Published in final edited form as:

J Geriatr Psychiatry Neurol. 2016 May ; 29(3): 142–148. doi:10.1177/0891988715627023.

Stroke symptoms with absence of recognized stroke are associated with cognitive impairment and depressive symptoms in older adults with diabetes

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Abstract

Self-reported stroke symptoms may represent unrecognized cerebrovascular events leading to poorer cognitive and mental health. We examined relationships between stroke symptoms, cognitive impairment, and depressive symptoms in a high-risk sample: 247 adults age 65 with diabetes. Stroke symptoms were assessed using the Questionnaire for Verifying Stroke-free Status, cognitive impairment was measured with the modified Telephone Interview for Cognitive Status, and depressive symptoms were measured using the 15-item Geriatric Depression Scale. In 206 participants without history of stroke/TIA, 27.7% reported stroke symptoms, with sudden loss of comprehension most frequently reported (11.7%). Having >1 vs. 0 stroke symptoms was associated with greater odds of cognitive impairment (OR=3.04, 95% CI, 1.15–8.05) and more depressive symptoms ($b=2.60$, $p<.001$) while controlling for age, race, gender, education, diabetes duration, diabetes severity, and cardiovascular comorbidities. Better recognition and treatment of cerebrovascular problems in older adults with diabetes may lead to improved cognition and mental health.

Keywords

Cognitive aging; Diabetes; Depression; Stroke

BACKGROUND

Diabetes is a significant health concern in the United States and disproportionately affects older adults,¹ with the 65+ age group projected to account for 55% of all cases by 2050.² While it is widely known that diabetes increases the risk of cardiovascular disease, evidence also links diabetes to greater risk of cognitive impairment and dementia,^{3,4} higher rates of depression,^{5,6} and more than double the risk of ischemic stroke.^{1,7} A significant relationship has also been found between diabetes and cerebral infarction pathology postmortem.⁸ Thus,

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Conflicts of interest: No disclosures to report

increased cerebrovascular disease may partially explain associations between diabetes and worse cognitive and mental health outcomes in older adulthood.^{4,7}

Understanding the clinical significance of stroke symptoms in diabetes is especially important when considering the large proportion of stroke symptoms that go unnoticed or ignored. In a large national sample, over 40% of those who reported stroke, TIA, or stroke symptoms did not seek medical care.⁹ A separate study similarly found that only 60% of those with evidence of ischemic stroke used emergency medical services and only 39% of those with a TIA used emergency medical services.¹⁰ Older individuals were more likely to use emergency medical services; however, surprisingly, knowledge of stroke symptoms was not associated with increased use of emergency medical services.¹⁰

In the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, 17.6% of older adults without previously diagnosed stroke or TIA reported having experienced at least one stroke symptom.¹¹ The most commonly reported stroke symptom in this sample was “sudden painless numbness on one side of the body.”¹² Importantly, reporting any stroke symptom was associated with a 36% increase in incident stroke, even after controlling for traditional stroke risk factors. Overall number of stroke symptoms reported was the most powerful predictor of incident stroke in this study. In terms of specific symptoms and risk of future stroke, endorsing sudden problems with comprehension or communication were the symptoms related to the largest increase in stroke risk.¹²

There is little existing research on the relationship between stroke symptoms and cognitive or mental health outcomes. One study based on REGARDS data found that stroke symptoms were significantly related to cognitive impairment on a brief mental status exam, but this association did not remain statistically significant after fully adjusting for covariates.¹³ In another REGARDS analysis, stroke symptoms were associated with higher risk of cognitive impairment when grouped with reported diagnosis of TIA.¹⁴ Thus, the relationship between stroke symptoms and cognitive impairment in the absence of known stroke or TIA remains unclear.

Research also links cerebrovascular changes to late-life depression.^{3, 15–17} It has been suggested that cerebrovascular pathology can precipitate depressive symptoms and cause “vascular depression,” with a consistent relationship seen between late-life depression and white matter hyperintensities.¹⁵ However, previous studies have not focused on the relationship between stroke symptoms and depressive symptoms in older adults.

Overall, research on the significance of self-reported stroke symptoms has been limited and has examined adults in the general population as opposed to groups who are at high-risk for stroke as well as cognitive impairment and depression, such as older adults with diabetes. The present study examined stroke symptoms in older adults with diabetes but without a history of diagnosed stroke or TIA, including how these symptoms were related to cognitive impairment and depressive symptoms.

METHODS

Sample

Participants included community-dwelling older adults in the Birmingham, Alabama area as well as patients from a diabetes clinic at the University of Alabama at Birmingham (UAB). All participants were age 65 or older and had diabetes identified either by self-report or physician diagnosis. Community-dwelling participants were recruited from a commercially available list of older adults (from Equifax) in the Birmingham metropolitan area, gathered and maintained by the UAB Roybal Center for Translational Research on Aging and Mobility. Clinic participants were recruited from patients of one physician (F.O.) at the UAB Diabetes & Endocrinology Clinic. All potential participants were contacted via a mailed letter followed by telephone contact. African Americans were oversampled because an overall goal of the study was to examine racial disparities in cognitive and mental health outcomes in older adults with diabetes.

Participants completed telephone interviews that included diabetes-specific measures of health and psychosocial factors as well as performance-based cognitive testing. Interviewers were supervised by two psychologists and a study coordinator with a Master's in Public Health. Interviewers included graduate and undergraduate psychology students who underwent extensive training on administration of measures for the study. This training included observations of a senior study member completing the protocol, followed by observations and feedback by a senior study member before completing data collection independently. All data for the current analyses were collected via telephone interviews. A total of 247 individuals (72% community-dwelling, 28% clinic patients) were enrolled in the study. The sample had an average education of 13.5 years, 44.5% were African American (3.9% identified as "other" race, which was combined with Caucasians for analyses), and 47.4% were male.

Measures

Stroke symptoms were assessed via the Questionnaire for Verifying Stroke-free Status (QVSS),¹⁸ a reliable and validated measure with high sensitivity (0.82) and moderate specificity (0.62) for the diagnosis of stroke or TIA compared with neurological examination.^{19,20} The QVSS includes six yes/no questions inquiring about specific stroke symptoms occurring over one's lifetime (e.g., "Have you ever suddenly lost the ability to understand what people were saying?"). Scores were coded into three categories for endorsing no stroke symptoms, one symptom, or more than one symptom. Previous research has shown that a greater number of stroke symptoms on the QVSS is a strong predictor of subsequent stroke.¹²

Cognitive function was assessed using the modified version of the Telephone Interview for Cognitive Status (TICS-M), a measure of global cognitive function. The TICS-M is a reliable and widely used screening measure for cognitive impairment in older adults, with scores ranging from 0–39. An advantage of the TICS-M is that it is less constrained by ceiling effects that limit the utility of other cognitive screening measures.²¹ The TICS-M also shows good sensitivity for detecting dementia when compared to full

neuropsychological assessment.²² A score below 21 is suggestive of clinically significant cognitive difficulties and was used to define cognitive impairment in the current study.²¹

Depressive symptoms were assessed using the Geriatric Depression Scale – Short Form (GDS), with scores ranging from 0–15.^{23,24} The GDS is widely used in research and clinical settings for depression screening in older adults. Higher scores indicate greater depressive symptoms.

Covariates included demographic variables of age, race (African American vs. Caucasian or “other” race), gender, and years of education. Diabetes health-related covariates included diabetes duration, diabetes severity, and cardiovascular comorbidities. Diabetes duration was coded as years with diabetes. Diabetes severity was computed as a combined score of insulin shot use (yes/no) plus number of self-reported diabetes complications including amputation, foot ulcers, neuropathy, nephropathy (i.e., renal or kidney disease), and diabetic retinopathy. Severity scores ranged from 0–6 with higher scores indicating greater diabetes severity. Cardiovascular comorbidities included angina/chest pain, hypertension, heart attack/myocardial infarction, and congestive heart failure; scores ranged from 0–4 with higher scores indicating more cardiovascular comorbidities.

Statistical analyses

The present study used data from participants with diabetes who also reported no history of stroke, “mini-stroke”, or TIA. Participants self-reporting Alzheimer’s disease or other forms of dementia were also excluded from analyses. We first examined the overall prevalence of having stroke symptoms in this sample as well as frequency of the different individual symptoms. We also conducted bivariate analyses to compare number of stroke symptoms for those with and without cardiovascular comorbidities and examined relationships between specific stroke symptoms and cognitive impairment and depressive symptoms.

Logistic regression was used to examine the relationship between stroke symptoms and cognitive impairment, defined as a TICS-M score below 21. Multiple regression modeling was used to examine the relationship between stroke symptoms, depressive symptoms, and the continuous measure of cognitive performance (i.e., TICS-M total). For all regression models, number of stroke symptoms was dummy coded into three levels, with the presence of one symptom and the presence of more than one symptom included in these models (with no stroke symptoms serving as the reference group). A series of incremental regression analyses was conducted (model 1: unadjusted; model 2: adjusted for age, race, gender, and years of education; model 3: adjusted for model 2 factors as well as diabetes duration, diabetes severity, and cardiovascular comorbidities). Additional analyses were conducted to examine whether the relationship between stroke symptoms and cognitive impairment or depressive symptoms varied by race. We used an ordinal variable for stroke symptoms with three levels (i.e., no symptoms, one symptom, and more than one symptom) to create a race by stroke symptoms interaction term. This interaction term was then included in the fully adjusted models. Analyses were performed using SPSS Statistics for Windows, Version 20.0 (Armonk, NY: IBM Corp.).

RESULTS

To ensure that participants had Type 2 as opposed to Type 1 diabetes, we classified individuals as having Type 1 diabetes if 1) they self-reported a diagnosis of Type 1 diabetes and an age of onset before 30 years old, or 2) they self-reported “don’t know” for diabetes type but had an age of onset before 30 years old and current insulin use. After excluding one participant with probable Type 1 diabetes, 36 participants with reported history of diagnosed stroke, 14 with “mini-stroke”/TIA, and 6 participants with Alzheimer’s disease/other dementia, a final sample of 206 participants was used in analyses (some participants had overlapping exclusionary criteria). Table 1 shows participant characteristics for the analytic sample. Compared to African Americans, Caucasians reported significantly fewer stroke symptoms, $t(204) = -2.12, p < .05$, fewer depressive symptoms, $t(204) = -2.76, p < .01$, and higher cognitive function scores, $t(204) = 4.45, p < .001$.

Over 27% of this stroke-free sample endorsed one or more stroke symptoms, with 15% endorsing one symptom and 12.6% reporting two or more symptoms (see Table 2). The most prevalent symptom reported in the sample was “sudden loss of ability to understand what people are saying” (11.7%), with “sudden loss of one half of vision” being the least reported symptom (4.9%). Those with cardiovascular comorbidities ($n = 172$) reported more stroke symptoms than those without these comorbidities ($n = 34$), $t(204) = -2.86, p < .01$. Overall, 96.5% of those endorsing one or more stroke symptoms also reported at least one comorbid cardiovascular condition.

Examining bivariate correlations revealed that greater number of stroke symptoms (three-level ordinal variable of no symptoms, one symptom, or more than one symptom) was significantly negatively correlated with years of education ($r = -.14, p < .05$) and cognitive performance ($r = -.21, p < .01$), while significant positive correlations were observed with diabetes severity ($r = .24, p < .01$), cardiovascular comorbidities ($r = .20, p < .01$), and depressive symptoms ($r = .40, p < .01$). For individual stroke symptoms, cognitive impairment was more common among those who endorsed “sudden painless weakness on one side of body” ($X^2 = 6.21, p < .05$), “sudden painless loss of vision in one or both eyes” ($X^2 = 4.0, p < .05$), “sudden loss of ability to understand what people are saying” ($X^2 = 17.12, p < .001$), and “sudden loss of ability to express yourself” ($X^2 = 5.19, p < .05$). Stroke symptoms of “sudden numbness on one side of body” and “sudden loss of one half of your vision” were not significantly associated with cognitive impairment. All of the individual stroke symptoms were associated with significantly higher depressive symptoms ($p < .05$).

In the initial model examining stroke symptoms and cognitive impairment (Table 3), reporting more than one stroke symptom was significantly related to higher odds of cognitive impairment. This association was reduced by approximately 17% in the fully adjusted model, but remained statistically significant. In this model, those endorsing more than one stroke symptom were three times more likely to be cognitively impaired compared to those without stroke symptoms (OR, 3.04, 95% CI, 1.15 - 8.05). Notably, when additionally including depressive symptoms to the fully adjusted model as a covariate, endorsing more than one stroke symptom was no longer significantly associated with cognitive impairment (OR, 2.66, 95% CI, 0.95 - 7.49). Results were similar when using

TICS-M score as a continuous outcome in linear regression models. Lower score on the TICS-M was significantly associated with reporting more than one stroke symptom in the fully adjusted model ($b = -2.59$, $SE = 1.03$, $p < .05$).

In all models examining stroke symptoms and depressive symptoms (Table 4), reporting more than one stroke symptom was significantly related to more depressive symptoms. The adjusted R^2 of .186 indicated that approximately 19% of the variability in depressive symptoms was predicted by demographic factors, diabetes health-related covariates, and number of stroke symptoms. Endorsing more than one stroke symptom was associated with reporting approximately 2.5 more depressive symptoms ($b = 2.60$, $SE = .506$, $p < .001$) and was the only variable significantly related to depressive symptoms in the final model. Including cognitive performance as an additional covariate to the fully adjusted model did not change the relationship between stroke symptoms and depressive symptoms.

The interaction of race and stroke symptoms was not significantly associated with cognitive impairment (OR, 1.68, 95% CI, 0.66 – 4.31). However, this race interaction was significantly associated with depressive symptoms ($b = 1.07$, $SE = 0.46$, $p < .05$), such that stroke symptoms were more strongly related to depressive symptoms in African Americans than in Caucasians. Endorsing more than one stroke symptom was associated with reporting approximately 2 more depressive symptoms for Caucasians vs. 4 more depressive symptoms for African Americans.

DISCUSSION

This study examined the relationship between self-reported stroke symptoms, in the absence of diagnosed cerebrovascular disease, and indicators of cognitive and mental health in a sample of older adults with diabetes. There was a much higher prevalence of reporting one or more stroke symptoms in this sample (27.7%) compared to prevalence among a sample of older adults from a national population-based study (17.7%).¹¹ Overall, the most prevalent symptom reported in this sample of participants with diabetes was sudden comprehension loss (11.7%). Interestingly, this symptom was the least prevalent in the general population¹¹ and was also previously found to be associated with the largest increase for incident stroke.¹²

Results from this study indicated that endorsing more than one stroke symptom was significantly associated with cognitive impairment defined by using a previously established cutoff. However, this relationship did not remain statistically significant after accounting for depressive symptoms. This might be due to a shared pathological process leading to both stroke symptoms and depressive symptoms.¹⁵ Thus, accounting for depressive symptoms may mask the relationship between stroke symptoms and cognitive impairment.

The current findings contribute to existing research highlighting the negative relationship between stroke symptoms and cognitive impairment in the general population.^{13,14} However, unlike previous analyses that utilized a six-point mental status screener, the use of a more comprehensive cognitive measure (i.e., TICS-M) in the present study extends previous findings. In addition, our findings suggest that the relationship between stroke symptoms

and cognitive function may be particularly salient among older adults with diabetes. Furthermore, African Americans reported significantly more stroke symptoms, had greater depressive symptoms, and had significantly lower cognitive function scores. African American race was also significantly associated with cognitive impairment independent from stroke symptoms and other covariates. These findings highlight the importance of understanding racial health disparities among older people with diabetes. Previous research has found that African Americans have higher risk of diabetes and stroke, as well as greater risk of cognitive decline with aging when compared to Caucasians.^{1,12,25,26}

The relationship between stroke symptoms and depressive symptoms has not been directly examined in previous studies. In the present study, endorsing more than one stroke symptom was significantly associated with more depressive symptoms. We also conducted a post-hoc analysis which revealed that this association remained unchanged when controlling for self-reported history of depression diagnosis or treatment (i.e., “Has a doctor or healthcare provider ever told you that you have depression or suggested a medication or psychological counseling for depression?”). Analyses revealed a modifying effect of race, such that stroke symptoms were more strongly related to depressive symptoms in African Americans than in Caucasians. This may be viewed as consistent with the finding of worse health outcomes in African Americans with diabetes, with depression being more strongly associated with poor diabetes control in African Americans compared to Caucasians.²⁷ Given the strong relationship between stroke symptoms and depressive symptoms, our findings underscore the need for potential interventions to consider comorbid mood and health problems in those with diabetes. This is especially important when considering that depression rates are two times greater in those with diabetes compared to the general population. Depression is also significantly related to reduced adherence to medication and self-care management, elevated risk of complications, and increased mortality for those with diabetes.^{28–31}

Late-life depression and cognitive dysfunction are both directly related to cerebrovascular disease. This likely occurs through a variety of mechanisms including inflammation, cerebral hypofusion, and neural disconnection.¹⁵ This concept of “vascular depression” is in line with our findings; stroke symptoms were significantly related to both cognitive impairment and depressive symptoms. However, it is also important to note that assessing for depressive symptoms does not elucidate causal mechanisms (e.g., endogenous vs. reactive symptoms). An interesting question is whether treatment for depression is effective in those with comorbid cognitive impairment or cerebrovascular disease. Response to antidepressants is poor for those with both late-life depression and cognitive changes (particularly executive dysfunction),¹⁵ suggesting that as cerebrovascular disease progresses medication for depression may become less effective. Therefore, pharmacological treatment of depression should be closely monitored in older adults with comorbid health conditions and more research is needed on treatment of depression among older adults with comorbid depression, cognitive impairment, and cerebrovascular disease.

While there is initial evidence demonstrating the importance of stroke symptoms in those without diagnosed stroke or TIA in the general population, this was the first study to examine stroke symptoms in a high-risk sample of older adults with diabetes. Prevalence of reported stroke symptoms in the absence of previously diagnosed cerebrovascular disease

was 36.5% for a sample of those with end-stage renal disease, higher than the frequency in this sample with diabetes and a national sample.³² Therefore, as cardiovascular disease risk increases, the risk of stroke symptoms that go ignored or unnoticed may also increase. It is also important to note that stroke symptoms were significantly negatively correlated with years of education in our sample. In a large population-based sample, higher socioeconomic status and education were strongly associated with greater likelihood of seeking medical care following a cerebrovascular event.⁹ Therefore, those with lower education may also have lower health literacy and be less likely to see a physician, resulting in worse health outcomes (e.g., more unrecognized stroke symptoms). Given that diabetes is major risk factor for vascular disease, it is crucial to target individuals with possible unidentified stroke or TIA for treatment and intervention as well as educate those with diabetes about the importance of identifying and seeking care for potential stroke symptoms.

Although the present study highlighted relationships between stroke symptoms, cognitive impairment, and depressive symptoms, there are some limitations. Because this study did not have access to medical records, an important question is whether self-reported medical information is accurate. Prior studies have found that reliability of self-reported diabetes is very high compared to information from general practitioners as well as medical records.^{33,34} Furthermore, in previous research, lower cognitive function measured via the Mini-Mental State Examination (MMSE) was not associated with poorer accuracy of reporting diabetes or other chronic diseases.³³ Additionally, in the current study, those self-reporting a dementia diagnosis were excluded from all analyses and if those with cognitive impairment underreported stroke symptoms our findings would underestimate any association between these symptoms and cognitive impairment. In general, interpretations should be made cautiously for these cross-sectional analyses since causal inferences cannot be drawn. As previous research has shown, the relationship between ischemia, cognition, and depression is complex and likely not unidirectional.^{17,35}

Another limitation is that the stroke symptom questionnaire (QVSS) does not assess symptom duration or whether a physician was consulted, so the severity of symptoms is unknown. However, use of the QVSS for measuring stroke symptoms is supported by previous research.^{11–14} Further work is needed to examine the potential effect of stroke symptom severity, including number of stroke symptom episodes, on health outcomes. Also, there is the possibility that some of the reported stroke symptoms could be related to conditions such as hypoglycemic events or even to false alarms (e.g., oversensitivity to normal transient bodily sensations), as opposed to cerebrovascular events. We cannot rule out the presence of additional confounds, but we did include a number of health-related covariates in our statistical models, such as diabetes duration, diabetes severity, and cardiovascular comorbidities. Furthermore, 96.5% of those endorsing one or more stroke symptoms also reported cardiovascular comorbidities, which is consistent with the idea that reported stroke symptoms are related to unrecognized cerebrovascular events.

The present study contributes to a growing body of evidence supporting the importance of stroke symptoms, even in the absence of diagnosed stroke or TIA, to cognitive and mental health in older adults.^{13,14} We found that stroke symptoms were relatively common in this sample of older adults with diabetes. Because this was the first study to directly examine the

relationship between stroke symptoms and depressive symptoms, future research should further examine this relationship longitudinally. Given current findings, as well as the fact that diabetes is a major vascular risk factor, those with diabetes should be screened regularly for potential stroke symptoms. This is especially important given evidence of increasing incidence of diabetes coupled with decreasing mortality that leads to more years spent with the disease.³⁶ These trends may result in prolonged exposure to the negative effects of diabetes on the brain, presumably including cerebrovascular pathology. Given that Type 2 diabetes is significantly related to behavioral and lifestyle factors such as diet and exercise, interventions should not only target these factors but mood and cognition as well. In addition, this study further highlights the need for proper screening and prevention efforts concerning cerebrovascular events in older adults with diabetes.

Acknowledgments

Study funding: This work was supported in part by National Institute on Aging (NIA) grant P30AG022838 (UAB Roybal Center) and National Center for Advancing Translational Sciences (NCATS) award number UL1TR00165 (UAB Center for Clinical and Translational Science).

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Table 1Participant characteristics (n = 206) ^a

	n (%)	M (SD)	Minimum	Maximum
Age		73.58 (6.21)	65	90
African American	92 (44.7%)			
Male gender	101 (49.0%)			
Education (yrs)		13.63 (2.58)	6	20
Diabetes duration (yrs)		14.92 (10.86)	0	56
Diabetes severity		1.89 (1.34)	0	6
CV cormorbidities		1.26 (0.92)	0	4
TICS-M score		23.43 (5.52)	8	39
GDS-15 score		2.35 (2.52)	0	13
Stroke symptoms				
0	149 (72.3%)			
1	31 (15.0%)			
2	26 (12.6%)			

^aCV = cardiovascular; TICS-M = Telephone Interview for Cognitive Status – Modified; GDS = Geriatric Depression Scale

Table 2

Number and distribution of reported stroke symptoms (n = 206)

Variable	n (%)
One or more stroke symptoms	57 (27.7)
Total no. of stroke symptoms reported	
0	149 (72.3)
1	31 (15.0)
2	13 (6.3)
3	9 (4.4)
4	2 (1.0)
5	1 (0.5)
6	1 (0.5)
Sudden painless weakness on one side of body	17 (8.3)
Sudden numbness or dead feeling on one side of body	20 (9.7)
Sudden painless loss of vision in one or both eyes	14 (6.8)
Sudden loss of one half your vision	10 (4.9)
Sudden loss of ability to understand what people are saying	24 (11.7)
Sudden loss of ability to express yourself verbally or in writing	18 (8.7)

Table 3ORs for associations between stroke symptoms and cognitive impairment^a

	Model 1	Model 2	Model 3
0 stroke symptoms (reference)	...	...	...
1 stroke symptom	2.01 (0.87–4.63)	1.99 (0.82–4.83)	2.00 (0.80–4.98)
>1 stroke symptom	3.66 (1.54–8.66) **	3.05 (1.20–7.75) *	3.04 (1.15–8.05) *
Age	...	1.05 (0.99–1.11)	1.05 (0.99–1.11)
African American	...	2.45 (1.19–5.04) *	2.59 (1.25–5.38) *
Male	...	1.50 (0.74–3.08)	1.58 (0.76–3.27)
Education	...	0.76 (0.65–0.89) ***	0.75 (0.64–0.88) ***
Diabetes duration	...	...	1.01 (0.98–1.04)
Diabetes severity	...	...	0.83 (0.58–1.19)
CV comorbidities	...	...	1.21 (0.81–1.80)

^aEstimates are odds ratio (95% confidence interval);

CV = cardiovascular;

p < .05*, p < .01**, p < .001***

Table 4Association between stroke symptoms and depressive symptoms^a

	Model 1	Model 2	Model 3
0 stroke symptoms (reference)	...	...	...
1 stroke symptom	.923 (.455)	.868 (.451)	.703 (.458)
>1 stroke symptom	3.10 (.490) ***	2.86 (.492) ***	2.60 (.506) ***
Age	...	-.015 (.027)	-.022 (.027)
African American	...	.600 (.340)	.631 (.340)
Male	...	.021 (.337)	.045 (.338)
Education	...	-.114 (.064)	-.110 (.064)
Diabetes duration	...	...	.001 (.016)
Diabetes severity	...	...	.134 (.166)
CV comorbidities	...	...	.319 (.183)
Adjusted R-square	0.160	0.179	0.186
Model F (df ₁ , df ₂)	20.58 (2, 203) ***	8.44 (6, 199) ***	6.20 (9, 196) ***

^aEstimates are unstandardized beta (standard error);

CV = cardiovascular;

p < .05*, p < .01**, p < .001***