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Clinical Research Article

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Severe Hypoglycemia Increases Dementia Risk and Related Mortality: A Nationwide, Population-Based Cohort Study

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Abbreviations: AD, Alzheimer disease; BMI, body mass index; eGFR, estimated glomerular filtration rate; HR, hazard ratio; ICD-10, International Statistical Classification of Disease and Related Health Problems, 10th Revision; NHIS, National Health Insurance Service; VaD, vascular dementia.

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Abstract

Context: There are few studies focused on the relationship between hypoglycemia and new-onset dementia in patients with type 2 diabetes and no study regarding mortality of dementia after hypoglycemia.

Objective: We investigated the effect of severe hypoglycemia on dementia subtypes and its relation to overall mortality in patients with type 2 diabetes.

Methods: We evaluated incident dementia, including Alzheimer disease and vascular dementia, among health checkup participants aged 40 years or older in the National Health Insurance System in Korea from January 2009 to December 2015. Episodes of severe hypoglycemia were examined for 3 years before the date of the health checkup.

Results: Among 2 032 689 participants (1 172 271 men, 860 418 women), 14 443 (0.7%) experienced severe hypoglycemia, during a mean follow-up period of 6.9 ± 1.7 years. Individuals in the severe hypoglycemia group were more likely to be diagnosed with dementia compared to individuals without severe hypoglycemia (23.3% vs 7.3%; $P < .001$) and the overall incidence of Alzheimer disease was higher than vascular dementia. Dementia risk rose with increasing number of severe hypoglycemic episodes (1 episode

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[hazard ratio (HR) = 1.54; 95% CI, 1.48-1.60], 2 or more episodes [HR = 1.80; 95% CI, 1.66-1.94]). Overall mortality was higher in participants with dementia, but without severe hypoglycemia (HR = 2.03; 95% CI, 1.96-2.10) and severe hypoglycemia, but without dementia (HR = 4.24; 95% CI, 4.29-4.40), and risk of death was highest in those with both severe hypoglycemia and dementia (HR = 5.08; 95% CI, 4.83-5.35).

Conclusion: Severe hypoglycemia is associated with dementia, especially Alzheimer disease and mortality; together, they have an additive effect on overall mortality.

Key Words: hypoglycemia, dementia, mortality, diabetes

Despite efforts to improve health care in older individuals, dementia remains a public health problem worldwide. More than 35.6 million people live with dementia and its prevalence almost doubles every 20 years (1). The known risk factors for the development and progression of dementia include demographics (older age, female sex, family history, low socioeconomic status, smoking, alcohol consumption), genetics (apolipoprotein E, sortilin-related receptor), and lifestyle (hypertension, diabetes, obesity, dyslipidemia, metabolic syndrome) (2). Diabetes is regarded as an important predictor of dementia, increasing the risk of all-cause dementia by 60% (3).

Hyperglycemia increases the risk of all-cause dementia including Alzheimer disease (AD) and vascular dementia (VaD) (4), and uncontrolled hyperglycemia can increase mortality risk in patients with dementia (5). However, intensive antihyperglycemic therapy can tend to increase the risk of hypoglycemia, which causes various sequelae including death. Regardless of severity, hypoglycemia is associated with increased mortality risk (6) and cardiovascular disease (7-9). Acute hypoglycemia significantly impairs executive function (10), and even reversible hypoglycemic episodes can induce focal neurological deficit (11). Therefore, it is of paramount importance to prevent hypoglycemia to protect against cognitive function decline by identifying high-risk patients receiving intensive treatment for diabetes.

A recent study reported that a decrease in glucose precedes dementia (12). However, the pathophysiologic link between hypoglycemia and dementia has not been fully elucidated. Hypoglycemia has the potential to trigger macrovascular impairment in the brain, thus inducing neuronal damage (12). There are few studies focused on the relationship between hypoglycemia and new-onset dementia in patients with type 2 diabetes and no study regarding mortality of dementia after one or more hypoglycemic episodes. Therefore, we investigated the association between hypoglycemic episodes and risk of dementia and all-cause mortality in patients with type 2 diabetes by analyzing data from the National Health Insurance Service (NHIS), which comprises the entire Korean population.

Materials and Methods

Study Participants

This longitudinal cohort study used data collected from participants in the NHIS, the single insurer in the Korean public health sector that provides health examinations comprising the entire Korean population (13), which can be used as a population-based source for medical research (14). The NHIS regular checkup includes anthropometric measurements, blood pressure, social habits, physical activity, and laboratory tests with overnight fasting. Laboratory samples are collected and measured as previously described (15). Past medical history, alcohol consumption, smoking history, and exercise habits are collected by standardized self-report questionnaires. Body mass index (BMI) is calculated as weight in kilograms divided by height in meters squared and obesity is defined as a BMI of 25 or greater using the Asian-Pacific criteria (16). This study was approved by the institutional review board of the Yonsei University College of Medicine (IRB No. 4-2016-0575) and was conducted in compliance with the Declaration of Helsinki.

Definition of Type 2 Diabetes, Hypoglycemia, and Dementia

To obtain information on incident dementia, we followed a cohort of 2 032 689 participants with type 2 diabetes who were aged 40 years or older and were dementia free (Fig. 1). Type 2 diabetes was defined as at least one service claim with a diagnosis of diabetes, either in outpatient or inpatient care. The diagnosis of type 2 diabetes was based on the International Statistical Classification of Disease and Related Health Problems, 10th Revision (ICD-10; codes E11, E14). Inclusion criteria were the following: 1) received health care checkups from January 1, 2006 through December 31, 2015; 2) treated with hypoglycemic agents (including insulin) per claims database; 3) not previously diagnosed with dementia. Patients with type 1 diabetes, gestational diabetes, other types of diabetes, and those with missing data were excluded.

Episodes of severe hypoglycemia were examined for 3 years before the date of the health checkup. To assess the incidence of dementia and mortality, participants were followed until death or December 31, 2015, after the first diagnosis of dementia (Fig. 2). We previously defined severe hypoglycemia as any hypoglycemic event requiring the assistance of another person to actively administer carbohydrates, or the need for corrective action, hospitalization, or adjustment of medical treatment (9, 17). We used ICD-10 codes E16.x, E11.63, E13.63, and E14.63 to assess severe hypoglycemia both in inpatient and emergency room claims.

Incident dementia was defined as an ICD-10 diagnostic code of F00, G30, F01, F02, F03, G23.1, G31.0, G31.1, G31.82, G31.83, G31.88, or F10.7 with simultaneous prescription of an antidementia medication (18, 19). Antidementia medications included an acetylcholinesterase inhibitor (rivastigmine, galantamine, or donepezil) or *N*-methyl-D-aspartate receptor antagonist (memantine). Patients with dementia were classified as AD (ICD-10 codes F00, G30) or VaD (ICD-10 code F01) for subgroup analyses. Date of dementia diagnosis was the date when prescription of an antidementia medication and a dementia code coincided. Type of dementia was considered the first diagnosis code of dementia.

Hypertension was defined as ICD-10 codes I10 to I13, I15 plus treatment with antihypertensive agents, or systolic/diastolic blood pressure greater than or equal to 140 mm Hg/greater than or equal to 90 mm Hg; dyslipidemia was ICD-10 code E78 plus treatment with lipid-lowering agents or total cholesterol greater than or equal to 240 mg/dL. A previous medical history of ischemic stroke or myocardial infarction was defined as ICD-10 codes I63 and I64 or I21 and I22 before the date of the health examination. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease Study equation, and chronic kidney disease was characterized as eGFR less than 60 mL/min/1.73 m^2 (20). We considered low social economic status as the lowest quartile for income in the study population (21). Heavy alcohol consumption was defined as 30 g/day or more, and regular exercise was categorized as 3 times or more per week of moderate to vigorous physical activity.

The primary outcome was development of dementia during the follow-up period or until death. For all-cause mortality, we used individuals who died of any cause. The secondary outcome was all-cause mortality after dementia diagnosis.

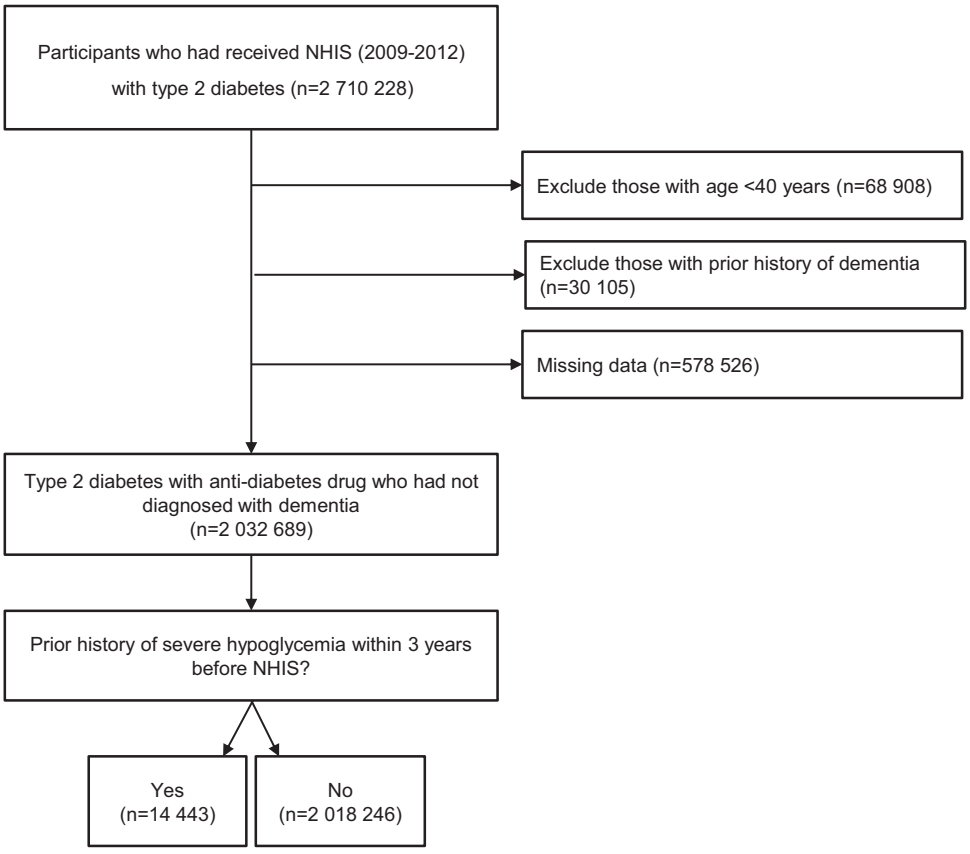

Figure 1. Study flow. NHIS, National Health Insurance Service.

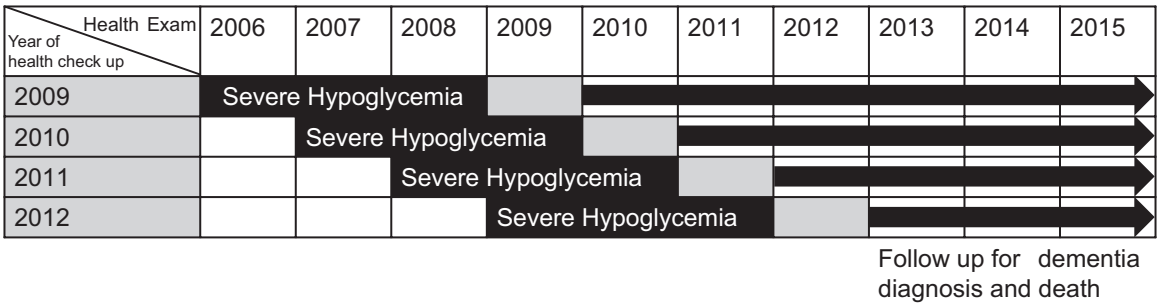

Figure 2. Study design summarizing participant selection and follow-up. Health care checkups (national health examination) performed from January 1, 2009 to December 31, 2012 were screened in patients with type 2 diabetes (light gray box). Presence of severe hypoglycemia occurring in the preceding 3 years of health care checkup date was evaluated from claim data (black box). After then, occurrence of dementia and mortality was investigated until December 31, 2015 (black arrow).

Statistical Analysis Plan

Descriptive characteristics were mainly presented as mean ± SD. The χ^2 test was used to determine differences in percentages of categorical variables, and the independent *t* test was used to evaluate differences between the means of 2 continuous variables. To determine the dose-response relationship between hypoglycemic events and incident dementia, we counted the number of severe events. Incidence rates were expressed as events per 1000 person-years and were adjusted for age and sex using the direct method. Cox proportional hazards regression analysis was used to identify the association between severe hypoglycemia and dementia after adjusting for other risk factors. Results were presented as hazard ratios (HRs) and 95% CIs. Subgroup analysis by age groups (aged 40-59 years vs > 60 years) was performed to limit age factor in the association between dementia and severe hypoglycemia. Dementia-free survival according to the number of severe hypoglycemic events and survival rate according to severe hypoglycemic events was analyzed using Kaplan-Meier expressed as adjusted HR and 95% CI. A 2-sided *P* value less than .05 was considered statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute).

Results

Baseline Characteristics of Study Population

A total of 2 032 689 individuals (1 172 271 men, 860 418 women) with type 2 diabetes were included in the final statistical analysis (see Fig. 1). Of these, 14 443 (0.7%) participants experienced severe hypoglycemia during a mean follow-up period of 6.9 ± 1.7 years. The clinical characteristics of the study population are presented in Table 1. Individuals with a prior history of severe hypoglycemia were significantly older (67.4 ± 10.1 vs 59.8 ± 10.6 years; $P < .001$) and the proportions of patients 60 years or older and female, respectively, were higher in the severe hypoglycemia group (79.1% vs 51.3% and 57.7% vs 48.7%). These individuals also tended to have longer type 2 diabetes duration, lower BMI (23.7 ± 3.5 vs 25.0 ± 3.3), and lower waist circumference (83.7 ± 9.1 vs 85.5 ± 8.4 cm). The presence of hypertension (86.1% vs 68.2%), dyslipidemia (64.4% vs 56.4%), cardiovascular disease (16.2% vs 8.3%), and chronic kidney disease (40.4% vs 12.8%) was higher in the severe hypoglycemia group. The proportion of current smokers (22.8% vs 17.1%) and heavy alcohol drinkers (9.2% vs 5.3%) was higher in the nonsevere hypoglycemia group, although they tended to exercise regularly (21.8% vs 16.1%).

According to laboratory tests, fasting blood glucose (133.3 ± 55.1 vs 140.3 ± 43.4 mg/dL), total cholesterol (180.3 ± 42.3 vs 194.7 ± 41.7 mg/dL), high-density lipoprotein (50.5 ± 22.3 vs 51.6 ± 21.3 mg/dL), and eGFR (67.9 ± 35.0 vs. 83.3 ± 36.1 mL/min/1.73 m^2) were significantly lower in participants with severe hypoglycemia vs those nonsevere hypoglycemia (all $P < .05$). In terms of antidiabetic medications, use was higher in individuals with a history of severe hypoglycemia: insulin (36.7% vs 8.6%); sulfonylurea (64.4% vs 45.4%); and meglitinide (8.5% vs 2.5%). Additionally, participants with severe hypoglycemic episodes were more likely to have dementia (23.3% vs 7.3%; $P < .001$), more often AD (17.1% vs 5.4%) rather than VaD (2.8% vs 1.0%; all $P < .001$).

Risk of Dementia According to Frequency of Severe Hypoglycemic Episodes

A total of 149 626 individuals were diagnosed as having dementia (110 681 as AD and 19 773 as VaD) during the follow-up periods. To investigate the risk of dementia according to frequency of severe hypoglycemic events, we categorized participants by number of episodes. Of the 14 443 participants with severe hypoglycemia, 2707 (18.7%) had 1 episode and 471 (3.3%) had 2 or more. Using a minimally adjusted model (model 1) that included age and sex,

Table 1. Characteristics of study population

	Participants without severe hypoglycemia (N = 2 018 246)	Participants with severe hypoglycemia (N = 14 443)	P
Age, y	59.8 ± 10.6	67.4 ± 10.1	< .001
Age > 60 y, n (%)	1 034 982 (51.3)	11 425 (79.1)	< .001
Sex, male, n (%)	1 165 235 (57.7)	7036 (48.7)	< .001
Type 2 diabetes duration (> 5 y), n (%)	716 134(35.5)	10 531 (72.9)	< .001
Follow-up duration, y	6.9 ± 1.7	5.6 ± 2.5	
Overall dementia, n (%)	146 268 (7.3)	3358 (23.3)	< .001
Alzheimer disease, n (%)	108 209 (5.4)	2472 (17.1)	< .001
Vascular dementia, n (%)	19 374 (1.0)	399(2.8)	< .001
Body mass index, kg/m^2	25.0 ± 3.3	23.7 ± 3.5	< .001
Body mass index category, n (%)			
< 18.5	29 813 (1.5)	767 (5.3)	< .001
18.5-25	1 022 592 (50.7)	8961 (62.1)	
> 25	965 841 (47.9)	4715 (32.6)	
Waist circumference, cm	85.5 ± 8.4	83.7 ± 9.1	< .001
Central obesity, n (%)	996 347 (49.4)	6712 (46.5)	< .001
Systolic blood pressure, mm Hg	129.2 ± 15.7	129.2 ± 17.3	< .001
Diastolic blood pressure, mm Hg	78.9 ± 10.1	76.8 ± 10.4	< .001
Hypertension, n (%)	1 376 602 (68.2)	12 440 (86.1)	< .001
Fasting blood glucose, mg/dL	140.3 ± 43.4	133.3 ± 55.1	< .001
Total cholesterol, mg/dL	194.7 ± 41.7	180.3 ± 42.3	< .001
HDL cholesterol, mg/dL	51.6 ± 21.3	50.5 ± 22.3	< .001
Triglycerides, mg/dL	146.3 (146.1-146.4)	128.9 (127.8-130.1)	< .001
Dyslipidemia, n (%)	1 138 483 (56.4)	9304 (64.4)	< .001
eGFR, mL/min/1.73m^2	83.3 ± 36.1	67.9 ± 35.0	< .001
Chronic kidney disease, n (%)	257 607 (12.8)	5839 (40.4)	< .001
Current smoking, n (%)	460 075(22.8)	2468 (17.1)	< .001
Heavy alcohol drinking, n (%)	184 889 (9.2)	766 (5.3)	< .001
Regular exercise, n (%)	439 441 (21.8)	2317 (16.1)	< .001
Lower income, n (%)	438 885 (21.8)	3671 (25.4)	< .001
Stroke, n (%)	52 583 (2.6)	820 (5.7)	< .001
Heart disease, n (%)	124 428 (6.2)	1655 (11.5)	< .001
Antidiabetes medication, n (%)	1 302 717 (64.6)	13 228 (91.6)	< .001
Insulin, n (%)	173 245 (8.6)	5297 (36.7)	< .001
Sulfonylurea, n (%)	917 032 (45.4)	9305 (64.4)	< .001
Metformin, n(%)	979 300 (48.5)	8923 (61.8)	< .001
Meglitinide, n (%)	50 487 (2.5)	1230 (8.5)	< .001
Thiazolidinedione, n (%)	143 371 (7.1)	1447 (10.0)	< .001
DPP4 inhibitor, n (%)	188 387 (9.3)	1818 (12.6)	< .001
Acarbose, n (%)	253 452 (12.6)	4194 (29.1)	< .001

Hypertension was defined as ICD-10 codes (I10-13, I15) plus treatment with antihypertensive agents, or systolic or diastolic blood pressure greater than or equal to 140 mm Hg/greater than or equal to 90 mm Hg.
Dyslipidemia was ICD-10 code of E78 plus treatment with lipid-lowering agents or total cholesterol greater than or equal to 240 mg/dL.
Stroke was defined as ICD-10 codes of I63 and I64.
Heart disease was defined as ICD-10 codes I21 and I22.
Chronic kidney disease was characterized as subjects with eGFR less than 60 mL/min/1.73 m^2.
Low social economic status was the lowest quartile for income in the study population.
Heavy alcohol consumption was defined as 30 g or more per day.
Regular exercise was categorized as 3 or more times per week of moderate to vigorous physical activity.
Abbreviations: DPP4 inhibitor, dipeptidyl-peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate, HDL, high-density lipoprotein; ICD-10, International Statistical Classification of Disease and Related Health Problems, 10th Revision.

individuals with severe hypoglycemia showed a higher risk of overall dementia compared to individuals without a severe hypoglycemic event. Additionally, risk for dementia gradually rose with increasing numbers of episodes (HR = 1.88; 95% CI, 1.81-1.95, $P < .001$ for 1 episode; HR = 2.36; 95% CI, 2.19-2.55, $P < .001$ for ≥ 2 episodes) (Table 2).

When the model was further adjusted for other variables, the independent and dose-dependent associations between severe hypoglycemia and risk of dementia were maintained (1 episode [HR = 1.54 ~ 88, all $P < .001$], 2 or more episodes [HR = 1.80 ~ 2.36, all $P < .001$]). When analyzed separately, by AD and VaD, the HR for individuals with AD, and 2 or more episodes of severe hypoglycemia were statistically significant. Contrarily, the dose-dependent relationship between the number of severe hypoglycemic episodes and HR was not observed in individuals with VaD. We further assessed the association of dementia with severe hypoglycemia by age (40-59 y vs > 60 y). The risk of dementia was increased in individuals who had severe hypoglycemia in both age groups across the dementia subtypes (Table 3).

Overall Mortality in Individuals According to the Presence of Severe Hypoglycemia and Dementia

Among 149 626 participants with newly diagnosed dementia, 41 567 (27.8%) died during the follow-up period. As expected, these individuals were statistically significantly older (70.7 ± 7.2 vs 74.4 ± 8.1 y; $P < .001$) and had more comorbidities (hypertension, stroke, heart disease, and chronic kidney disease) (Table 4), although they had lower BMI and waist circumference. Prior history of severe hypoglycemia was greater among individuals who died (1868 [1.7%] vs 1490 [3.6%]; $P < .001$).

We used stratification to analyze the independent association between severe hypoglycemia and dementia relative to overall mortality. As shown in Table 5, overall mortality gradually increased in participants with sole dementia (HR = 2.03; 95% CI, 1.96-2.10) and sole severe hypoglycemia (HR = 4.34; 95% CI, 4.29-4.40), and risk of death was highest in the participants with both severe hypoglycemia and dementia (HR = 5.08; 95% CI, 4.83-5.35).

Next, we investigated mortality risk according to number of severe hypoglycemic episodes (Table 6). The incidence ratio of mortality gradually increased with the greater numbers of episodes, but individuals with dementia showed a markedly higher incidence ratio (102.09 to 188.70) compared to those without dementia. A dose-dependent association was observed in participants with hypoglycemia absent dementia (1 episode [HR = 1.86; 95% CI, 1.79-1.93], 2 or more episodes [HR = 2.40; 95% CI, 2.22-2.58]) compared with participants with hypoglycemia and dementia (1 episode [HR = 1.29; 95% CI, 1.22-1.37], 2 or more episodes [HR = 1.35; 95% CI. 1.21-1.51]).

Discussion

In this large, national population-based study, we observed that individuals with severe hypoglycemia had a higher risk of developing dementia, independent of glycemic status and other important potential confounders. The number of severe hypoglycemic episodes had a linear relationship with risk of dementia. In particular, the influence of severe hypoglycemia on developing dementia was more evident for AD compared to VaD. Moreover, one severe hypoglycemic episode increased the mortality risk in participants with and without dementia. While severe hypoglycemia and dementia had an additive effect on overall mortality, the risk appears to be higher with the former vs the latter.

The effect of chronic exposure to hyperglycemia on dementia has been well established; likewise, severe hypoglycemia causes cognitive dysfunction. Type 2

Table 2. Risk of dementia by number of hypoglycemic episodes

No.		Duration, y	Incidence rate	Model 1	Model 2	Model 3	Model 4
	Overall dementia						
0	146 268	13 884 678.2	10.535	1 (reference)	1 (reference)	1 (reference)	1 (reference)
1	2707	69 396.2	39.008	1.88 (1.81-1.95)	1.85 (1.78-1.92)	1.77 (1.70-1.84)	1.54 (1.48-1.60)
> 2	651	12 033.2	54.100	2.36 (2.19-2.55)	2.30 (2.13-2.49)	2.16 (2.00-2.33)	1.80 (1.66-1.94)
	Alzheimer disease						
0	108 209	13 884 678.2	7.793	1 (reference)	1 (reference)	1 (reference)	1 (reference)
1	1977	69 396.2	28.489	1.83 (1.75-1.92)	1.81 (1.73-1.89)	1.74 (1.66-1.82)	1.52 (1.45-1.59)
> 2	495	12 033.2	41.136	2.41 (2.21-2.64)	2.36 (2.16-2.58)	2.22 (2.03-2.43)	1.87 (1.71-2.04)
	Vascular dementia						
0	19 374	13 884 678.2	1.395	1 (reference)	1 (reference)	1 (reference)	1 (reference)
1	334	69 396.2	4.813	1.91 (1.71-2.13)	1.87 (1.68-2.09)	1.77 (1.59-1.97)	1.50 (1.34-1.67)
> 2	65	12 033.2	5.402	1.97 (1.54-2.52)	1.91 (1.50-2.45)	1.78 (1.39-2.27)	1.43 (1.12-1.83)

Model 1: adjusted for age and sex.
Model 2: adjusted for model 1 + smoking, alcohol drinking, exercise, and lower income.
Model 3: adjusted for model 2 + body mass index, hypertension, and dyslipidemia.
Model 4: adjusted for model 3 + insulin use, antidiabetes drug number, heart disease, stroke history, and duration of type 2 diabetes (> 5 y).

Table 3. Risk of dementia among patients with prior severe hypoglycemia by age group

Age, y	Overall dementia			Alzheimer disease			Vascular dementia		
	No. with dementia/ No. in group	HR	95% CI	No. with dementia/ No. in group	HR	95% CI	No. with dementia/ No. in group	HR	95% CI
40-59	198/3018	3.08	2.49-3.81	146/3018	3.05	2.30-4.05	24/3018	2.87	1.85-4.46
≥ 60	3160/11 425	1.59	1.53-1.65	2326/11 425	1.61	1.53-1.68	375/11 425	1.42	1.26-1.60

Adjusted for age, sex, smoking, alcohol drink, exercise, lower income, body mass index, hypertension, dyslipidemia, insulin use, antidiabetes drug number, heart disease, stroke history, and duration of type 2 diabetes (> 5 y).
Abbreviation: HR, hazard ratio.

diabetes has a known association, with a 1.5- to 2.5-fold increased risk of dementia compared to normoglycemic individuals (19, 22), and dementia risk in type 2 diabetes with hypoglycemia has been reported as a 1.2- to 1.6-fold increase, comparable with our results (23, 24). Consistent with previous findings (10, 23, 24), the present study clearly demonstrated that individuals with multiple episodes of severe hypoglycemia were associated with a gradual increase in dementia risk, which could be explained by several mechanisms. First, a hypoglycemic episode is associated with selective neuronal death in the hippocampus and cerebral cortex, and accelerates the process of dementia (25, 26). Second, hypoglycemia directly induces thrombosis activation and indirectly increases the concentration of adrenaline, which induces blood coagulation (27). Third, endothelial dysfunction and vascular injury evoked by hypoglycemia contribute to cognitive decline (28, 29). In an animal study, hypoglycemia enhanced amyloid precursor protein messenger RNA expression in astroglial cells and processing of amyloid precursor protein messenger RNA to a form that may encourage β-amyloid deposits in AD (30). Another in vitro and in vivo study demonstrated that hypoglycemia upregulates the adenosine monophosphate–activated protein kinase–protein kinase B–GSK3 pathway and leads to tau hyperphosphorylation, and that cerebral hypoglycemia/hypometabolism directly contributes to the development of AD (31). The present study showed that hypoglycemic episodes increased the risk of both AD and VaD, with the risk higher in AD vs VaD. Although it is difficult to distinguish between AD and VaD (both pathologies are commonly observed in a single patient), our results suggest that hypoglycemia could make the brain more vulnerable to AD pathology, and that mechanisms of hypoglycemia and dementia could be explained beyond microinfarction or macroinfarction complications. Differences in dementia subtype pathophysiology might influence the effect of hypoglycemia. Insulin resistance, which is an essential feature of type 2 diabetes, also occurs in the brain even in the absence of diabetes, particularly precipitating AD development and progression (32). Indeed, insulin plays a crucial role in neurons, managing synapses and modulating glial cells, with insulin signaling in the central nervous system regulating metabolic pathways in peripheral tissues (32). Metabolic imaging with ^{18}F-fludeoxyglucose–positron emission tomography has shown decreased brain glucose metabolic activity and regional cortical hypometabolism in individuals with insulin resistance (33-35). In addition, there is evidence to support the independence of vascular pathology and AD burden in cognitive decline (36, 37). Repeated episodes of hypoglycemia could accelerate cognitive dysfunction already vulnerable because of preexisting metabolic factors (mainly insulin resistance), and this might reflect the dose-dependent increased risk in AD.

Diabetes is the sixth and seventh leading cause of death in Korea and the United States, respectively (38, 39). With the development of revascularization and statins, the mortality rate related to cardiovascular disease has declined from previous decades (39). However, death from dementia has increased and dementia lessens overall survival time (40). Hypoglycemia increases mortality in patients with diabetes. In a 5-year follow-up study, self-report of severe hypoglycemia was associated with a 3.4-fold increased risk of death independent of diabetes duration or glycated hemoglobin A_{1c} concentration (6). Considering the relationship between hypoglycemia and dementia, it is reasonable to expect a higher risk of death in those patients. The present study is one of the first epidemiologic studies to show that the association of severe hypoglycemia with incident dementia may be most pronounced for outcomes strongly linked to all-cause mortality. We observed that, after multivariable adjustment, both prior history of hypoglycemia and incident dementia were statistically significantly associated with increased mortality (HR = 5.08). Additionally, the present study showed that dose dependency (number of hypoglycemic episodes and overall mortality) was diminished in individuals with dementia. Dementia is known to increase the overall mortality rate (41, 42), whereas

Table 4. Comparison of dead and alive individuals among participants of incident dementia

	Alive (n = 108 059)	Dead (n = 41 567)	P
Age, y	70.7 ± 7.2	74.4 ± 7.1	< .001
Age > 60 y, n (%)	101 168 (93.6)	40 480 (97.4)	< .001
Male sex, n (%)	37 422 (34.6)	21 104 (50.8)	< .001
Diabetes duration (> 5 y), n (%)	52 411 (48.5)	22 131 (53.2)	< .001
Follow-up duration, y	4.7 ± 2.2	3.4 ± 2.0	< .001
Severe hypoglycemia, n (%)	1868 (1.7)	1490 (3.6)	< .001
Alzheimer disease, n (%)	81 261 (75.2)	29 414 (70.8)	< .001
Vascular dementia, n (%)	14 019 (13.0)	5754 (13.8)	< .001
Body mass index	24.63 ± 3.24	23.6 ± 3.4	< .001
Body mass index category, n (%)			< .001
< 18.5	2182 (2.0)	2132 (5.1)	
18.5-25	59 479 (55.0)	26 223 (63.1)	
> 25	46 398 (42.9)	13 212 (31.8)	
Waist circumference, cm	85.3 ± 8.4	84.7 ± 8.9	< .001
Central obesity, n (%)	65 142 (60.3)	20 762 (50.0)	< .001
Systolic blood pressure, mm Hg	131.0 ± 16.5	131.5 ± 17.4	< .001
Diastolic blood pressure, mm Hg	78.1 ± 10.2	78.0 ± 10.6	.15
Hypertension, n (%)	90 398 (83.7)	36 158 (87.0)	< .001
Fasting blood glucose, mg/dL	132.9 ± 42.8	137.3 ± 50.1	< .001
Total cholesterol, mg/dL	193.7 ± 42.3	190.5 ± 43.1	< .001
HDL cholesterol, mg/dL	51.7 ± 22.7	50.7 ± 25.3	< .001
Triglycerides, mg/dL	141.0 (140.6-141.4)	138.0 (137.3-138.7)	< .001
Dyslipidemia, n(%)	68 020 (63.0)	23 178 (55.8)	< .001
eGFR, mL/min/1.73 m^2	76.6 ± 32.7	71.3 ± 35.1	< .001
Chronic kidney disease, n (%)	25 880 (24.0)	13 888 (33.4)	< .001
Current smoking, n (%)	11 842 (11.0)	6491 (15.6)	< .001
Heavy alcohol drinking, n (%)	4470 (4.2)	1931 (4.7)	< .001
Regular exercise, n (%)	18 136 (16.8)	5715 (13.8)	< .001
Lower income, n (%)	24 140 (22.3)	9336 (22.5)	.62
Stroke, n (%)	6528 (6.0)	3034 (7.3)	< .001
Heart disease, n (%)	11 348 (10.5)	4738 (11.4)	< .001
Antidiabetes medication, n (%)	82 110 (76.0)	31 641 (76.1)	.59
Insulin, n (%)	14 096 (13.0)	7746 (18.6)	< .001
Sulfonylurea, n (%)	61 532 (56.9)	24 701 (59.4)	< .001
Metformin, n (%)	59 782 (55.3)	22 135 (53.3)	< .001
Meglitinide, n (%)	3870 (3.6)	1937 (4.7)	< .001
Thiazolidinedione, n (%)	8021 (7.4)	2989 (7.2)	.12
DPP4 inhibitor, n (%)	9335 (8.6)	3099 (7.5)	< .001
Acarbose, n (%)	19 654 (18.2)	9009 (21.7)	< .001

Hypertension was defined as ICD-10 codes (I10-13, I15) plus treatment with antihypertensive agents, or systolic or diastolic blood pressure greater than or equal to 140 mm Hg/greater than or equal to 90 mm Hg.
Dyslipidemia was ICD-10 code of E78 plus treatment with lipid-lowering agents or total cholesterol greater than or equal to 240 mg/dL.
Stroke was defined as ICD-10 codes I63 and I64.
Heart disease was defined as ICD-10 codes I21 and I22.
Chronic kidney disease was characterized as participants with eGFR less than 60 mL/min/1.73 m^2.
Low social economic status was the lowest quartile for income in the study population.
Heavy alcohol consumption was defined as 30 g or more per day.
Regular exercise was categorized as 3 or more times per week of moderate to vigorous physical activity.
Abbreviations: DPP4 inhibitor, dipeptidyl-peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol; ICD-10, International Statistical Classification of Disease and Related Health Problems, 10th Revision.

this diminution of hypoglycemic effect might suggest that the hypoglycemic condition directly increases the risk of death. Indeed, hypoglycemia is more common in patients who are older adults or who have comorbidities (43), and these characteristics were also observed in our results.

The present study has several strengths. First, the cohort size was sufficient to investigate the independent

Table 5. Risk of death according to severe hypoglycemia and dementia

	Death	Duration, y	Incidence rate	Model 1	Model 2	Model 3	Model 4
Severe hypoglycemia (–), dementia (–)	144 105	13 250 183.5	10.876	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Severe hypoglycemia (–), dementia (+)	3300	69 200.8	47.687	2.80 (2.70-2.90)	2.70 (2.61-2.80)	2.49 (2.41-2.58)	2.03 (1.96-2.10)
Severe hypoglycemia (+), dementia (–)	40 077	392 564.6	102.090	4.79 (4.73-4.85)	4.67 (4.61-4.73)	4.55 (4.49-4.60)	4.34 (4.29-4.40)
Severe hypoglycemia (+), dementia (+)	1490	9021.5	165.161	7.13 (6.77-7.51)	6.79 (6.45-7.15)	6.27 (5.96-6.61)	5.08 (4.83-5.35)

Model 1: adjusted for age and sex.
Model 2: adjusted for model 1 + smoking, alcohol drink, exercise, and lower income.
Model 3: adjusted for model 2 + body mass index, hypertension and dyslipidemia.
Model 4: adjusted for model 3 + insulin use, antidiabetes drug number, heart disease, stroke history, and duration of type 2 diabetes (> 5 y).

Table 6. Risk of mortality according to presence of dementia and number of severe hypoglycemic episodes

No.	Death	Duration, y	Incidence rate	Model 1	Model 2	Model 3	Model 4
Overall							
0	184 182	13 642 748.1	13.500	1 (reference)	1 (reference)	1 (reference)	1 (reference)
1	3777	66 644.8	56.674	3.38 (3.18-3.60)	2.36 (2.29-2.44)	2.19 (2.12-2.26)	1.80 (1.74-1.86)
> 2	1013	11 577.5	87.497	2.44 (2.36-2.52)	3.22 (3.02-3.42)	2.83 (2.66-3.02)	2.18 (2.04-2.31)
Dementia (–)							
0	144 105	13 250 183.5	10.876	1 (reference)	1 (reference)	1 (reference)	1 (reference)
1	2616	59 366.8	44.065	2.57 (2.47-2.67)	2.48 (2.39-2.58)	2.29 (2.21-2.39)	1.86 (1.79-1.93)
> 2	684	9834.0	69.555	3.84 (3.57-4.15)	3.64 (3.38-3.93)	3.18 (2.95-3.43)	2.40 (2.22-2.58)
Dementia (+)							
0	40 077	392 564.6	102.09	1 (reference)	1 (reference)	1 (reference)	1 (reference)
1	1161	7278	159.522	1.50 (1.42-1.59)	1.48 (1.40-1.57)	1.43 (1.35-1.52)	1.29 (1.22-1.37)
> 2	329	1743.6	188.696	1.68 (1.50-1.87)	1.64 (1.47-1.83)	1.54 (1.38-1.72)	1.35 (1.21-1.51)

Model 1: adjusted for age and sex.
Model 2: adjusted for model 1 + smoking, alcohol drinking, exercise, and lower income.
Model 3: adjusted for model 2 + body mass index, hypertension and dyslipidemia
Model 4: adjusted for model 3 + insulin use, antidiabetes drug number, heart disease, stroke history, and duration of type 2 diabetes (> 5 y).

risk of dementia according to severe hypoglycemia and risk of death according to dementia and severe hypoglycemia, stratifying by number of hypoglycemia episodes. Data were obtained from a nationwide sample according to well-established procedures, coupled with cohort size, ensuring statistical reliability. Furthermore, the incidence of dementia in individuals with diabetes (~ 7.4%) was similar to those in a previous study (24). Second, to our knowledge this is the first study to investigate the influence of severe hypoglycemia and dementia on death in participants with type 2 diabetes. Previous studies investigated the role of either severe hypoglycemia or dementia alone on death (6, 7, 41). Third, adjusting for variables related to demographic characteristics, laboratory findings and metabolic factors reinforced the independent correlation between dementia and severe hypoglycemic episodes and the effect of those conditions on mortality. Last, we demonstrated the dose-dependent associations among severe hypoglycemia, dementia, and death according to the number of severe hypoglycemic episodes.

There are also some limitations in the present study. First, owing to the study design, we could not account for genetics, including apolipoprotein E, and educational status, which influences the development of dementia. Moreover, because we analyzed nationwide check-up data, necessary information such as baseline cognitive function was unavailable and confounding factors such as education history and familial environment may also be lacking. Second, we analyzed dementia type based on diagnosis code rather than imaging or functional cognitive testing. Third, our results focused on overall mortality, which did not elucidate direct death from dementia or severe hypoglycemia. In addition, severe hypoglycemia may be a marker for undiagnosed cognitive impairment, and we cannot rule out the possibility of reverse causation between hypoglycemia and dementia. As based on the observational and longitudinal

data, the present study provided the association between severe hypoglycemia and dementia, and did not elucidate the causal relationship of severe hypoglycemia and dementia. Finally, owing to national policy, we could not assess the cause of death. If information on causes of death were to be provided, it would be more intuitive to elucidate the association among severe hypoglycemia, dementia, and death.

In conclusion, severe hypoglycemia may be associated with a higher risk of dementia and may be responsible in part for the higher risk of death in patients with type 2 diabetes. Our findings can be useful for physicians to be attentive for hypoglycemia and to establish surveillance strategies for high-risk patients. It will be important to investigate in the future whether interventions intended to address brain damage from severe hypoglycemia may offer a pathway for the prevention of dementia.

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Additional Information

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Data Availability: The data can be accessed on the National Health Insurance Data Sharing Service homepage of the NHIS (http://nhiss.nhis.or.kr). Applications to use the NHIS-HEALS data will be reviewed by the inquiry committee of research support and, once approved, raw data will be provided to the applicant with a fee.

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