

# Association of Prediabetes and Diabetes With Stroke Symptoms

The REasons for Geographic And Racial Differences in Stroke (REGARDS) study\*

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**OBJECTIVE**—Stroke symptoms among individuals reporting no physician diagnosis of stroke are associated with an increased risk of future stroke. Few studies have assessed whether individuals with diabetes or prediabetes, but no physician diagnosis of stroke, have an increased prevalence of stroke symptoms.

**RESEARCH DESIGN AND METHODS**—This study included 25,696 individuals aged  $\geq 45$  years from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study who reported no history of stroke or transient ischemic attack at baseline (2003–2007). Glucose measurements, medication use, and self-reported physician diagnosis were used to categorize participants into diabetes, prediabetes, or normal glycemia groups. The presence of six stroke symptoms was assessed using a validated questionnaire.

**RESULTS**—The prevalence of any stroke symptom was higher among participants with diabetes (22.7%) compared with those with prediabetes (15.6%) or normal glycemia (14.9%). In multivariable models, diabetes was associated with any stroke symptom (prevalence odds ratio [POR] 1.28 [95% CI 1.18–1.39]) and two or more stroke symptoms (1.26 [1.12–1.43]) compared with normal glycemia. In analyses of individual stroke symptoms, diabetes was associated with numbness (1.15 [1.03–1.29]), vision loss (1.52 [1.31–1.76]), half-vision loss (1.54 [1.30–1.84]), and lost ability to understand people (1.34 [1.12–1.61]) after multivariable adjustment. No association was present between prediabetes and stroke symptoms.

**CONCLUSIONS**—In this population-based study, almost one in four individuals with diabetes reported stroke symptoms, which suggests that screening for stroke symptoms in diabetes may be warranted.

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More than 40% of adults in the U.S. have diabetes or prediabetes (1), which increases the risk of microvascular and macrovascular complications, including stroke. In a recent meta-analysis of 102 epidemiologic studies, adults with diabetes were two to three times as likely as adults without diabetes to have an ischemic stroke (2). Additionally, diabetes has been associated with an increased risk of various ischemic stroke subtypes, including lacunar and thrombotic stroke (3,4), while weaker associations have been reported for diabetes and hemorrhagic stroke (2). In contrast, inconsistent findings have been reported for the association between prediabetes and stroke. Several studies have reported an association between prediabetes and ischemic stroke (5–8), while others have reported no association (9,10).

Although individuals with diabetes have an increased risk of stroke, not all strokes come to clinical attention. In the general population, stroke symptoms among individuals reporting no history of a stroke diagnosis have been associated with an increased risk of future stroke, suggesting that at least some reported stroke symptoms may be indicative of clinically unrecognized strokes (11–14). However, few studies have examined the association between prediabetes or diabetes and stroke symptoms. If individuals with prediabetes and diabetes have an increased prevalence of stroke symptoms without a stroke diagnosis, screening this population for stroke symptoms may be warranted and used to guide clinical management programs for the prevention of stroke. The purpose of this study was to evaluate the association of prediabetes and diabetes with the prevalence of stroke symptoms in a large national study of U.S. adults aged  $\geq 45$  years without a history of stroke or transient ischemic attack (TIA). Additionally, the association between metabolic syndrome and stroke symptoms among participants without diabetes was investigated in a secondary analysis.

## RESEARCH DESIGN AND METHODS

The current study is a cross-sectional analysis of baseline data

from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. The REGARDS study is a prospective, population-based cohort study designed to investigate racial and geographic differences in stroke incidence and stroke mortality. Details of the study objectives and design have previously been published (15). In brief, 30,239 African American and white adults aged  $\geq 45$  years were enrolled between 2003 and 2007, with 56% of participants recruited from the “stroke buckle” (defined as the coastal North Carolina, South Carolina, and Georgia areas) and “stroke belt” (the remainder of North Carolina, South Carolina, and Georgia as well as Alabama, Mississippi, Tennessee, Arkansas, and Louisiana) regions and the remaining 44% of participants recruited from the other 40 contiguous U.S. states and the District of Columbia. The REGARDS study protocol was approved by the institutional review boards of each participating institution, and all participants provided written informed consent.

Individuals reporting a history of stroke or TIA at baseline ( $n = 3,033$ ), missing data on stroke or TIA history ( $n = 279$ ), missing data on stroke symptoms ( $n = 376$ ), and missing data on glucose level or oral diabetes medications ( $n = 855$ ) were excluded from this study, resulting in 25,696 participants in this cross-sectional analysis.

### Data collection and variables

Structured telephone interviews, self-administered questionnaires, and in-home examinations were used to assess demographic, lifestyle, and clinical factors at baseline. Age, sex, race, education, annual household income, health insurance, smoking status, alcohol consumption, and current use of insulin, oral diabetes, and antihypertensive medications were self-reported. Participants were asked up to two questions about alcohol consumption during the telephone interview: 1) “Do you presently drink alcoholic beverages, including beer, wine, and other drinks made with hard liquor, even occasionally?” and if the response was yes, then 2) “How many alcohol beverages do you presently drink?” Moderate alcohol consumption was defined as one drink daily or less for women and two drinks daily or less for men, and heavy alcohol consumption was defined as more than one drink daily for women and more than two drinks daily for men based on federal dietary guidelines (16). Geographic region (stroke buckle, stroke belt, and other) and urban/rural residence (urban, rural,

and mixed) was determined using participant address and census data. During the in-home examination, blood pressure, height, and weight were measured following a standardized protocol. In brief, after the participant had been sitting for several minutes, two seated systolic and diastolic blood pressure measurements were taken by a trained technician using an aneroid sphygmomanometer (American Diagnostic Corporation, Hauppauge, NY) that was regularly evaluated for quality control (17). Blood pressures were taken following a standardized protocol in the left arm of participants and using a large-size cuff if the participant’s arm circumference exceeded 13 inches. The average of the two blood pressure measurements was used in this analysis. BMI was calculated as weight in kilograms divided by the square of height in meters. An electrocardiogram was also recorded during the in-home examination and analyzed at a central reading center to determine the presence of atrial fibrillation, myocardial infarction, and left ventricular hypertrophy (LVH). Atrial fibrillation and prior myocardial infarction were defined using Minnesota code criteria (18), and LVH was defined using sex-specific Cornell voltage cut points (19). History of coronary heart disease was defined as myocardial infarction on electrocardiogram, self-reported myocardial infarction, or prior coronary revascularization procedures. Blood samples were collected during the in-home examination following standardized protocols and were analyzed at a central laboratory. Serum glucose was measured using colorimetric reflectance spectrophotometry on the Ortho Vitros 950 IRC Clinical Analyzer (Johnson & Johnson Clinical Diagnostics) with a coefficient of variation of 1%.

### Diabetes, prediabetes, and metabolic syndrome

Diabetes was defined as a fasting serum glucose  $\geq 126$  mg/dL ( $\geq 7$  mmol/L) (20) (or a random serum glucose  $\geq 200$  mg/dL [ $\geq 11.1$  mmol/L] for the 13% of participants who did not fast for a minimum of 8 h), current use of insulin or oral diabetes medications, or a self-reported physician diagnosis of diabetes while not pregnant. Prediabetes was defined as a fasting serum glucose between 100 and 125 mg/dL (5.6 and  $< 7$  mmol/L) (20) or a random serum glucose between 140 and 199 mg/dL (7.8 and  $< 11.1$  mmol/L) among participants not using insulin or oral diabetes medications and without a history of diabetes. Normal glycemia was defined as a fasting

serum glucose  $< 100$  mg/dL ( $< 5.6$  mmol/L), a random serum glucose  $< 140$  mg/dL ( $< 7.8$  mmol/L), no use of insulin or oral diabetes medications, and no history of diabetes. Metabolic syndrome was calculated only among participants without diabetes and who fasted overnight prior to the REGARDS study visit ( $n = 17,054$ ). Metabolic syndrome was defined based on having three or more of the following components: 1) systolic blood pressure  $\geq 130$  mmHg, diastolic blood pressure  $\geq 85$  mmHg, or current antihypertensive medication use; 2) HDL cholesterol  $< 40$  mg/dL in men and  $< 50$  mg/dL in women; 3) triglycerides  $\geq 150$  mg/dL; 4) fasting glucose  $\geq 100$  mg/dL; and 5) waist circumference  $> 102$  cm in men and  $> 88$  cm in women (21).

### Stroke symptoms

Stroke symptoms were assessed during the baseline telephone interview using the Questionnaire for Verifying Stroke-Free Status (QVSS), a validated questionnaire (22,23) consisting of eight questions designed to identify stroke-free individuals in the general population (24). The first two questions inquire about a physician diagnosis of stroke or TIA, and the remaining six questions (Supplementary Table 1) inquire about the sudden onset of each of six stroke symptoms: weakness (unilateral), numbness (unilateral), vision loss in one or both eyes, half-vision loss, lost ability to understand people, and lost ability to express self verbally or in writing. We reported good sensitivity (82%) and reasonable specificity (62%) for a positive response to any of the stroke symptoms compared with a neurologist diagnosis of stroke or TIA (25).

The association of diabetes status with stroke symptoms was evaluated using the following classification: 1) any of the six stroke symptoms, 2) each stroke symptom individually, 3) two or more of the six stroke symptoms, and 4) specific stroke symptom clusters that are similar to common clinical presentations (25). The stroke symptom clusters evaluated were as follows: 1) weakness (unilateral) and numbness (unilateral), 2) lost ability to understand people and lost ability to express oneself verbally or in writing, and 3) weakness (unilateral) and lost ability to express oneself verbally or in writing.

### Statistical analysis

Participant characteristics were calculated by diabetes category (i.e., diabetes, prediabetes, and normal glycemia). Logistic regression was used to calculate prevalence

odds ratios (PORs) (95% CI) for the association of diabetes, prediabetes, and stroke symptoms, using normal glycemia as the reference group. Initial models included adjustment for age, race, and sex. Subsequent models included additional adjustment for education, annual household income, health insurance, geographic region, urban/rural residence, systolic blood pressure, antihypertensive medication use, smoking status, alcohol consumption, BMI, atrial fibrillation, LVH, and history of coronary heart disease. A secondary analysis was also performed to evaluate the association between metabolic syndrome and stroke symptoms. Effect modification by age, race, sex, and geographic region was evaluated in fully adjusted models using interaction terms. Multiple imputation with five datasets (26) was used to obtain values for 19% of participants who were missing data on covariates. The most commonly missing covariate was income. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

## RESULTS

### Diabetes, prediabetes, and stroke symptoms

Participant characteristics are presented in Table 1 by diabetes category. Overall, 23.6% of participants had diabetes, 15.6% had prediabetes, and 60.8% had normal glycemia. Each participant characteristic investigated was associated with diabetes status except health insurance and current smoking.

Participants with diabetes had the highest prevalence of any stroke symptom (22.7%) followed by participants with prediabetes (15.6%) or normal glycemia (14.9%). They also had a higher prevalence of each stroke symptom compared with individuals with prediabetes or normal glycemia (Fig. 1). Participants with diabetes were more likely to report any stroke symptom after adjustment for age, race, and sex (POR 1.56 [95% CI 1.45–1.69]) and in a fully adjusted model (1.28 [1.18–1.39]). Additionally, diabetes was associated with each stroke symptom individually after adjustment for age, race, and sex, but the associations remained statistically significant after multivariable adjustment only for numbness on one side, vision loss, half-vision loss, and lost ability to understand people (Table 2). Prediabetes was not associated with having any of the six stroke symptoms in crude or adjusted models. Differences in

**Table 1—Characteristics of the REGARDS study participants by diabetes status**

	Normal glycemia	Prediabetes	Diabetes	P
n	15,615	4,011	6,070	
Age (years)	64.0 (9.5)	64.2 (9.1)	65.3 (8.8)	<0.001
Women	56.6	51.0	53.0	<0.001
African American	34.7	40.6	55.5	<0.001
Geographic region				
Other	45.8	41.8	41.8	Ref.
Stroke belt	34.3	35.8	35.6	<0.001
Stroke buckle	20.0	22.4	22.6	<0.001
Urban/rural residence				
Urban	69.5	71.5	72.4	Ref.
Rural	20.3	18.4	18.1	<0.001
Mixed	10.2	10.1	9.4	0.024
High school education	90.7	89.7	81.8	<0.001
Annual household income (USD)				
<20,000	16.4	17.5	27.2	Ref.
20,000–34,999	26.0	25.0	30.6	<0.001
35,000–74,999	35.9	37.3	30.7	<0.001
≥75,000	21.8	20.3	11.5	<0.001
Health insurance	93.5	92.6	92.9	0.101
Current smoking	14.0	15.3	13.8	0.829
Alcohol consumption				
None	57.7	59.0	72.6	Ref.
Moderate	37.7	35.4	25.3	<0.001
Heavy	4.6	5.6	2.2	<0.001
BMI (kg/m <sup>2</sup> )	28.0 (5.6)	30.4 (6.0)	32.1 (6.6)	<0.001
Systolic blood pressure (mmHg)	125.2 (16.0)	129.3 (16.2)	130.9 (16.8)	<0.001
Antihypertensive medication use <sup>†</sup>	60.7	64.4	82.0	<0.001
Statin use	23.9	30.3	44.7	<0.001
Atrial fibrillation	7.1	8.0	9.6	<0.001
Left ventricular hypertrophy	4.5	5.1	7.5	<0.001
History of coronary heart disease	12.9	15.5	23.5	<0.001

Data are means (SD) or percent. <sup>†</sup>Among individuals with hypertension.

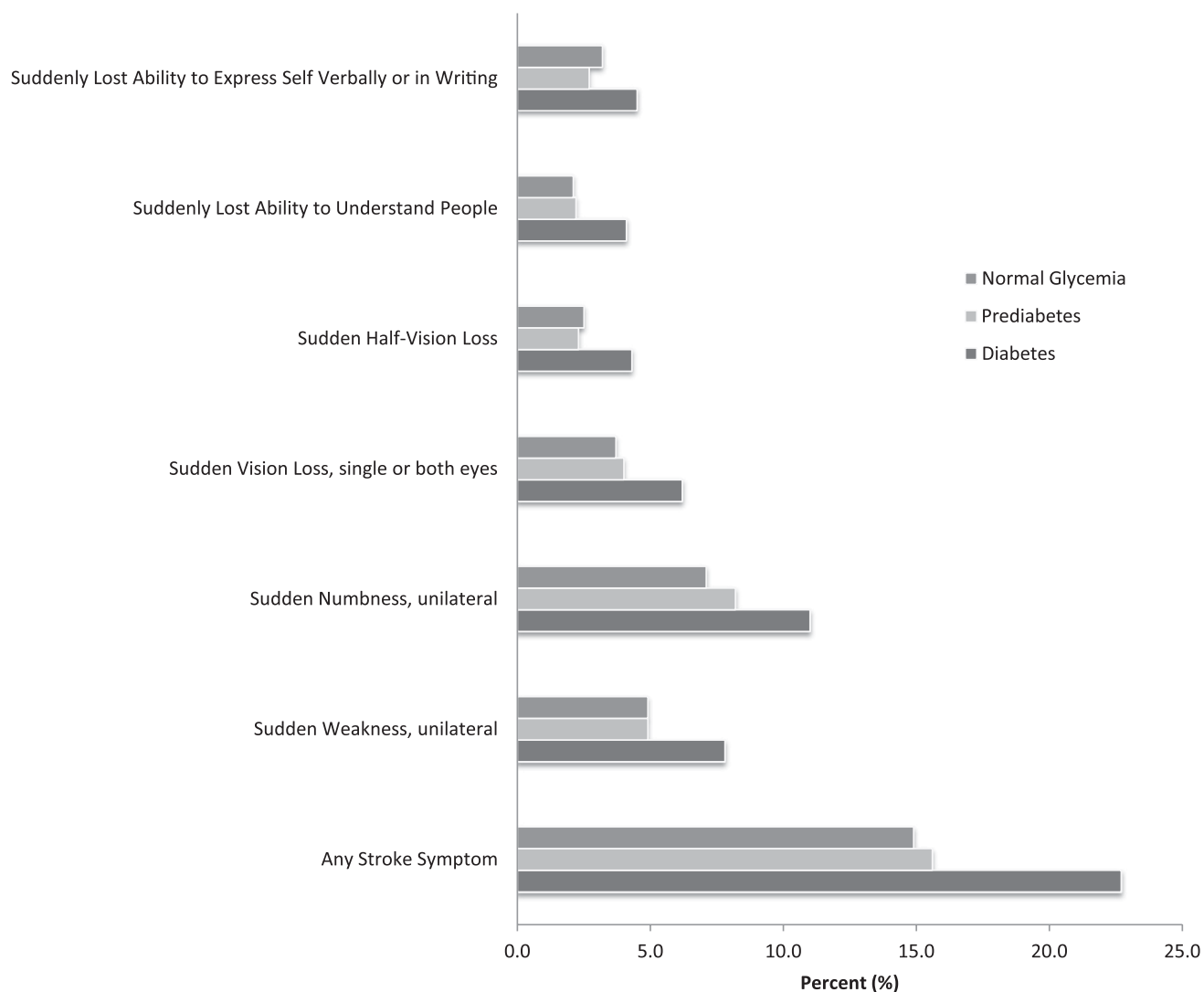
the association of diabetes and stroke symptoms were investigated by age, race, sex, and geographic region, but none were statistically significant ( $P > 0.10$ ).

The prevalence of stroke symptom clusters is presented in Fig. 2. Participants with diabetes had a higher prevalence of any two or more stroke symptoms (9.6%) compared with participants with prediabetes (5.8%) or normal glycemia (5.7%). The prevalence of stroke symptom clusters was also higher among participants with diabetes compared with those with prediabetes or normal glycemia. After multivariable adjustment, participants with diabetes were more likely to have two or more stroke symptoms (Table 2) compared with those with normal glycemia. Diabetes was also associated with stroke symptom clusters after adjustment for age, race, and sex, but these associations were attenuated and no longer statistically significant after additional multivariable adjustment. Prediabetes was not associated with having two

or more stroke symptoms or any of the stroke symptom clusters.

### Metabolic syndrome and stroke symptoms

Among participants without diabetes, 29.2% had metabolic syndrome. Among those with metabolic syndrome, 87.9% had elevated blood pressure, 79.6% had abdominal obesity, 68.5% had low HDL cholesterol, 57.9% had elevated triglycerides, and 51.6% had elevated glucose. Metabolic syndrome was associated with any stroke symptom (POR 1.13 [95% CI 1.03–1.24]) and with sudden weakness and sudden numbness individually after multivariable adjustment (Supplementary Table 2). Additionally, metabolic syndrome was associated with having two or more stroke symptoms (1.26 [1.10–1.44]) and the cluster of unilateral weakness and numbness (1.41 [1.17–1.71]) after adjustment for age, race, and sex, but both of these associations were



**Figure 1**—Prevalence of any stroke symptom and each individual stroke symptom by diabetes status: the REGARDS study.

attenuated and not statistically significant after multivariable adjustment (Supplementary Table 3).

**CONCLUSIONS**—In this population-based study of middle-aged and older adults, almost one in four individuals with diabetes but without a physician diagnosis of stroke had experienced stroke symptoms. Diabetes was associated with both individual stroke symptoms and multiple stroke symptoms. Because diabetes heightens the risk for vascular complications, the association between diabetes and stroke symptoms observed in this study among those without a reported stroke diagnosis could reflect a high prevalence of unrecognized strokes. Prediabetes was not associated with any stroke symptom or two or more stroke symptoms. However, metabolic syndrome was associated with the occurrence

of any stroke symptom but not two or more stroke symptoms.

The association between diabetes and stroke symptoms has been investigated in previous studies. In the Atherosclerosis Risk in Communities (ARIC) study of middle-aged white and African American adults, diabetes was associated with stroke symptoms in each race-sex group after adjustment for age and study site, but additional multivariable adjustment was not reported and individuals with a prior history of stroke were not excluded (27). Another study of middle-aged adults in Scotland that did exclude those with a history of stroke reported that men with diabetes were more likely to report two or more stroke symptoms, while no difference in stroke symptoms was reported among women (12). The current study found that both men and women with diabetes were more likely to report any

stroke symptom and two or more stroke symptoms even though they reported no stroke diagnosis and that these associations persisted after multivariable adjustment. The prior studies used different questionnaires and assessed different stroke symptoms than the current study but suggest that our finding of a 50% greater prevalence of stroke symptoms among individuals with diabetes warrants further investigation of the occurrence of clinically unrecognized strokes in this high-risk population.

Prediabetes was not associated with individual stroke symptoms or clusters of stroke symptoms among the individuals without a reported stroke diagnosis in the current study. Few data have been published on the association between prediabetes and stroke symptoms without a stroke diagnosis. In prior studies, the association between prediabetes and

Table 2—PORs (95% CI) for stroke symptoms associated with prediabetes and diabetes among REGARDS study participants

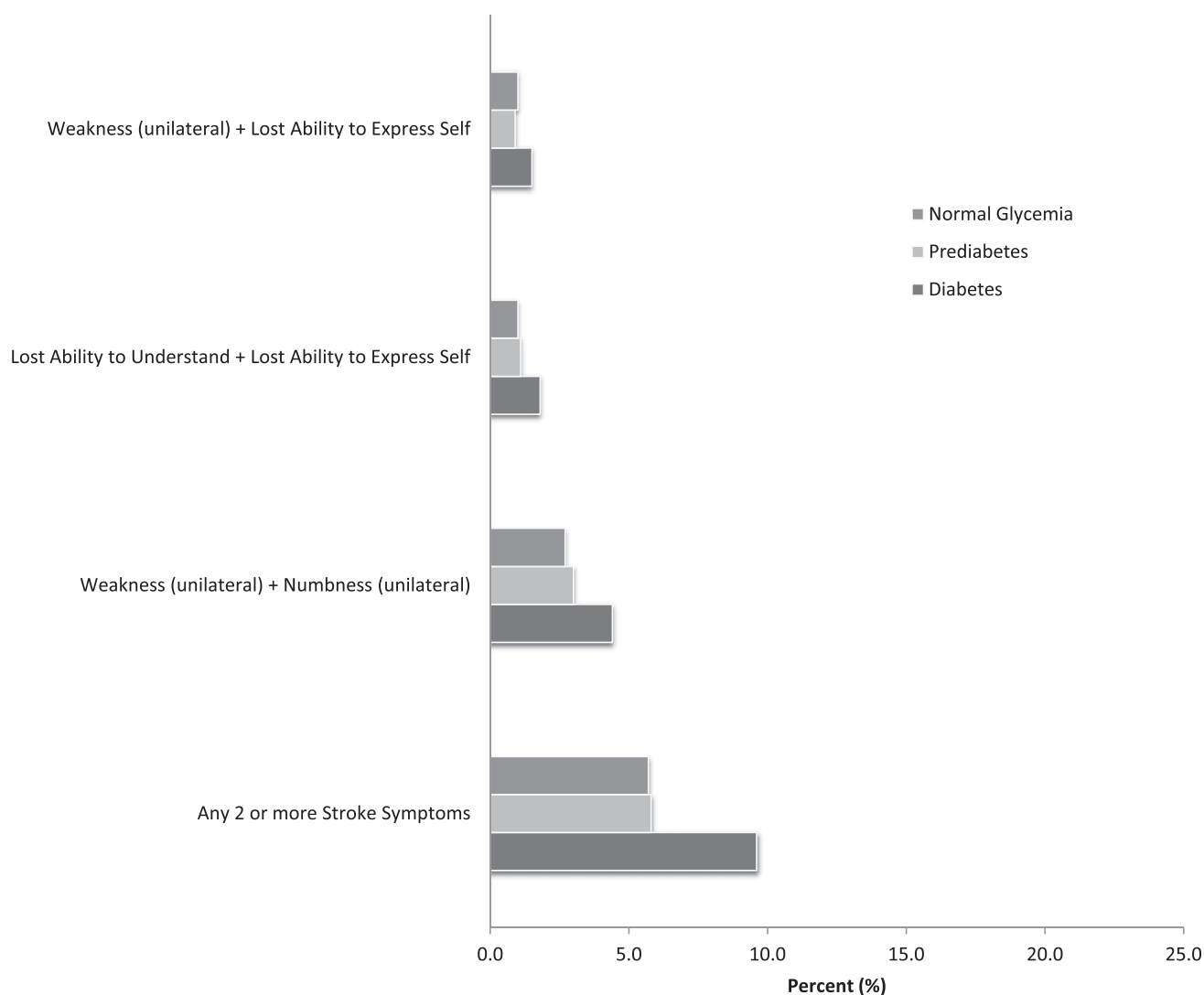
	POR (95% CI)		
	Normal glycemia (n = 15,615)	Prediabetes (n = 4,011)	Diabetes (n = 6,070)
<b>Any stroke symptom</b>			
Model 1	1 (ref.)	1.03 (0.94–1.14)	1.56 (1.45–1.69)***†††
Model 2	1 (ref.)	0.98 (0.89–1.08)	1.28 (1.18–1.39)***†††
<b>Individual stroke symptoms</b>			
<b>Sudden weakness, unilateral</b>			
Model 1	1 (ref.)	0.97 (0.82–1.14)	1.49 (1.32–1.68)***†††
Model 2	1 (ref.)	0.88 (0.75–1.04)	1.10 (0.97–1.26)†
<b>Sudden numbness, unilateral</b>			
Model 1	1 (ref.)	1.13 (0.99–1.29)	1.47 (1.32–1.63)***†††
Model 2	1 (ref.)	1.04 (0.91–1.19)	1.15 (1.03–1.29)*
<b>Sudden painless loss of vision in one or both eyes</b>			
Model 1	1 (ref.)	1.11 (0.93–1.32)	1.73 (1.51–1.98)***†††
Model 2	1 (ref.)	1.09 (0.91–1.31)	1.52 (1.31–1.76)***†††
<b>Sudden loss of half-vision</b>			
Model 1	1 (ref.)	0.93 (0.74–1.17)	1.71 (1.45–2.02)***†††
Model 2	1 (ref.)	0.94 (0.74–1.19)	1.54 (1.30–1.84)***†††
<b>Suddenly lost ability to understand people</b>			
Model 1	1 (ref.)	1.00 (0.79–1.27)	1.72 (1.45–2.04)***†††
Model 2	1 (ref.)	0.98 (0.77–1.25)	1.34 (1.12–1.61)**†
<b>Suddenly lost ability to express self verbally or in writing</b>			
Model 1	1 (ref.)	0.85 (0.69–1.04)	1.36 (1.17–1.59)***†††
Model 2	1 (ref.)	0.81 (0.65–1.00)	1.10 (0.93–1.29)††
<b>Any 2 or more stroke symptoms</b>			
Model 1	1 (ref.)	1.00 (0.86–1.17)	1.63 (1.46–1.83)***†††
Model 2	1 (ref.)	0.94 (0.81–1.10)	1.26 (1.12–1.43)***†††
<b>Stroke symptom clusters</b>			
<b>Weakness (unilateral) plus numbness (unilateral)</b>			
Model 1	1 (ref.)	1.08 (0.88–1.32)	1.51 (1.28–1.77)***††
Model 2	1 (ref.)	0.97 (0.78–1.19)	1.07 (0.90–1.27)
<b>Lost understanding plus lost expression</b>			
Model 1	1 (ref.)	1.08 (0.77–1.52)	1.73 (1.34–2.23)***†
Model 2	1 (ref.)	1.04 (0.73–1.47)	1.29 (0.98–1.70)
<b>Weakness (unilateral) plus lost expression</b>			
Model 1	1 (ref.)	0.92 (0.64–1.33)	1.46 (1.12–1.91)**†
Model 2	1 (ref.)	0.82 (0.56–1.19)	0.97 (0.73–1.30)

Model 1 adjusts for age, race, and sex. Model 2 adjusts for model 1 variables plus income, education, health insurance, geographic region, urban/rural residence, systolic blood pressure, antihypertensive medication use, BMI, smoking status, alcohol consumption, atrial fibrillation, left ventricular hypertrophy, and history of cardiovascular disease. \* $P < 0.05$  compared with normal glycemia. \*\* $P < 0.01$  compared with normal glycemia. \*\*\* $P < 0.001$  compared with normal glycemia. † $P < 0.05$  compared with prediabetes. †† $P < 0.01$  compared with prediabetes. ††† $P < 0.001$  compared with prediabetes.

cardiovascular outcomes has been weaker than the association reported for diabetes (28). Additionally, no association has been reported for prediabetes and stroke in some studies (9,10). It is possible that some people with prediabetes may have been misclassified in this study because only fasting or random glucose was used to determine prediabetes status and not oral glucose tolerance tests or A1C. Furthermore, while each of these testing methods is acceptable for assessing prediabetes status, there is considerable discordance among their results (29), reflecting current challenges in classifying prediabetes.

Metabolic syndrome has been associated with an increased risk of stroke among individuals without diabetes (30), but data investigating the association between metabolic syndrome and stroke symptoms are limited. The current study observed an association between metabolic syndrome and any stroke symptom but not two or more stroke symptoms after multivariable adjustment. Additionally, metabolic syndrome was not associated with the individual stroke symptoms of vision loss and lost ability to understand, although these symptoms were associated with diabetes in this study.

It is unclear whether the stroke symptoms reported among people with diabetes in this study represent unrecognized cerebral infarcts specifically or some other pathophysiologic process, possibly related to diabetes complications (e.g., retinopathy, neuropathy). Brain imaging was not available in this study; thus, we could not confirm the prevalence of imaging-confirmed strokes. It is notable that previous studies have reported mostly null findings for the association between diabetes and silent cerebral infarctions (31–35), with the exception of the Rotterdam Scan Study, which reported an association between diabetes and incident silent



**Figure 2**—Prevalence of two or more stroke symptoms and stroke symptom clusters by diabetes status: the REGARDS study.

cerebral infarctions over 3.5 years of follow-up (36). Additionally, inconsistent findings have been reported for the association between prediabetes and silent cerebral infarctions (37,38). The current study focused on clinically overt symptoms, which may or may not have been evaluated by a physician, and the relationship between these overt stroke symptoms and truly silent cerebral infarcts is not clear. The QVSS used in this study assessed the sudden onset of unilateral numbness and weakness, whereas diabetic neuropathy typically does not have a sudden onset and often presents bilaterally. Stroke symptom clusters, which may be less prone to misclassification, were also more common among individuals with diabetes in the current study. However, the prevalence of stroke symptom clusters was low

overall, limiting the power of this analysis. While the QVSS has demonstrated good sensitivity and modest specificity compared with stroke status determined by a neurologist in a general medicine population (25), its performance in a population of people with diabetes has not been evaluated.

This study has additional potential limitations. A history of stroke/TIA was determined using self-reported physician diagnosis. These questions have been shown to be reliable (23) but are subject to recall bias. Additionally, the classification for diabetes, prediabetes, and normal glycemia was determined using a single fasting or random glucose measurement among those who did not use insulin or oral diabetes medications and did not report a history of diabetes. For a clinical diagnosis of diabetes, it is recommended

that a repeat test is performed to verify a diagnosis, but this was not available in this study, and duration of diabetes was not assessed either. Additionally, residual confounding is a possibility in this analysis. The REGARDS study also has several strengths, including its large national sample of middle-aged and older adults, inclusion of a large sample of African Americans who are at high risk of both stroke and other diabetes complications, and the collection of demographic, behavioral, clinical, and laboratory data following a standardized study protocol.

In summary, in this study of individuals from a large national, population-based study who reported no diagnosis of stroke, stroke symptoms were common among those with diabetes, and diabetes was independently associated with stroke symptoms. Given that 42% of participants

with stroke symptoms have reported not seeking medical care for these symptoms (39), the need for physicians to actively query about potential stroke symptoms and implement stroke risk reduction strategies, including pharmacologic therapy when indicated, is underscored. These findings have implications for stroke prevention efforts and suggest that screening for stroke symptoms among individuals with diabetes may be warranted.

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A.P.C. and P.M. researched data, contributed to the discussion, wrote the manuscript, and reviewed and edited the manuscript. B.M.K. and D.O.K. contributed to the discussion and reviewed and edited the manuscript. V.J.H. researched data, contributed to the discussion, and reviewed and edited the manuscript. J.F.M., L.S.W., and R.J.P. contributed to the discussion and reviewed and edited the manuscript. G.H. and M.M.S. researched data, contributed to the discussion, and reviewed and edited the manuscript. A.P.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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