Association of Prediabetes and Type 2 Diabetes With Cognitive Function After Stroke

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A STROKOG Collaboration Study

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Background and Purpose—Type 2 diabetes mellitus (T2D) is associated with cognitive impairment and an increased risk of dementia, but the association between prediabetes and cognitive impairment is less clear, particularly in a setting of major cerebrovascular events. This article examines the impact of impaired fasting glucose and T2D on cognitive performance in a stroke population.

Methods—Seven international observational studies from the STROKOG (Stroke and Cognition) consortium (n=1601; mean age, 66.0 years; 70% Asian, 26% white, and 2.6% African American) were included. Fasting glucose level (FGL) during hospitalization was used to define 3 groups, T2D (FGL ≥7.0 mmol/L), impaired fasting glucose (FGL 6.1–6.9 mmol/L), and normal (FGL <6.1 mmol/L), and a history of diabetes mellitus and the use of a diabetes mellitus medication were also used to support a diagnosis of T2D. Domain and global cognition *Z* scores were derived from standardized neuropsychological test scores. The cross-sectional association between glucose status and cognitive performance at 3 to 6 months poststroke was examined using linear mixed models, adjusting for age, sex, education, stroke type, ethnicity, and vascular risk factors.

Results—Patients with T2D had significantly poorer performance in global cognition (SD, −0.59 [95% CI, −0.82 to −0.36]; *P*<0.001) and in all domains compared with patients with normal FGL. There was no significant difference between impaired fasting glucose patients and those with normal FGL in global cognition (SD, −0.10 [95% CI, −0.45 to 0.24]; *P*=0.55) or in any cognitive domain.

Conclusions—Diabetes mellitus, but not prediabetes, is associated with poorer cognitive performance in patients 3 to 6 months after stroke. **(*Stroke*. 2020;51:1640-1646. DOI: 10.1161/STROKEAHA.119.028428.)**

Key Words: cognition ■ diabetes mellitus ■ prediabetic state ■ stroke

Type 2 diabetes mellitus (T2D) is one of the most significant global epidemics of the twenty-first century. T2D is the basis for a growing public health burden, and there is mounting evidence that T2D is associated with cognitive impairment, accelerated cognitive decline, and an increased risk of dementia.[1–4] This relationship is supported by several biologic mechanisms. T2D promotes both subclinical and clinically evident cerebrovascular disease, and it serves as a

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*A list of STROKOG collaborators is provided in Table I in the Data Supplement.

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well-established risk factor for stroke, which is itself a strong risk factor for dementia.[5] Stroke outcomes, including cognitive impairment and mortality, are worse in stroke patients with T2D compared with those without diabetes mellitus, suggesting an additive effect of T2D and stroke on brain health. T2D has also been found to be associated with Alzheimer disease through a variety of mechanisms, including the important relationship between insulin, insulin-degrading enzyme, and metabolism of amyloid-β—the constituent protein of Alzheimer disease plaques.[2,6]

While intermediate hyperglycemia (prediabetes) or impaired fasting glucose (IFG) is associated with a higher risk of a progression to T2D in some patients,[7] evidence of its relationship with cognitive impairment has been conflicting. Some studies suggested that a higher glucose level is associated with cognitive impairment,[2,8] whereas other studies found no association.[9–11] To our knowledge, only 1 study examined this association in a stroke population, and the authors concluded that prediabetes was associated with poststroke cognitive impairment.[12] Discrepancies in these findings may be due to methodologic differences, such as in study populations, study design, the definition of diabetes mellitus/prediabetes, and assessment tools. The STROKOG (Stroke and Cognition) consortium provides an opportunity to address these inconsistencies using harmonized individual participant data from international poststroke cohorts.

We have previously found that stroke patients with a history of T2D have significantly poorer cognitive function in all cognitive domains compared with those without T2D.[13] In this article, we investigate the relationship between IFG diagnosed during hospitalization for acute stroke and cognitive impairment, with a specific emphasis on the magnitude of its effects in multiple cognitive domains. We hypothesized that patients with IFG would exhibit poorer cognitive function in all cognitive domains after stroke compared with those with a normal fasting glucose level (FGL).

Methods

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Population

Seven cohorts from Australia, France, Korea, the Netherlands, Singapore, and the United States were included in this project based on FGL or HbA1c (glycated hemoglobin) being available and that detailed neuropsychological test batteries had been administered (Table 1). These studies recruited patients with stroke consecutively admitted to hospitals, and psychologists or trained research assistants administered neuropsychological tests at each study center 3 to 6 months poststroke. All studies except one excluded patients with transient ischemic attack at recruitment, and we excluded them (1.6% of the total cohort) to make the studies compatible. All studies provided data on FGL, and 4 studies provided HbA1c values; blood measurement was taken on between 2 days and 3 months poststroke (Table II in the Data Supplement). Although the clinical management of patients enrolled in participating studies was usually separate from research protocols, it is likely that treating physicians avoided the use of glucose containing IV solutions that could confound FGL. Blood test data were missing for between 1% and 82% of patients in the 7 cohorts (Table II in the Data Supplement). Data on key potential risk factors for poststroke cognitive impairment that were collected by all studies included histories of hypertension, diabetes mellitus, stroke, atrial fibrillation, smoking (past or present), and body mass index, whereas other variables such as apolipoprotein E and coronary artery disease status were not collected by >3 studies and were, therefore, not included in the analyses. A history of depression was collected by 4 studies. Details regarding each study and the methods of harmonizing demographic variables have been published previously.[13] Procedures of the consortium have been approved by the University of New South Wales Human Research Ethics Committee (Ref No. HC14359), which waived the need for patient consent, as all studies obtained ethical approval from local institutional review boards.

Table 1. STROKOG Study Cohorts Included in the Present Study

Study Name	n	Country	Year Study Began
Bundang VCI	628	Korea	2007
CASPER	156	The Netherlands	2013
EpiUSA	81	The United States	1988
K-VCIHS	348	Korea	2007
NNI	139	Singapore	2009
STROKDEM	141	France	2011
SSS	108	Australia	1997

Bundang VCI indicates Bundang Vascular Cognitive Impairment cohort; CASPER, Cognition and Affect After Stroke: Prospective Evaluation of Risks; EpiUSA, Epidemiological Study of the Risk of Dementia After Stroke; K-VCHIS, Korean-Vascular Cognitive Impairment Harmonization Standards Study; NNI, National Neuroscience Institute; SSS, Sydney Stroke Study; STROKDEM, Study of Factors Influencing Post-Stroke Dementia; and STROKOG, Stroke and Cognition Consortium.

Diagnosis of Diabetes Mellitus and IFG

We assigned patients to 1 of 3 glucose status groups, T2D, IFG, and normal FGL, according to the World Health Organization criteria. T2D was defined as FGL ≥7 mmol/L, having a previous diagnosis of diabetes mellitus, or using a diabetes mellitus medication; IFG was defined as FGL 6.1 to 6.9 mmol/L; and normal was defined as FGL <6.1 mmol/L.[14] The T2D group may have included a few patients with type 1 diabetes mellitus since we were not able to distinguish between the 2 types in patients with a previous diagnosis of diabetes mellitus. In a secondary analysis, the 2003 American Diabetes Association criteria were used to define a broader range of IFG (5.6–6.9 mmol/L).[15] A subgroup analysis in 4 studies was conducted based on HbA1c ≥6.5% to define diabetes mellitus and HbA1c between 5.7% and 6.4% to define prediabetes.[15]

Cognitive Function

We harmonized different neuropsychological tests (Table III in the Data Supplement) by converting them to standardized scores (*Z* scores), adjusting for sex, age, and education level. As is common practice in neuropsychological testing, *Z* scores for each study were obtained based on the distribution of test scores within the study's own control group, or an appropriate normative group, which were stroke-free nondemented individuals from the same national and ethnoracial group (see Lo et al[13] for details). Each test was assigned to 1 of 5 domains (attention and processing speed [attention], memory, language, perceptual motor, and executive function). Domain *Z* scores were derived as the standardized average of all available tests in a domain. We computed a global cognition score as the standardized average of the 5 domains.

Statistical Analyses

ANOVA and Pearson χ^2 test were used as appropriate to compare baseline characteristics between patients included in the analyses and those excluded because of missing FGL. Similarly, glucose group differences were examined with regard to stroke characteristics, vascular risk factors, and background variables. In the first step of the key analyses, we used linear mixed models to examine the association between cognitive scores and glucose status, adjusted by sex, age, and education (model 1). In the second step, model 1 was extended to include type of stroke and stroke location (left/right hemisphere or bilateral; model 2). Since there were 12% of patients with missing data for stroke location, that variable was only retained if the significance level was <0.1 to maintain a larger sample size for subsequent analyses. Next, we extended model 2 to include ethnicity and important vascular risk factors (hypertension, previous stroke, atrial fibrillation, smoking, and body mass index; fully adjusted model 3). In all models, study was included as the random effect to account for clustering (patients nested within cohorts).

We conducted several supplementary analyses based on the fully adjusted model 3. First, we used the wider American Diabetes Association definition for IFG. Second, we used HbA1c instead of FGL to define glucose status. Third, we excluded patients with diabetes mellitus and examined FGL as a continuous rather than a categorical measure. Fourth, we additionally adjusted for a history of depression. Fifth, we tested for interactions between glucose status and sex, ethno-racial groups, and age. The Koreans were examined separately and together with the Chinese in a combined Asian subgroup due to small numbers of Chinese, who came from one study; African Americans were excluded in this analysis due to small numbers that came from one study. Finally, we tested the possible effect of hyperglycemia being a function of a stress response poststroke by assuming an elevation of 20% in FGL in all patients except CASPER (Cognition and Affect After Stroke: Prospective Evaluation of Risks; which measured FGL at 3 months) and reducing FGL values proportionally before assigning patients to the glucose groups.

The significance level was assessed at the 0.05 level (2 sided). All analyses were performed using Stata 15.1. The reporting in this article adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Results

Seven studies provided individual participant data for 1601 stroke patients with FGL; 611 (28%) patients from the original cohorts were excluded due to missing FGL. Those who were excluded were significantly older and in poorer health (histories of smoking, hypertension, and stroke were more frequent; Table IV in the Data Supplement), but there were no significant differences between included and excluded patients on global cognition *Z* scores.

The mean age of those included was 66.0 years (range, 22–96), with 63% men. Seventy percent were Asian, 26% were white, and 2.6% were African American. Almost all patients (99%) had had an ischemic stroke. Thirty-six percent were categorized as having T2D, 12% had IFG, and 52% were normal. Table 2 shows patient characteristics by glucose status and the results of exploratory tests of differences between glucose groups. See Table II in the Data Supplement for patient characteristics in each cohort.

Mixed models showed that patients with T2D had significantly poorer cognitive function in global cognition and in all domains compared with patients with normal FGL in the partially adjusted and fully adjusted models (Table 3). Patients with T2D had more than half an SD lower global cognition *Z* scores compared with those with normal FGL after covariate adjustments (SD, −0.59 [95% CI, −0.82 to −0.36]; $P<0.001$). Stroke location was not found to be significant ($P>0.1$) in model 2 for any cognitive outcome except the memory domain ($P<0.001$). We performed exploratory analyses by adding stroke location to model 3, and the results were similar, with less than a 10% change in effect sizes (Table V in the Data Supplement). For T2D patients, the greatest relative deficits in cognition were in the attention domain, with scores on average 0.54 SD lower than patients with normal FGL, followed by the perceptual motor and executive function domains (SD, −0.39 and −0.36, respectively; Table 3).

The models did not show any significant differences in cognitive function between IFG patients and those with normal FGL. The effect sizes were small; in the memory, language, and perceptual motor domains, they were nearly zero (Table 3).

Analyses using the second definition of IFG produced similar results, with effect sizes changing between ±2% and 13% (T2D versus normal) or remaining near zero (IFG versus normal; Table VI in the Data Supplement). A history of depression was not significantly related to global cognition ($P=0.91$) or any cognitive domain, but the sample size was reduced to 454 due to 72% having missing data for depression. Using HbA1c from 4 studies (n=1176) to define diabetes mellitus (33%) and prediabetes (31%) produced similar results (Table VI in the Data Supplement). In the analysis performed in the subgroup of patients without diabetes mellitus (n=1023), FGL as a continuous measure was not significantly related to global cognition or performance in any cognitive domain, and the effect sizes were close to zero (Table VII in the Data Supplement).

There were no significant interactions between IFG and sex for global cognition or any cognitive domain. There were significant associations between T2D and poorer cognitive function in women but not men in the memory ($P=0.025$), perceptual motor ($P=0.040$), and executive function domains ($P=0.044$; Table VIII in the Data Supplement). There were also no significant interactions between IFG and age for global cognition or any domain. We did not find any significant interactions between T2D and age except for the memory domain ($P=0.03$); there was a stronger association between T2D and poorer memory in younger stroke patients. In the subgroup analysis of white and Asian participants (n=1108), interactions between ethnicity and glucose status were not significant, although the effect sizes were large for global cognition and the attention domain (SD, −0.49; $P=0.09$ and SD, −0.54; $P=0.08$, respectively, for diabetes mellitus versus normal; Table IX in the Data Supplement). Results were similar when the Koreans were examined separately, with effect sizes or *P* changing by zero up to 17% (Table IX in the Data Supplement). Finally, when we assumed a 20% elevation in FGL due to stress hyperglycemia, similar results with small changes in effect sizes (Table X in the Data Supplement) were observed despite the new glucose group sizes (30.8% T2D, 4.4% IFG, and 64.8% normal).

Discussion

In this individual participant data (IPD) meta-analysis of 7 international poststroke cohorts, we found that stroke patients with IFG, or prediabetes, did not have significantly poorer

Table 2. Characteristics of the Diabetes Mellitus, IFG, and Normal FGL Groups

	Diabetes Mellitus	IFG	Normal FGL	*P* Value (Overall; Diabetes Mellitus vs Normal; IFG vs Normal)*
n	578	193	830	
Age, y	66.8 (10.2)	66.2 (11.5)	65.5 (12.8)	0.16; 0.06; 0.46
Male sex, %	370 (64%)	124 (64%)	512 (62%)	0.60; 0.36; 0.44
Education level				0.05; 0.19; 0.02
<High school	343 (59%)	116 (60%)	449 (54%)	
Completed high school	89 (15%)	29 (15%)	154 (19%)	
Technical school	65 (11%)	30 (16%)	93 (11%)	
≥University	81 (14%)	18 (9.3%)	134 (16%)	
Ethnicity				<0.001; <0.001; 0.47
White	107 (18%)	58 (30%)	258 (31%)	
Asian	436 (75%)	132 (68%)	548 (66%)	
African American	25 (4.3%)	3 (1.6%)	14 (1.7%)	
Other	10 (1.7%)	0	10 (1.2%)	
BMI, kg/m^2†	25.1 (4.7)	25.2 (5.3)	24.6 (4.1)	0.07; 0.03; 0.12
Hypertension†	427 (74%)	126 (65%)	534 (64%)	0.001; <0.001; 0.82
AF†	71 (12%)	41 (21%)	118 (14%)	0.01; 0.30; 0.016
History of past stroke†	82 (14%)	30 (16%)	99 (12%)	0.29; 0.23; 0.18
Smoking (ever)†	244 (47%)	80 (47%)	377 (47%)	0.99; 0.89; 0.99
A history of depression†	11 (8.5%)	8 (13%)	40 (15%)	0.16; 0.06; 0.60
Stroke subtype†				0.004; 0.004; 0.22
Large artery	230 (40%)	63 (33%)	287 (35%)	
Small vessel	152 (26%)	48 (25%)	199 (24%)	
Cardioembolic	94 (16%)	49 (25%)	158 (19%)	
Other ischemic	7 (1.2%)	4 (2.1%)	32 (3.9%)	
Undetermined ischemic	90 (16%)	28 (15%)	137 (17%)	
Hemorrhagic	3 (0.5%)	1 (0.5%)	10 (1.2%)	
Stroke location‡				0.66; 0.49; 0.84
Right	238 (48%)	77 (50%)	341 (45%)	
Left	220 (44%)	66 (43%)	362 (48%)	
Bilateral	38 (7.7%)	10 (6.5%)	58 (7.6%)	

Figures are mean (SD) or n (%). AF indicates atrial fibrillation; BMI, body mass index; FGL, fasting glucose level; and IFG, impaired fasting glucose.

*Pearson χ^2 tests, ANOVA, and *t* tests were used to examine group differences. For tests between stroke subtypes, the undetermined ischemic and hemorrhagic categories were not included.

†These variables contained (n) missing data: BMI (137), hypertension (1), AF (6), smoking data (107), prior stroke (3), stroke subtype (8), and history of depression (1148).

‡One hundred ninety-one had missing stroke location data; brain stem and cerebellar strokes were excluded from this classification.

cognitive function than those with normal FGL 3 to 6 months poststroke. As expected, stroke patients with T2D had significantly poorer cognitive function compared with patients with normal FGL, and the association was not confounded by the presence of other vascular risk factors, stroke features, or other background characteristics. All domains were affected among patients with T2D but not equally; the largest reduction in cognitive function was observed in the attention and processing speed domain, with an average *Z* score more than half an SD lower in diabetic patients compared with patients with normal FGL, whereas memory function had the smallest effect size observed.

The only previous study that examined patients with stroke found an association between prediabetes and poststroke cognitive impairment.[12] This conflicting finding may be due to 2 key factors. First, in that study, FGL was obtained during the first 24 hours after admission (compared with an average of 10 days poststroke in our study)—a period during which FGL

Table 3. Relationship Between Glucose Status (Diabetes Mellitus, IFG, and Normal Fasting Glucose Level) and Cognitive Function

Cognitive Function (*Z* Scores)	Model 1* (Max n=1601)		Model 2† (Max n=1337)		Model 3‡ (Max n=1132)	
	Diabetes Mellitus vs Normal	IFG vs Normal	Diabetes Mellitus vs Normal	IFG vs Normal	Diabetes Mellitus vs Normal	IFG vs Normal
	β (95% CI); *P* Value	β (95% CI); *P* Value	β (95% CI); *P* Value	β (95% CI); *P* Value	β (95% CI); *P* Value	β (95% CI); *P* Value
Global cognition	−0.59 (−0.78 to −0.41); <0.001	−0.11 (−0.38 to 0.16); 0.43	−0.59 (−0.80 to −0.38); <0.001	−0.18 (−0.48 to 0.12); 0.23	−0.59 (−0.82 to −0.36); <0.001	−0.10 (−0.45 to 0.24); 0.55
Attention and processing speed	−0.46 (−0.66 to −0.26); <0.001	−0.08 (−0.37 to 0.21); 0.59	−0.44 (−0.66 to −0.21); <0.001	−0.11 (−0.43 to 0.22); 0.52	−0.54 (−0.79 to −0.29); <0.001	−0.13 (−0.51 to 0.24); 0.48
Memory	−0.22 (−0.35 to −0.09); 0.001	−0.04 (−0.23 to 0.14); 0.65	−0.20 (−0.35 to −0.05); 0.008	−0.10 (−0.31 to 0.11); 0.36	−0.21 (−0.38 to −0.05); 0.012	−0.07 (−0.32 to 0.18); 0.58
Language	−0.27 (−0.42 to −0.11); 0.001	0.06 (−0.17 to 0.28); 0.63	−0.30 (−0.47 to −0.13); 0.001	0.003 (−0.24 to 0.25); 0.98	−0.28 (−0.47 to −0.09); 0.004	−0.05 (−0.33 to 0.24); 0.75
Perceptual motor	−0.50 (−0.69 to −0.31); <0.001	−0.20 (−0.47 to 0.08); 0.16	−0.47 (−0.69 to −0.26); <0.001	−0.28 (−0.60 to 0.03); 0.08	−0.39 (−0.62 to −0.15); 0.001	−0.02 (−0.39 to 0.35); 0.91
Executive function	−0.44 (−0.64 to −0.24); <0.001	−0.22 (−0.51 to 0.06); 0.13	−0.45 (−0.67 to −0.23); <0.001	−0.32 (−0.63 to −0.01); 0.046	−0.36 (−0.61 to −0.12); 0.004	−0.17 (−0.53 to 0.19); 0.35

IFG indicates impaired fasting glucose; and Max, maximum.

*Model 1 adjusts for age, sex, and education.

†Model 2 adjusts for age, sex, education, and stroke subtype.

‡Model 3 adjusts for age, sex, education, stroke subtype, ethnicity, hypertension, smoking, previous stroke, atrial fibrillation, and body mass index.

was likely to be elevated due to a stress response to stroke. Second, the authors used criteria for FGL and HbA1c simultaneously to define diabetes mellitus and prediabetes, and the use of diabetes mellitus medications was not considered. These factors potentially contributed to their study having a higher percentage of patients with prediabetes (42% versus 12% in our study). Moreover, their assessment was based only on the Mini-Mental State Examination, which was conducted 1 month poststroke—a period when a number of factors could have confounded the assessment.

Interestingly, a few recent population-based studies have found that prediabetes was associated with structural brain abnormalities. A longitudinal study of aging in healthy individuals found that high blood glucose levels in nondiabetics were associated with greater cortical atrophy.[16] Another study reported that prediabetes was associated with the presence of lacunar infarcts, larger white matter hyperintensities, and smaller white matter volumes.[17] Evidence regarding the relationship between brain tissue volumes and cognitive function is inconsistent, however, with a recent study finding no significant relationship in a sample with T2D.[18]

Our results regarding T2D and poorer cognitive function are supported by most recent studies and reviews linking diabetes mellitus with an increased risk of cognitive impairment, decline, and dementia[6,19,20]; yet few studies examined that relationship in patients with stroke. A retrospective study from Israel found that T2D was associated with lower Mini-Mental State Examination scores in patients with ischemic stroke 1 week after admission.[21] A Canadian study found that stroke patients with both depression and diabetes mellitus had an increased risk of severe cognitive impairment (Montreal Cognitive Assessment <20) and deficits in executive function.[22] Our study adds to this evidence and provides more robust findings by examining FGL and not solely medical history data, assessing multiple cognitive domains and relying on cognitive assessments that were not conducted during the acute phase.

It should be noted that stroke patients with normal FGL exhibited significantly poorer cognitive performance (eg, on average 1.03 SD lower on global cognition) compared with stroke-free control subjects in this study. Our findings suggest that those who have diabetes mellitus in addition to stroke may experience even greater cognitive deficits and may, therefore, be at a higher risk of dementia. While the mechanism of the interaction between stroke and diabetes mellitus on cognition is not clear, it has been suggested that the proinflammatory processes associated with diabetes mellitus may be exacerbated by cerebral ischemia, which may lead to greater ischemic damage in the brain.[23]

We did not find any significant interactions between ethno-racial groups and diabetes mellitus, although our results showed a tendency for the association between diabetes mellitus and poorer cognitive function to be stronger in Asians compared with Whites. T2D is generally much more common in people of Asian descent, and a recent IPD meta-analysis on 20 population-based cohorts found that there was greater cognitive decline associated with diabetes mellitus in Asian participants.[24] Greater numbers of studies from Asia are needed to better understand this relationship. We found no evidence of effect modification by age other than an association between T2D and poorer memory in younger stroke patients. There were significant sex differences in the association of T2D with cognitive function that were domain specific, with women performing more poorly in memory, perceptual motor, and executive function. Few studies have addressed the potential modifying effect of sex on cognitive impairment in patients with T2D, and the current evidence is conflicting. A 2016 meta-analysis of population-based studies found that

for individuals with T2D, the risk of developing vascular dementia was greater in women than in men[25]; however, a new American study found that men with T2D had a higher prevalence of cognitive impairment and they performed worse in verbal learning and memory.[26] While there is growing evidence that the adverse effects of diabetes mellitus on vascular risk are stronger in women,[27] it is not clear whether T2D affects the brain differently in men and women. Future research is required to explore this interesting sex difference.

Some of our studies had large proportions of patients with missing FGL, and typically, this was due to blood work not being part of the study protocol (see Table II in the Data Supplement for possible reasons for missing data). Although we found that patients who were excluded due to missing FGL had slightly poorer health, there was no significant difference between the included and excluded groups in the proportions with a history of diabetes mellitus or on mean global cognition *Z* scores. Therefore, it is unlikely that the omission of patients from the analysis due to missing FGL would have significantly affected our results.

Hyperglycemia in the acute phase after stroke may reflect preexisting abnormalities in glucose metabolism, or it may be a stress response to neurological insult.[28] Since some of our studies measured FGL within the first few days of stroke, we conducted 2 sensitivity analyses to assess the potential bias caused by stress hyperglycemia. First, we assumed an elevation of 20% in FGL based on previous research.[29,30] Second, since HbA1c is considered a reflection of average glucose level in the preceding 3 months and is, therefore, less affected by stress hyperglycemia, we conducted a subgroup analysis using HbA1c in place of FGL. We found no change from our main conclusions, which suggests that our results are robust and unlikely to have been confounded by stress hyperglycemia.

Our study has many strengths, including the ethno-racial and regional diversity from 7 studies around the world, meaning our results are more generalizable. We examined 5 cognitive domains based on neuropsychological tests rather than the Mini-Mental State Examination, and the use of standardized scores allowed for the magnitude of differences between groups and domains to be described and compared. Additionally, we were able to adjust for possible confounders including age, sex, education, vascular risk factors, and stroke features. Limitations include our inability to assess the impact of the duration and severity of diabetes mellitus on cognitive function due to our limited diabetes mellitus dataset, the measurement of FGL at only one point in time, and a lack of data regarding diabetes mellitus medication use for 2 of the contributing studies. Our study is limited by being cross-sectional, raising the possibility that the poststroke cognitive deficits in those classified as having diabetes mellitus might have existed before stroke. Longitudinal data would also have allowed us to examine whether IFG is associated with cognitive decline and dementia in later years. Our results could be biased by unmeasured or unknown confounding variables, such as the presence of Alzheimer disease in this older population. Furthermore, we must acknowledge that combining studies from different periods is complicated by changing standards of diagnostic assessment and care. Even though EpiUSA (Epidemiological Study of the Risk of Dementia After Stroke) was an older study which began in 1988, it was a landmark study and set the trend for such studies worldwide, and the quality of its assessments was exemplary.

Given our finding that stroke patients with diabetes mellitus have significantly greater deficits than nondiabetic patients in global cognition and all cognitive domains, our study has important clinical implications for their care after stroke. Diabetes mellitus self-care requires careful attention to glucose levels, managing glucose-monitoring devices and often-complex medication regimens, judging medication doses, self-administering insulin, as well as understanding food labels and portion sizes. All of these skills may be compromised in patients with cognitive deficits. Therefore, our findings highlight the importance of assessing the capacity for self-care in patients with diabetes mellitus following the acute phase after stroke to ensure that the patient is competent to manage these often-complex tasks.

In conclusion, T2D, but not prediabetes, is associated with poorer cognitive performance in patients 3 to 6 months after stroke. This emphasizes the importance of interventions to prevent the progression of prediabetes to diabetes mellitus in stroke patients, as well as the evaluation of diabetes mellitus self-care skills in diabetic patients and the simplification of those routines whenever possible. Given the increasing global impact of diabetes mellitus, the identification and effective management of patients with prediabetes who are at risk of progression to diabetes mellitus could provide a great public health benefit.

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Disclosures

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