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FEATURED ARTICLE

Association of diabetes with stroke and post-stroke dementia: A population-based cohort study

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Abstract

Introduction: The impact of prediabetes and diabetes on stroke and the development of dementia after a stroke remain unclear.

Methods: A total of 2655 dementia-free participants (including a stroke-free cohort and a prevalent stroke cohort) were followed-up for 12 years. Dementia and post-stroke dementia were determined by clinical examinations and national registry data. Diabetes was ascertained via medical examination, medication use, medical records, or glycated hemoglobin (HbA1c) ≥6.5%. Prediabetes was defined as HbA1c ≥5.7% in diabetes-free participants.

Results: In the stroke-free cohort, 236 participants developed ischemic stroke, and 47 developed post-stroke dementia. Diabetes was associated with ischemic stroke (hazard ratio [HR] 1.76, 95% confidence interval [CI] 1.16 to 2.67) and post-stroke dementia (HR 2.56, 95% CI 1.04 to 6.25). In the prevalent stroke cohort, diabetes was also related to dementia risk. Prediabetes was not significantly related to stroke or post-stroke dementia.

Discussion: Diabetes, but not prediabetes, is associated with an increased risk of ischemic stroke and post-stroke dementia.

KEYWORDS

dementia, ischemic stroke, population-based cohort study, post-stroke dementia, prediabetes, type 2 diabetes

1 | INTRODUCTION

Type 2 diabetes (hereafter diabetes), stroke, and dementia are three common disorders in older adults, of which stroke and dementia are the leading causes of disability and mortality in aging populations.[1] Although there has been a substantial reduction in the incidence of ischemic stroke among older people over the last decade, survival after stroke has been improved and this has led to an increasing number of people at risk of developing dementia.[2,3] Strong evidence supports an increased risk of dementia in stroke patients, suggesting that the underlying mechanisms of both diseases might be inter-related, as they share some vascular factors, such as diabetes.[4]

Previous population-based cohort studies have shown that diabetes confers about a two-fold risk for both ischemic stroke and dementia.[5-7] Several studies also reported the increased risk of stroke and dementia in people with prediabetes, with inconsistent findings.[5,7] However, the associations between diabetes/prediabetes and post-stroke dementia remain controversial.[8-14] Some clinical studies have shown that diabetes was associated with increased dementia risk in prevalent stroke,[8,9] while others reported non-significant associations.[10,11] Few population-based cohort studies investigated the association of diabetes with post-stroke dementia in people with incident stroke,[12,13] and only one indicated an association between diabetes and post-stroke dementia.[12] Open questions remain regarding whether prediabetes/diabetes may increase the risk of stroke and accelerate the progression from stroke to dementia, and to what extent stroke may mediate the diabetes–dementia association. To our knowledge, no population-based longitudinal studies have so far systematically addressed these questions.

Currently, there is no cure for dementia, and stroke is associated with an increased dementia risk. Thus, it is critical to identify and control other modifiable medical conditions (such as diabetes) that are linked to both stroke and dementia. In this study, we aimed to (1) examine the association of prediabetes and diabetes with the risk of stroke, (2) assess the role of stroke in the association between diabetes and dementia, and (3) examine whether and to what extent diabetes may accelerate the progression from stroke to dementia using 12-year follow-up data from a population-based cohort of Swedish older adults.

HIGHLIGHTS

- Older people with diabetes had greater risk of both ischemic stroke and subsequent dementia.
- Diabetes accelerated the development from ischemic stroke to dementia.
- Prediabetes was not related to ischemic stroke or post-stroke dementia.
- Close monitoring and control of diabetes are needed to prevent ischemic stroke and subsequent dementia.

RESEARCH IN CONTEXT

1. **Systematic review**: PubMed and Web of Science databases were searched and titles and abstracts were screened. Few population-based studies have addressed the relationship between prediabetes and post-stroke dementia, whereas some studies examined the association of diabetes with post-stroke dementia with mixed results. Additionally, few studies have investigated whether and to what extent prediabetes and diabetes accelerate the development of dementia, using a population-based sample, initially free from dementia and/or stroke.
2. **Interpretation**: We observed an increased risk of ischemic stroke and post-stroke dementia in older adults with diabetes. The cumulative incidence of dementia substantially increased in people with diabetes over time after stroke was diagnosed. Prediabetes was not significantly associated with stroke or post-stroke dementia.
3. **Future directions**: Our findings address the role of diabetes as a key strategy on dementia prevention through stroke prevention. Future studies examining whether cerebral small vessel diseases, stroke characteristics (eg, severity, location) influence the diabetes–dementia association, and the biological pathways linking diabetes with dementia and stroke are needed.

2 | METHODS

2.1 | Study population

Data were collected from the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K).[15] A random sample of 4590 people who were aged ≥60 years and living at home or in institutions in central Stockholm were invited. Of them, 3363 (73.3%) agreed and were examined at baseline (March 2001 to June 2004). The SNAC-K study involved 11 age cohorts at baseline, and they were assigned to younger old groups (60, 66, and 72 years), and older old groups (78, 81, 84, 87, 90, 93, 96, and ≥99 years). The younger old groups were followed every 6 years, and the re-examination was conducted every 3 years in older old groups owning to the relatively high mortality and rapid health changes expected in the older old groups.

From the 3363 participants, we excluded 310 with prevalent dementia, 11 with missing dementia status, 16 with schizophrenia or developmental disorders, 9 with type 1 diabetes, and 5 with missing blood glucose measurements, leaving 3012 dementia-free participants for the current study. Of these, 2851 were stroke-free participants and

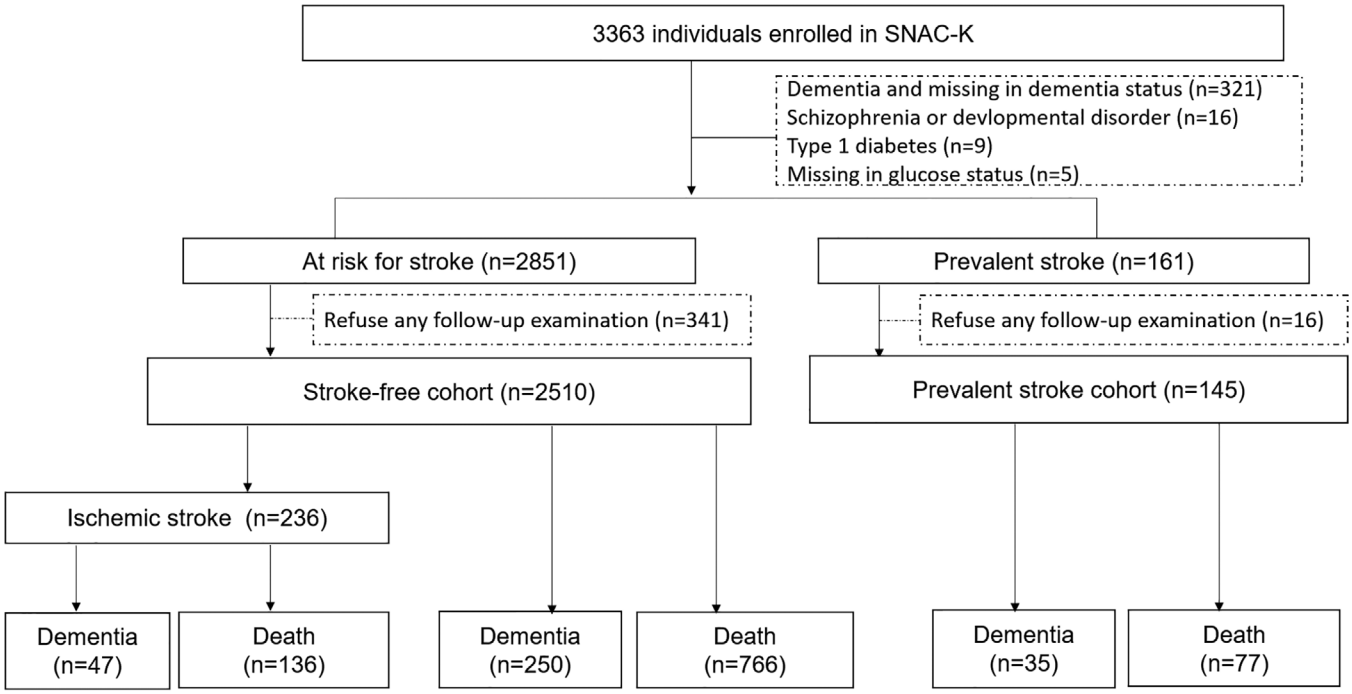

FIGURE 1 Flowchart of the study population. Abbreviation: SNAC-K, Study on Aging and Care-Kungsholmen

161 had a history of stroke. We further excluded those who refused to participate in the first follow-up examination (n = 341 for stroke-free participants and n = 16 for stroke participants), leading to a "Stroke-free cohort" of 2510 persons, and a "Prevalent stroke cohort" of 145 individuals. The two cohorts were followed for 12 years (until 2016), during which incident stroke and dementia cases were detected. The flowchart of the two cohorts from baseline to the end of the last available follow-up (2013–2016) is shown in Figure 1.

SNAC-K was approved by the Ethics Committee at Karolinska Institutet and by the Regional Ethical Review Board in Stockholm. Written informed consent was obtained from all participants or from a proxy if the participant had cognitive impairment.

2.2 | Data collection

Data on demographics, lifestyle factors, current medication use, and medical conditions were collected through extensive structured interviews and clinical examinations conducted by trained nurses and physicians (protocol available at http://www.snac-k.se/). Peripheral blood samples were taken from all participants for laboratory tests. Data on medical conditions were available also from the Swedish National Patient Registry (NPR).

Age was categorized into younger old groups (60 to 72 years) versus older old groups (≥78 years), according to the study design.[15] Education level was measured by the maximum level of formal schooling, and dichotomized as elementary school (<8 years of schooling and/or vocational training), and high school or university (≥8 years).[16] Smoking status was categorized as current, former, and never smoking. Alcohol consumption was dichotomized into no/occasional (<1 drink per week) versus drinking (>1 drink per week).[17] Information on the intensity and frequency of physical exercise was gathered, and categorized as inactive (never engaged or engaged ≤2 to 3 times per month in any intensity of exercise) versus active (engaged in light/moderate to intense exercise several times per week or every day).[18] Weight and height were measured in participants without shoes and heavy clothes. Body mass index (BMI) was calculated as weight divided by the square of height and treated as continuous variables in the model.

Arterial blood pressure was measured twice at minimum 5-minute intervals on the left arm using a sphygmomanometer while participants were seated in a quiet room. The average of the two readings was used to determine systolic and diastolic blood pressure (SBP and DBP). Hypertension was defined as having SBP ≥140 or DBP ≥90 mm Hg, or current use of antihypertensive medication. High total cholesterol was defined as having non-fasting total cholesterol of ≥6.22 mmol/L or use of cholesterol-lowering agents. The Mini-Mental State Examination (MMSE) was used to evaluate global cognitive function.[19] *APOE* genotype was dichotomized into any ε4 versus non-ε4 carriers.

Information on heart disease (atrial fibrillation, ischemic heart disease, heart failure, cardiac valve disease, bradycardias, and conduction diseases) were derived from clinical examination, electrocardiogram, medication use, or NPR, and dichotomized as having heart disease versus not having any of the conditions.[20]

For participants who died during follow-up, information on vital status, date of death, and cause of death (primary and secondary diagnoses) was extracted via linkage with the Swedish Cause of Death Registry (SCDR; June 2001–December 2016).

2.3 | Assessment of prediabetes and diabetes

Glycated hemoglobin A1c (HbA1c) was assessed with Swedish Mono-S filament high performance liquid chromatography, and 1.1% was added to the individual's values to render them equal to international values in accordance with the National Glycohemoglobin Standardization Program.[21] Type 2 diabetes was identified on the basis of medical examination, antidiabetic drug use, diagnoses in the NPR (International Classification of Disease [ICD] ICD-9: code 250; ICD-10: code E11), or HbA1c ≥6.5% (48 mmol/mol) according to the American Diabetes Association criteria.[20,22] In diabetes-free participants, prediabetes was defined as HbA1c of ≥5.7% to 6.4% (39 to 46 mmol/mol) and normoglycemia was defined as HbA1c <5.7% (39 mmol/mol).[22]

2.4 | Diagnosis of stroke

Stroke was ascertained based on the stroke diagnosis status from the Swedish NPR and the SCDR, and included only clinical stroke with symptomatology. The diagnosis of stroke was based on the clinical practice routine considering both clinical manifestation and brain imaging, and the diagnosis was recorded regularly in the Swedish NPR with ICD codes. For participants who died from an acute stroke or stroke related disorders, relevant ICD codes were recorded in SCDR. Appendix A in supporting information shows detailed information on the registries and their validations.

The ICD codes that we applied to identify the stroke event include: hemorrhagic stroke (ICD-10: I60-I62; ICD-9 and ICD-8: 430-432) and ischemic stroke (ICD-10: I63-I64; ICD-9 and ICD-8: 433-434; Appendix B in supporting information).

In this study, medical records on stroke were requested and reviewed by nurses or physicians, and the ICD codes from the registers were verified and recorded in the questionnaires. Participants had a history of stroke if they had been diagnosed with stroke before the baseline examination (ie, from December 1974 until February 2003) and were considered as to have prevalent stroke. Incident stroke was defined as first-ever stroke over the follow-up among the stroke-free participants at baseline.

2.5 | Diagnosis of dementia and post-stroke dementia

Dementia was diagnosed at each wave according to the Diagnostic and Statistical Manual of Mental Disorders (4th edition) criteria, using a validated three-step procedure.[23] Briefly, two physicians independently made diagnoses of dementia on the basis of the participant's physical, neurological, and cognitive status (steps one and two). In case of discrepancies, a neurologist was consulted to reach a concordant diagnosis (step three). For people who died during follow-up, one physician performed an extensive review of the medical records at hospital discharge and/or death certificates to determine whether the participant had dementia. In the stroke-free cohort, dementia without ischemic stroke was defined as having dementia without any incident ischemic stroke. In both cohorts, post-stroke dementia was defined as having dementia after stroke occurrence.

2.6 | Statistical analysis

Baseline characteristics of participants with different glycemic status were compared to the Chi-square test for categorical variables, or one-way analysis of variance (ANOVA) with pairwise mean comparisons with Bonferroni correction for continuous variables.

In the stroke-free cohort, we constructed a multi-state Markov model with a clock-reset approach to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of prediabetes/diabetes with ischemic stroke and dementia.[24,25] All participants started in an initial healthy state, from which they could transit to incident ischemic stroke and incident dementia. The transition from incident ischemic stroke to incident dementia was also possible, as were transitions to death (competing event). Observations were censored at the end of follow-up or in case of loss to follow-up. The multi-state model allowed simultaneous and transition-specific estimation of the risk of prediabetes/diabetes on (1) incident ischemic stroke, (2) incident dementia in those with ischemic stroke, and (3) incident dementia in those who were free of ischemic stroke. Each transition was modeled using flexible parametric survival analysis, with three degrees of freedom for the baseline hazard function guided by the Akaike information criterion. We further calculated and plotted the cumulative incidence of dementia after ischemic stroke by glycemic status using a competing risk model including death. The cumulative incidence was predicted after fitting flexible parametric survival models for dementia and death, with time since ischemic stroke diagnosis as the underlying time scale. Potential confounders were controlled for by standardization.

We repeated the analysis by excluding those who developed dementia within 6 months after ischemic stroke, to exclude participants with early mortality or possible false-positive dementia diagnosis in the acute period caused by delirium or by stroke-related motor or language barriers to cognitive assessment.[10]

In the prevalent stroke cohort, the flexible parametric survival analysis was also used to estimate HRs and 95% CIs for the association between prediabetes/diabetes and prevalent stroke and post-stroke dementia. As mentioned above, we used three degrees of freedom for the baseline hazard. Further, we calculated and plotted the standardized cumulative incidence of dementia with time since baseline examination as underlying time scale.

The confounders were selected based on literature and a forward stepwise procedure. Confounders including age, sex, education, physical activity, BMI, SBP, heart disease, and/or *APOE* ε4 were adjusted in all models. As people with prediabetes may progress to diabetes,[26] we repeated the analysis treating diabetes as a time-varying variable, taking into account both prevalent and incident diabetes during the first

6 years of follow-up. Finally, missing data on covariates (<5% for stroke-free cohort and <10% for prevalent stroke cohort) were imputed using multiple imputation. *P*-value <0.05 (two-tailed) was considered statistically significant. All the analyses were performed using STATA 15.0 (StataCorp, College Station, TX, USA).

3 | RESULTS

3.1 | Characteristics of the study population

Table 1 shows the participants' characteristics by diabetes status in the stroke-free and prevalent stroke cohorts, respectively. Among 2510 stroke-free participants, 835 (33.3%) had prediabetes and 213 (8.4%) had diabetes. Participants with prediabetes or diabetes were older, and more likely to be male, less educated, and physically inactive; consumed less alcohol; and had hypertension, heart disease, and lower MMSE score, than those with normoglycemia. Among the 145 participants with a history of stroke—including 120 cases (82.6%) of ischemic stroke and 25 cases (17.4%) of hemorrhagic stroke—53 (36.6%) had prediabetes and 25 (17.2%) had diabetes. In this cohort, people with prediabetes or diabetes were more likely to have hypertension and ischemic stroke than those with normoglycemia (Table 1). The clinical features of people with diabetes in both cohorts are shown in Appendix C in supporting information.

3.2 | Diabetes and risk of stroke and dementia in the stroke-free cohort

In the stroke-free cohort, during 12-year follow-up (21,025 person-years, mean 8.3 years per person, standard deviation [SD] = 3.8 years), 254 (10.1%) participants developed ischemic stroke (including 236 ischemic stroke without dementia and 18 ischemic stroke after dementia), and 50 (1.9%) developed hemorrhagic stroke. As diabetes was related to a higher risk of ischemic stroke, not hemorrhagic stroke, we excluded hemorrhagic stroke from the following analyses. Among the 236 incident ischemic stroke cases, 47 developed dementia. In the meanwhile, over the follow-up period (21,430 person-years, with mean 8.5 years per person, SD 3.6 years), 250 (10.0%) people developed dementia without prior ischemic stroke.

Figure 2 shows the number of events and the association of prediabetes/diabetes with each transition. In the multi-state model, diabetes was associated with a 1.76 times higher risk of ischemic stroke (95% CI 1.16 to 2.67). Diabetes was also significantly associated with an increased risk of incident dementia in those with ischemic stroke (HR 2.56, 95% CI 1.04 to 6.25), but not in those free of ischemic stroke (HR 1.45, 95% CI 0.88 to 2.40). The numbers of events and the hazard ratios for each transition are shown in Table S1 in Appendix D in supporting information.

Figure 3A shows the standardized cumulative incidence of dementia on time since ischemic stroke diagnosis by glycemic status. Participants with diabetes at baseline had the highest probability of developing dementia after ischemic stroke, followed by participants with prediabetes. For example, in the third year after ischemic stroke diagnosis, the cumulative incidence of dementia was 22.9% for those with diabetes, 16.1% for those with prediabetes, and 14.4% for those with normoglycemia. Six years after ischemic stroke diagnosis, the corresponding estimates were 34.8% (diabetes), 24.9% (prediabetes), and 22.8% (normoglycemia). Furthermore, 20% of people with diabetes were diagnosed with dementia by 2.3 years after incident ischemic stroke, compared to 4.3 years in people with normoglycemia. Therefore, diabetes accelerated the development from incident ischemic stroke to dementia by 2 years.

3.3 | Diabetes and risk of post-stroke dementia in the prevalent stroke cohort

In the prevalent stroke cohort, during the 12-year follow-up, 35 (24.1%) patients developed dementia. Among them, 32 cases were derived from ischemic stroke and 3 cases from hemorrhagic stroke. Diabetes was associated with a three-fold risk of dementia (HR 3.82, 95% CI 1.40 to 9.89; Table 2). The association between prediabetes and dementia was not statistically significant. After we repeated the analysis in those with prevalent ischemic stroke (n = 120), diabetes was associated with a two-fold risk of dementia (HR 2.36, 95% CI 1.44 to 8.98; data not shown).

The standardized cumulative incidence of dementia on time since baseline examination by glycemic status is shown in Figure 3B. The probability of dementia was highest among participants with diabetes than those with prediabetes or normoglycemia over time. After 6-year follow-up, the cumulative incidence of dementia was 21.1% for people with diabetes, 10.9% for those with normoglycemia, and 10.0% for those with prediabetes.

3.4 | Supplementary analysis

Similar results were obtained when we conducted the following analyses in the stroke-free cohort (see details in Appendix D): (1) excluding four ischemic stroke cases who developed dementia within 6 months, the association between diabetes and post-stroke dementia remained significant (HR 2.58, 95% 1.04–6.04; Table S2). (2) Considering incident diabetes during the first 6-year follow up, we treated diabetes as a time-varying exposure and the association of diabetes with incident ischemic stroke was slightly attenuated. Although the trend of association of diabetes with incident post-stroke remained similar to the results from the initial analysis, the association was no longer significant (Table S3). (3) When we repeated the analysis using age and education as continuous variables, the results were similar to our original analysis when these variables were dichotomized according to the original study design (Tables S4 and S5).

TABLE 1 Characteristics of dementia-free participants by diabetes status in the stroke-free cohort and prevalent stroke cohort

Characteristics	Stroke-free cohort (*n* = 2510)				Prevalent stroke cohort (*n* = 145)			
	Normoglycemia (*n* = 1462)	Prediabetes (*n* = 835)	Diabetes (*n* = 213)	*P*	Normoglycemia (*n* = 67)	Prediabetes (*n* = 53)	Diabetes (*n* = 25)	*P*
Baseline								
Age (years)	71 (±10.2)	74 (±10.5)[a]	74 (±9.7)[a]	<0.001	81 (± 10.1)	82 (± 8.6)	79 (± 9.0)	0.453
60–78	940 (64.3)	430 (51.2)	109 (50.9)	<0.001	16 (23.9)	11 (20.8)	9 (36.0)	0.337
≥78	522 (35.7)	405 (48.8)	104 (49.1)		51 (76.1)	42 (79.3)	16 (64.0)	
Female sex	931 (63.4)	543 (65.2)	107 (50.2)	<0.001	42 (63.7)	36 (67.9)	11 (44.0)	0.123
Education > elementary	1276 (87.3)	702 (84.1)	167 (78.4)	0.001	51 (78.5)	39 (73.6)	18 (72.0)	0.749
Body mass index (kg/m^2)	25 (±3.9)	25 (±4.1)[a]	27 (±4.5)[a]	<0.001	24.4 (± 3.6)	25.1 (± 4.5)	26.6 (± 4.7)	0.125
Smoking status								
Never smoker	707 (48.7)	366 (44.0)	88 (42.0)	0.033	29 (44.6)	25 (48.0)	13 (52.0)	0.790
Previous smoker	557 (38.4)	327 (39.2)	93 (44.3)		24 (36.9)	20 (38.5)	10 (40.0)	
Current smoker	188 (12.9)	139 (16.7)	29 (13.8)		12 (18.5)	7 (13.5)	2 (8.0)	
Alcohol consumption	1066 (73.1)	520 (62.3)	115 (54.7)	<0.001	31 (48.4)	32 (60.4)	9 (36.0)	0.118
Physically inactive	363 (24.9)	244 (29.7)	82 (38.3)	<0.001	34 (50.7)	33 (58.9)	11 (36.7)	0.043
SBP (mm Hg)	142 (±19.9)	144 (±19.7)	145 (±20.4)	0.148	144 (± 18.4)	145 (± 20.3)	145 (±13.8)	0.946
DBP (mm Hg)	82 (±10.5)	81 (±9.5)	80 (±11.5)	0.221	78 (± 10.8)	78 (± 12.1)	77 (± 11.2)	0.939
Hypertension	1042 (71.3)	638 (76.4)	186 (87.3)	<0.001	57 (85.1)	52 (98.1)	24 (96.0)	0.025
High cholesterol	683 (49.1)	444 (53.2)	106 (50.5)	0.169	29 (48.3)	26 (49.1)	8 (36.4)	0.569
Heart disease	249 (17.4)	204 (24.7)	90 (42.5)	<0.001	33 (49.3)	31 (58.5)	19 (76.0)	0.068
Stroke type								
Ischemic stroke	NA	NA	NA		50 (74.6)	46 (86.8)	24 (96.0)	0.034
Hemorrhagic stroke	NA	NA	NA		17 (26.9)	7 (16.9)	1 (4.0)	0.089
MMSE score	28.8 (±2.6)	28.6 (±1.6)	28.4 (±1.7)[a]	0.009	27 (± 4.2)	28 (± 2.2)	29 (± 10.2)	0.177
Any *APOE* ε4 allele	406 (29.5)	231 (29.2)	48 (24.0)	0.270	17 (30.6)	13 (26.0)	4 (20.0)	0.656
During 12-year follow-up								
Incident ischemic stroke	119 (8.1)	99 (11.8)	36 (16.9)	<0.001	NA	NA	NA	
Incident hemorrhagic stroke	32 (2.5)	15 (2.4)	3 (2.8)	0.935	NA	NA	NA	
Incident dementia	155 (10.6)	93 (11.1)	30 (14.0)	0.318	14 (20.9)	12 (22.6)	9 (36.0)	0.330

Data are n (%) or mean ± SD.

Abbreviations: *APOE* ε4, apolipoprotein ε4 allele; DBP, diastolic blood pressure; MMSE, Mini-Mental State Examination; NA, non-applicable; SBP, systolic blood pressure.

Pairwise means comparison with Bonferroni correction: $P < 0.05$ (reference group = normoglycemia). Missing variables: 4 were missing data on education, 18 on smoking, 15 on alcohol consumption, 109 on body mass index, and 90 on total cholesterol.

4 | DISCUSSION

In this Swedish population-based cohort, we found that (1) diabetes, but not prediabetes, was associated with an increased risk of ischemic stroke; (2) diabetes was also associated with post-ischemic stroke dementia but not significantly associated with dementia without ischemic stroke; and (3) in both prevalent and incident ischemic stroke, diabetes was related to a higher risk of dementia. Our findings highlight the need to control diabetes for the prevention of both ischemic stroke and post-stroke dementia.

The association of diabetes with stroke has been widely investigated in population-based studies. A meta-analysis including 530,083 middle-aged participants (mean age of 52 years) reported about two times higher risk of ischemic stroke in individuals with diabetes.[27] However, in the studies of older adults aged >60 years, the results on the association between diabetes and stroke are inconsistent. Some studies showed that diabetes is associated with ischemic stroke,[28,29] whereas others did not.[13,30] Although diabetes has been linked to stroke, the effect of prediabetes on risk of future stroke has not been established. In a meta-analysis of 15 cohort studies, eight studies showed a non-significant association between prediabetes and stroke after adjustment for established cardiovascular risk factors.[31] In the current study, we found that diabetes, not prediabetes, was independently associated with almost 1.8 times risk of ischemic stroke. The non-significant association of prediabetes with ischemic stroke may be due to low sensitivity of detecting prediabetes using HbA1c.[32]

Beyond the consistent evidence for the association between diabetes and stroke, diabetes is also one of the major risk factors for

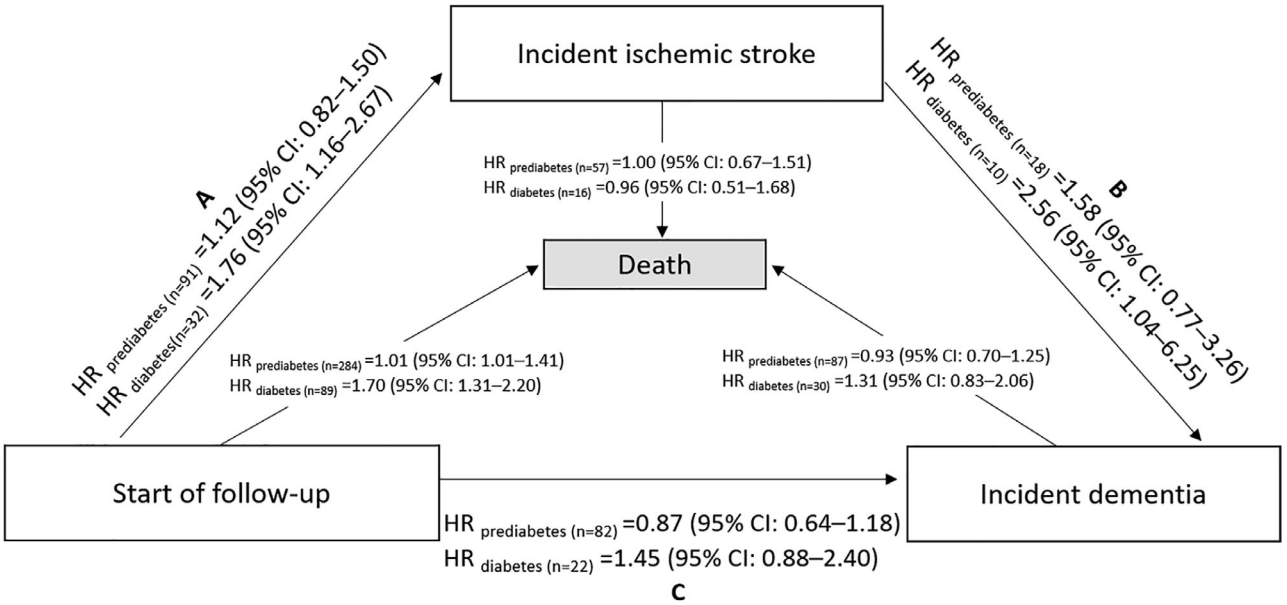

FIGURE 2 A multi-state model examining the role of prediabetes and diabetes on the risk of ischemic stroke and dementia in the stroke-free cohort. Start of follow-up is a state in which participants were stroke- and dementia-free. Hazard ratios (HR) due to prediabetes and diabetes on the risk of transition from: (A) stroke and dementia-free to incident ischemic stroke; (B) ischemic stroke to incident dementia; (C) stroke and dementia-free to incident dementia. The reference group is people with normoglycemia. N represents the number of prediabetes or diabetes transit to a specific state. All HRs adjusted for age, sex, education, physical activity, body mass index, systolic blood pressure, and heart disease. The HRs of transition to dementia were also adjusted for apolipoprotein E ε4

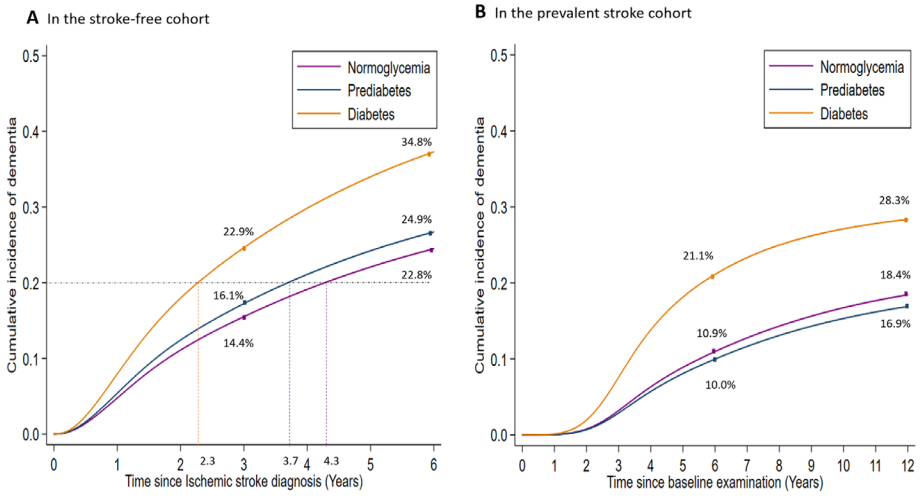

FIGURE 3 Adjusted cumulative incidence of dementia by glycemic status in stroke-free cohort (A) and prevalent stroke cohort (B). Cumulative incidence function of dementia by normoglycemia (purple), prediabetes (blue), and diabetes (orange) over time since ischemic stroke diagnosis in stroke-free cohort (A), or over time since baseline examination in prevalent stroke cohort (B). The cumulative incidence functions were derived from flexible parametric competing risk models adjusted for age, sex, education, physical activity, body mass index, systolic blood pressure, heart disease in both cohorts (A and B). The model was additionally adjusted for apolipoprotein E ε4 in stroke-free cohort (A). In stroke-free cohort (A), cumulative incidence of dementia by glycemic status after 3 and 6 years since diagnosis of ischemic stroke was calculated. The time (years) for 20% of participants diagnosed with dementia (long dash dotted line) by normoglycemia, prediabetes, and diabetes was also noted. In prevalent stroke cohort (B), cumulative incidence of dementia by glycemic status after 6 and 12 years since baseline examination was noted

dementia.[33] Thus, stroke might represent the cornerstone for the association between diabetes and dementia. The combined effect of diabetes and stroke on dementia is stronger than that of a single disease;[14] however, the pathways underlying the contribution of stroke to the association between diabetes and dementia remain unclear. A previous study showed that diabetes was not associated with cognitive decline without stroke,[14] and several studies suggested that the diabetes–dementia association is partially explained by ischemic stroke.[34,35] We

TABLE 2 Incident post-stroke dementia: number of cases, incidence rate (IR; per 1000 person-years), and hazard ratio (HR) and 95% confidence interval (CI) related to diabetes in prevalent stroke cohort

Diabetes status	No. cases	IR	HR (95% CI)[a]	HR (95% CI)[b]
Normoglycemia	14	31.3	1.00 (Reference)	1.00 (Reference)
Prediabetes	12	35.7	0.95 (0.42–2.12)	0.88 (0.36–2.16)
Diabetes	9	77.3	3.32 (1.36–8.10)	3.82 (1.40–9.89)

[a]Adjusted for age, sex, and education.
[b]Adjusted for age, sex, education, physical activity, body mass index, systolic blood pressure, and heart disease.

have previously reported that diabetes was associated with a two-fold risk of dementia after adjustment for baseline cardio- and cerebrovascular diseases.[6] In the current study, we took a step forward and examined the dynamics of the triangular associations among diabetes, stroke, and dementia. We found that diabetes was significantly associated with an increased risk of post-ischemic stroke dementia, but not dementia without a prior stroke. These findings suggest that the increased risk of dementia in diabetes may be partially due to ischemic stroke. This means that among people with diabetes, it is important to prevent stroke to reduce the risk of dementia.

Numerous previous studies addressing the association between diabetes and dementia among patients with stroke have shown inconsistent results, which might be due to methodological reasons. First, in these studies, prevalent dementia cases were not reliably excluded. Second, contrary to the guidelines which suggest that the diagnosis of post-stroke dementia should be carried out at least 6 months after stroke,[36] these previous studies diagnosed dementia within 3 months after stroke, when cognitive function might still be recovering.[10] In our study, we addressed this issue by confining the analysis to patients after 6 months of ischemic stroke diagnosis, and found that diabetes was associated with 2.6 times higher risk of dementia.

The underlying mechanisms of linking diabetes to stroke and further to post-stroke dementia remain unclear. Diabetes is associated with stiffer arteries, decreased elasticity, and atherosclerosis formation in the cerebrovascular vessels.[37] Moreover, diabetes may disrupt microvascular functions through several mechanisms such as excess production of oxidative stress, activation of protein kinase C, and receptor for advanced glycation end products. Diabetes has also been associated with reduced cerebral blood flow and increased blood viscosity.[38,39] These biological pathways would lead to an accumulation of vascular damage over time and further trigger the occurrence of stroke. Diabetes might further interact with vascular damage, accelerate the inflammation, and lead to faster brain deterioration, as suggested in animal studies that diabetes was associated with post-stroke brain damage.[40] In addition, diabetes is associated with reduced recovery of cognitive function after stroke.[41]

The main strength of our study is the population-based longitudinal design with long follow-up, very high participation rate, and integration of diagnosis from multiple sources. All participants were examined by the study physicians and cases were also identified from NPR. Those persons who died during follow-up were identified from death certificates with medical records available. However, some limitations should be acknowledged. First, due to the lack of neuroimaging data in our entire study population, subclinical cerebrovascular disease could not be identified, and stroke was defined as only clinical stroke with symptomatology. Thus, the given associations might be underestimated in this study. Moreover, the location and severity of the lesions in the brain at stroke onset could not be taken into account. These might have played a role in the association of diabetes and post-stroke dementia. Second, HbA1c was used to define prediabetes and diabetes. Considering the low sensitivity of HbA1c in identifying diabetes and prediabetes comparing fasting plasma glucose and oral glucose tolerance test,[32] the prevalence and incidence in our study might be underestimated and thus might lead to non-differential misclassification. As a result, the given associations in this study might be underestimated. Moreover, prediabetes should not be viewed as a clinical entity but rather as a high-risk state for developing diabetes and cardiovascular disease.[42] Third, due to the insidious nature of dementia onset, the exact date of dementia occurrence could not be determined. Thus, the temporality of incident stroke and dementia in the stroke-free cohort was unclear, and dementia could have developed before stroke onset. However, we also observed a significant association between diabetes and post-stroke dementia in the prevalent stroke cohort, in which the temporality was clear. Fourth, selection bias might not be ruled out due to dropouts and deaths at baseline and during follow-ups. Individuals who dropped out (12%) were older and likely to have vascular risk factors. Hence, the observed associations among diabetes, stroke, and post-stroke dementia might have been underestimated. Finally, the SNAC-K population consists of mostly highly educated white residents in urban areas, thus, cautions are needed when generalizing our findings to other populations.

In summary, our results provide evidence that diabetes, not prediabetes, increases the risk of ischemic stroke and further accelerates the development of dementia in patients with stroke. Our findings suggest that ischemic stroke plays an important role in the diabetes–dementia association. Our study underscores the need to closely monitor and control diabetes for the prevention of ischemic stroke and subsequent dementia. Future studies are required to clarify the mechanisms underlying the links among diabetes, stroke, and dementia, such as the contribution of cerebral small vessel diseases and inflammation.

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CONFLICTS OF INTEREST

No potential conflicts of interest relevant to this article were reported.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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