chronic kidney disease and depression

Abbreviation: *HR* hazard ratio, *IFG* impaired fasting glucose, *NODM* new-onset diabetes mellitus, *IR* incidence rate

Discussion

In this nationwide, population-based cohort study, we found a significant association between T2DM and an increased risk of developing all-cause dementia, AD, and VaD. Additionally, a longer duration of T2DM was linked to a higher risk of all-cause dementia and AD. NODM exhibited an elevated risk for all-cause dementia in initial analyses; however, this association diminished after adjusting for potential confounders. IFG did not show a link to increased dementia risk in this cohort. The impact of T2DM and its duration on dementia risk appeared consistent across different sexes and age groups, yet it was more pronounced in younger demographic groups, specifically those under 65 years old.

Over a median 7.3-year follow-up, all-cause dementia occurred in 16.7% of stroke population in Korea, with an incidence rate of 22.89 per 1000PY. Previous studies have shown that the incidence of PSD varies by study design, population, and length of follow-up [2]. In European studies of prevalence stroke population followed for 5 to 8.3 years, the incidence of dementia was 20.7–24.1% [5, 24]. The greater mean ages of 80 and 74 years in these studies compared to our cohort may largely explain the lower incidence of dementia in our study.

In our study, the prevalence of T2DM among stroke population was 24.0%, which was higher than that in a previous report (16.7%) in the general Korean population over the age of 30 [25]. This elevated prevalence underscores the significant role of T2DM as a vascular risk factor within stroke populations. Hyperglycemia has a deleterious effect on vascular health, promoting free radical production, inflammatory responses, atherosclerosis progression, and accelerated thrombus formation, all of which contribute to increased stroke risk [26]. Beyond vascular effects, hyperglycemia is implicated in dementia development through mechanisms like chronic inflammation, mitochondrial dysfunction, and microglial activation, pathways that are increasingly recognized in both AD and VaD [27, 28].

The progression and duration of DM were identified as critical factors influencing the risk of dementia, which aligns with previous studies indicating that an

earlier onset of diabetes and a longer duration, particularly exceeding 10 years, are linked to cognitive decline [18, 29]. While previous studies have examined the impact of T2DM on dementia incidence in post-stroke patients, the association between T2DM duration and dementia risk has not been extensively investigated [24, 30]. Prolonged exposure to hyperglycemia likely intensifies neurovascular and neurodegenerative changes over time, suggesting that both the timing and duration of T2DM may compound dementia risk, particularly in stroke survivors. These results highlight the importance of vigilant diabetes management to mitigate cognitive decline in at-risk populations.

The influence of the IFG on the development of PSD remains a subject of debate. A prior observational study noted a significant association between prediabetes and cognitive impairment one month after stroke; however, the study's validity may be constrained by its relatively small sample size of 251 patients [31]. Conversely, our study indicated that IFG patients did not experience an increased risk of dementia when compared to the normoglycemic population. This observation aligns with the results from the analysis of the STROKOG consortium, which investigated the association of diabetes, prediabetes, and cognitive function at 3 to 6 months after stroke in 1,601 patients and revealed that, unlike diabetes, prediabetes did not exhibit significant differences in cognition compared to that of normal controls [32]. Additionally, a Chinese study found that diabetes, but not prediabetes, was associated with an increased risk of dementia after stroke [24].

In our cohort, T2DM was found to significantly increase the risk for both AD and VaD, with a slightly larger increase in the aHR for VaD. This outcome is expected since T2DM has a significant role in exacerbating vascular pathologies – more so than its influence on the neurotoxic pathways associated with all-cause dementia, including AD [33]. However, the relatively small proportion of VaD patients within our cohort necessitates a cautious interpretation of the results.

Although the relationship between diabetes status and the risk of all-cause dementia did not significantly differ across sex or age groups, the impact of diabetes on increasing the risk of dementia was more pronounced in younger population. This observation aligns with a previous study indicating that early-onset diabetes heightens the risk of dementia [18]. Although diabetes appeared to increase the risk of dementia in post-stroke population more in women than in men, this association did not persist after adjusting for other variables. This finding is consistent with a prior study that investigated the sex-specific effects of diabetes on dementia [34, 35]. The potentially greater influence of diabetes on women is partly due to their generally lower prevalence of other risk factors [34]. However, since women also tend to be older at the time of stroke, conclusions should be drawn cautiously.

This study is subject to several limitations. First, the nature of a population-based cohort study based on claims data introduces a lack of detailed clinical information. Crucial factors such as stroke severity, stroke subtypes, neuroimaging markers, and medications for stroke prevention that contribute to the risk of dementia after stroke are not available. In particular, the cohort included individuals who participated in a national health examination and completed a structured questionnaire in person, potentially leading to an overrepresentation of mild stroke population. Second, although diabetes status at study inclusion was examined, the dataset provided limited information on specific anti-diabetic medications and the quality of diabetes management throughout the follow-up period. Recent studies suggest that certain anti-diabetic medications, such as metformin, may reduce dementia risk [36]. Therefore, further research is warranted to explore the impact of T2DM treatments on dementia outcomes in the post-stroke population. Third, the use of ICD-10 diagnostic codes to identify dementia subtypes may not be precise, possibly resulting in an underestimation of the incidence of VaD. Fourth, our study focused exclusively on individuals with T2DM as identified by ICD-10 codes E11–E14, and did not include cases of Type 1 DM (ICD-10 code E10). This limits the generalizability of our findings to all diabetes types, and further research is needed to explore the relationship between Type 1 DM and dementia risk, particularly in younger populations. Fourth, because the K-NHIS database has only been systematically recording data since 2002, it is not possible to reliably assess diabetes duration beyond 10 years. While previous studies have often used longer duration categories, such classifications in our study would risk inaccuracies due to data limitations. To ensure methodological rigor, we adopted a five-year threshold, which allowed for a more balanced distribution across groups while minimizing potential biases. Additionally, other subtypes, such as mixed-type dementia, were not included in the analysis as separate outcomes due to limitation of operational diagnosis. Finally, since this study used Korean national data, the findings may not be generalizable to other ethnic or geographic populations.

In conclusion, our study highlights a significant association between extended T2DM duration following a stroke and an elevated risk of all-cause dementia, including AD and VaD. Moreover, this correlation between T2DM duration and dementia risk was notably stronger in younger stroke survivors, particularly those aged

65 years or younger. These findings underscore the importance of implementing proactive measures for dementia prevention in stroke survivors, especially those with a prolonged duration of T2DM.

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
JK and ML wrote the main manuscript text. KDH designed and performed statistical analysis. JYL, YSY, DYC and JJL revised the manuscript.

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Data availability
The data underlying the results presented in the study are available from the Korean National Health Insurance Service. All researchers who wish to use NHIS data, after selecting specific research topic, should first get IRB approval. Then they can apply for data use related to the topic through the Korean National Health Insurance Service homepage (URL: https://nhiss.nhis.or.kr/). After passing through the NHIS deliberation period, researchers receive approval for data use. Data should be handled and analyzed on site only (via direct visit to Korean National Health Insurance Service center). Anyone can analyze the data using the same procedure, detailed above, as the authors. The authors confirm that they did not have any special access or privileges using the data.

Declarations

Ethics approval and consent to participate
Authorization to utilize the K-NHIS data was obtained following the study's endorsement by the official review committee of the Korean government. The Dongtan Sacred Heart Hospital's institutional review board (IRB HDT: 2023-12-005) also approved the study. Individuals who participated in the national health examinations provided written consent for the use of their data in this research. This investigation was carried out in alignment with the principles of the Declaration of Helsinki and adhered to the STROBE guidelines.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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