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Body mass index and stroke risk among patients with type 2 diabetes

Weiqin Li, MSc, **Peter T. Katzmarzyk, PhD**, **Ronald Horswell, PhD**, **Yonggang Zhang, MSc**, **Wenhui Zhao, MD, PhD**, **Yujie Wang, PhD**, **Jolene Johnson, MD**, and **Gang Hu, MD, PhD**
Pennington Biomedical Research Center, Baton Rouge, Louisiana (W.L., P.T.K., R.H., Y.Z., W.Z., Y.W., G.H.); Tianjin Women's and Children's Health Center, Tianjin, China (W.L.); China Japan Friendship Hospital, Beijing, China (W.Z.); Louisiana State University Health, Baton Rouge, Louisiana (J.J.)

Abstract

BACKGROUND AND PURPOSE—Previous studies have evaluated the association of body mass index (BMI) with the risk of all-cause and cardiovascular disease (CVD) mortality among diabetic patients, and results were controversial. No studies have focused on the association between BMI and stroke risk among diabetic patients. We aimed to examine the association of BMI with stroke risk among diabetic patients.

METHODS—We performed a prospective cohort study with 29,554 patients with type 2 diabetes. Cox proportional hazards regression models were used to estimate the association of different levels of BMI with stroke risk.

RESULTS—During a mean follow-up period of 8.3 years, 2,883 participants developed stroke (2,821 ischemic and 109 hemorrhagic). The multivariable-adjusted (age, sex, race, smoking, income and type of insurance) hazard ratios associated with different levels of BMI at baseline (18.5–24.9 [reference group], 25–29.9, 30–34.9, 35–39.9, and ≥40 kg/m^2) were 1.00, 0.86, 0.83, 0.76, and 0.70 (P_{trend} <0.001) for total stroke, 1.00, 0.87, 0.85, 0.78, and 0.72 (P_{trend} <0.001) for ischemic stroke, and 1.00, 0.76, 0.72, 0.54, and 0.53 (P_{trend} =0.034) for hemorrhagic stroke, respectively. When we used an updated mean or the last visit value of BMI, the inverse association of BMI with stroke risk did not change. This inverse association was consistent among patients of different races, sex, ages, HbA1c levels, never and current smoking, and patients with and without using glucose-lowering, cholesterol-lowering or antihypertensive agents.

CONCLUSIONS—The present study demonstrates an inverse association between BMI and stroke risk among patients with type 2 diabetes.

Keywords

Body Mass Index; Stroke; Diabetes; incident stroke; type 2 diabetes

Corresponding: Gang Hu, M.D., Chronic Disease Epidemiology Laboratory, Pennington Biomedical Research Center, 6400 Perkins Road, Baton Rouge, LA 70808, Tel: 225-763-3053, Fax: 225-763-3009, gang.hu@pbrc.edu.

Disclosures
None

Diabetes is considered 'the epidemic of the 21st century', affecting nearly 12% of US adults.[1] Obesity is another important public health problem in the US, as two in three adults are classified as overweight or obese (body mass index [BMI] ≥ 25 kg/m^2) and one-third are frankly obese (BMI ≥ 30 kg/m^2).[2] Among patients with diabetes in the US, approximately 45–65% of them are obese.[3] It has been shown that diabetes[4] and obesity[5] are two independent risk factors for stroke in the general population. However, whether and how obesity is associated with CVD risk among diabetic patients are seldom studied.

Several studies have focused on the associations between obesity and all-cause or CVD mortality among diabetic patients, but the results have been inconsistent. Some studies showed positive associations,[5, 6] while others found inverse associations,[3, 7] U-shaped associations[8, 9] or no associations[10] between BMI and mortality among diabetic patients. Moreover, most of these studies have been limited by small samples, and suboptimal control for smoking status and preexisting chronic conditions. In addition, all of the above studies focused on the association between BMI and CVD mortality, and no studies to our knowledge have assessed the association between BMI and incident stroke among patients with diabetes. The aim of this study was to examine the association between different levels of BMI at baseline, during follow-up and at the last visit with stroke risk among patients with type 2 diabetes in the Louisiana State University Hospital-Based Longitudinal Study (LSUHLS).

Methods

Study Population

From 1997 through June 2013 the LSU Health Care Services Division (LSUHCSD) operated seven public hospitals and affiliated clinics in Louisiana.[11–15] Since 1997, administrative, anthropometric, laboratory, clinical diagnosis, and medication data collected at these facilities are available in electronic form for both inpatients and outpatients. Overall, LSUHCSD facilities served about 1.6 million patients. The LSUHLS was established in 2010 by using these data.[11] We established a cohort of diabetic patients who used LSUHCSD hospitals between January 1, 1999 and December 31, 2009, using the International Classification of Diseases (ICD)-9 (code 250). All patients with diabetes in the LSUHCSD hospitals were diagnosed using the American Diabetes Association (ADA) criteria.[16] We validated the diabetes diagnosis in LSUHCSD hospitals. The agreement of diabetes diagnosis was 97%: 20,919 from a sample of 21,566 hospital discharge diagnoses based on ICD codes also had physician-confirmed diabetes by ADA diabetes diagnosis criteria.[16]

In the present study, we only included patients who had newly diagnosed diabetes. These patients had used the LSUHSCD system for a mean time of 5.0 years before the diagnosis of diabetes. After excluding individuals with a history of stroke and coronary heart disease at the diagnosis and individuals with incomplete data on any of the required variables for analysis, the final sample included 29,554 patients with type 2 diabetes (17,143 African Americans and 12,410 White Americans), who were 30–94 years of age. The study and analysis plan were approved by Pennington Biomedical Research Center and LSU Health Sciences Center Institutional Review Boards. We did not obtain informed consent from

participants involved in our study because we used anonymized data compiled from electronic medical records.

Baseline and follow-up measurements

The patient's characteristics, including age of diabetes diagnosis, sex, race/ethnicity, family income, smoking status, type of health insurance, BMI, blood pressure, low-density lipoprotein (LDL) cholesterol, HbA1c, estimated glomerular filtration rate (eGFR), and medication (antihypertensive drug, cholesterol lowering drug and anti-diabetic drug) within a half year before or after the diabetes diagnosis (baseline), during follow-up after the diabetes diagnosis (follow-up) and the last visit value were extracted from the computerized hospital records. For the present analysis, we chose the BMI measures within a half year before the diagnosis of diabetes as baseline measurement. The updated mean values of HbA1c, LDL cholesterol, BMI, systolic blood pressure (SBP) and eGFR over time were calculated for each participant from baseline to each year of follow up. For example, at one year the updated mean is the average of the baseline and one year values and at three years it is the average of baseline, one year, two year, and three year values. In the case of an event during follow-up, the period for estimating updated mean value was from baseline to the year before the event occurred. The average number of BMI measurements during the follow-up period was 15.0.

Prospective follow-up

Follow-up information was obtained from the LSUHLS database by using the unique number designated to every patient who visits the LSUHCSD hospitals each time. The ICD-9 codes were used to identify stroke (430–436) from the LSUHCSD database. Follow-up of each cohort member continued until the date of the diagnosis of stroke, the date of the last LSUHCSD encounter if the subject stopped use of LSUHCSD hospitals, death (other than death from stroke), or May 31, 2012.

Statistical analysis

The Cox proportional hazard model was used to estimate the association between BMI and risk of stroke. BMI was evaluated in the following 2 ways: (1) as 5 categories (18.5–24.9, 25–29.9, 30–34.9, 35–39.9, and ≥40 kg/m^2), and (2) as a continuous variable. All multivariable analyses were adjusted for age and sex, and further for smoking, income, type of insurance, and other risk factors (LDL cholesterol, SBP, HbA1c, eGFR, history of atrial fibrillation, use of antihypertensive drugs, glucose-lowering agents, and cholesterol-lowering agents). The different categories of BMI were included in the models as dummy variables, and the significance of the trend over different categories was tested in the same models with the median of each category as a continuous variable. A time-dependent Cox model was also used for the multiple observations of BMI for each subject with the counting process style of input.[17] To avoid the potential bias due to premature death or the presence of occult diseases at baseline, additional analyses were carried out after excluding the patients who died or were diagnosed with stroke during the first two years of follow-up. All statistical analyses were performed with PASW for Windows, version 20.0 (IBM SPSS Inc, Chicago, III) and SAS for Windows, version 9.3 (SAS Institute, Cary, NC).

Results

Table 1 shows characteristics of the study population. During a mean follow-up period of 8.3 years, 2,883 (2,821 ischemic and 109 hemorrhagic) subjects developed stroke. The multivariable-adjusted (age, sex, race, smoking, income and type of insurance) HRs associated with different levels of BMI at baseline (18.5–24.9 [reference group], 25–29.9, 30–34.9, 35–39.9, and ≥40 kg/m^2) were 1.00, 0.86, 0.83, 0.76, and 0.70 (P_{trend}<0.001) for total stroke, 1.00, 0.87, 0.85, 0.78, and 0.72 (P_{trend}<0.001) for ischemic stroke, and 1.00, 0.76, 0.72, 0.54, and 0.53 (P_{trend}=0.034) for hemorrhagic stroke, respectively (Table 2 and Online Table I). When BMI was examined as a continuous variable, the multivariable-adjusted HRs for each 1-unit increase in BMI at baseline were 0.986 (95% CI 0.981–0.991) for total stroke, 0.987 (95% CI 0.982–0.992) for ischemic stroke, and 0.978 (95% CI 0.954–1.004) for hemorrhagic stroke, respectively. After further adjustment for other potential confounding factors, these inverse associations were significant (all P_{trend}<0.05). When we excluded patients with incident subdural hemorrhage (n=35) and patients with transient ischemic attack (n=662) during follow-up (Online Table II), the inverse association of BMI with stroke risk did not change. When we did an additional analysis by using an updated mean or the last visit value of BMI, we found the same inverse association between BMI and stroke risk (Table 2 and Online Table I). When BMI was included in the Cox model as a time-dependent variable, we found the same inverse associations between BMI and stroke risk (Online Table III).

After excluding subjects who were diagnosed with stroke during the first two years of follow-up (n=847), the multivariable-adjusted HRs of stroke for each 1-unit increase in BMI at baseline were 0.987 (95% CI 0.981–0.993) for total stroke, 0.987 (95% CI 0.982–0.993) for ischemic stroke, and 0.978 (95% CI 0.950–1.007) hemorrhagic stroke, respectively (data not shown). After excluding subjects who died during the first two years of follow-up (n=426), the multivariable-adjusted HRs of stroke for each 1-unit increase in BMI at baseline were 0.987 (95% CI 0.982–0.992) for total stroke, 0.988 (95% CI 0.9823–0.993) for ischemic stroke, and 0.981 (95% CI 0.955–1.008) hemorrhagic stroke, respectively (data not shown).

In the subgroup analyses, the significant inverse association of BMI with stroke risk was confirmed among patients with different ages, sex, races, HbA1c levels (<7% and ≥7%), never smoking and current smoking, using or not using cholesterol-lowering agents, antihypertensive drugs, glucose-lowering agents, and oral hypoglycemic agents or insulin (all P_{trend}<0.05 except never smoking at baseline or using insulin during follow-up) (Table 3 and Online Table IV). There was no effect modification according to different ages, sex, races, smoking status, and use of antihypertensive drugs and cholesterol-lowering agents (all $P_{interaction}$>0.05). There were significant interactions of use of glucose-lowering agents and BMI with stroke risk (all $P_{interaction}$<0.05) which indicated a stronger inverse association of BMI and stroke risk among patients using oral hypoglycemic agents or not using hypoglycemic agents than those using insulin. There were significant interactions of HbA1c levels and BMI measurements with stroke risk (all $P_{interaction}$<0.05) which indicated a stronger inverse association of BMI with stroke risk among patients with HbA1c levels <7% than those with HbA1c levels ≥7%.

Discussion

Our study found an inverse association of BMI with the risks of total, ischemic and hemorrhagic stroke among patients with type 2 diabetes. This association was consistent among patients of different ages, sex, never smoking and current smoking, and using or not using glucose-lowering agents.

Epidemiological studies have previously examined the association of BMI with mortality among patients with diabetes, but the results were inconsistent. Some studies provided support for an "obesity paradox" which describes an inverse association between BMI and mortality,[3, 7] while other studies reported positive associations,[5, 6] U-shaped associations,[8, 9] and no associations.[10] The reasons for the difference in the associations across studies are not clear yet. However, most of these studies have been limited by small samples, suboptimal control for smoking status, and preexisting chronic conditions, and even use of BMI after diabetes diagnosis. All limitations might lead to spurious relationships between BMI and outcomes such as stroke among diabetic patients. Considering all of the above limitations, a recent analysis demonstrated a J-shaped association between BMI and mortality among diabetic patients and among those who had ever smoked, and a direct linear relationship among those who had never smoked.[18] However, as subjects in this study were female nurses and male health professionals, the results are limited to be generalized to the overall population.

To our knowledge, the present study is the first to assess the association of BMI with stroke risk among patients with type 2 diabetes, and we found a significant inverse association of BMI measurements at baseline, during follow-up and at the last visit with the risks of total, ischemic and hemorrhagic stroke. To make the methodology more rigorous, we have conducted several analyses. First, we used the BMI measures within a half year before the diagnosis of diabetes as a baseline measurement, which can avoid substantial BMI change by disease severity and methods of treatment. Second, we excluded people with a history of stroke or coronary disease before and at the diagnosis of diabetes, which can minimize the influence of reverse causation, and the inverse association between BMI and stroke did not change. Third, some studies found that "metabolically obese" normal-weight (MONW) diabetics may harbor an underlying illness that predisposes to premature death.[19] To avoid this bias, we performed sensitive analyses by excluding patients who died or were diagnosed with stroke during the first two years of follow-up, and the inverse association was still present. Moreover, after further control of potential physiologic effects of excess fatness, such as hypertension, HbA1C, dyslipidemia, and eGFR, the inverse association was still consistent. Furthermore, when we restricted the analysis to subjects who had never smoked, the results did not change. Finally, we assessed effect modification according to different subgroups, and the inverse association of BMI with incident stroke was confirmed among diabetic patients with different ages, sex, races, HbA1c, and using oral hypoglycemic agents, using insulin, and not using any glucose-lowering agents. However, the association of BMI with stroke risk was not significant among diabetic patients using insulin during follow-up, and the major reason might be that patients using insulin were more severe and were more likely to be lean, and they may have a hybrid type of diabetes and a high risk of stroke.

The potential mechanisms behind the obesity paradox are not yet clear. However, recent findings from the Look AHEAD (Action for Health in Diabetes) showed that an intensive lifestyle intervention focusing on weight loss did not reduce the rate of cardiovascular events in overweight or obese adults with diabetes.[20] Some researchers suggested that overweight and obesity might be protective against premature death, as aging[21] and growing of chronic diseases characterized by compromised nutrition, weakness, impaired physical function, and frailty[22, 23] could make 'overweight' or 'class I obese' the nadir of weight-mortality curve. But in the present study, BMI was inversely associated with stroke in both older (≥50 years of age) and younger (<50 years of age) patients with type 2 diabetes. There is a hypothesis that diabetic patients with normal weight might be MONW, who have hyperinsulinemia, insulin resistance, and dyslipidemia,[19] all of which predispose to the development of stroke. There is another hypothesis that low-normal weight is associated with a clinical sign of insufficient insulin secretion which could potentially lead to faster progression of nephropathy and subsequent mortality.[9] However, all hypotheses were drawn on the point that lean or normal weight was still at increased risk. In the present study, participants who were extremely obese (BMI ≥40 kg/m^2) still have reduced risk of incident stroke. The mechanism of an obesity benefit is still unknown.

There are several strengths in our study, including the large sample size, long follow-up time, and the use of administrative databases to avoid differential recall bias. Second, we have used BMI levels immediately before a diagnosis of type 2 diabetes, updated mean values and the last visit value, which can avoid potential bias from a single baseline measurement. Third, participants in this study used the same public health care system which minimizes the influence from the accessibility to health care. The present study also has limitations. First, our analysis was not performed on a representative sample of diabetic patients, which limits the generalizability of the results. LSUHCSD hospitals are public hospitals and cover over 1.6 million patients, most of whom are low income persons in Louisiana. Thus, the results of the present study will have wide applicability for diabetic patients with low income and without health insurance in the US. Another limitation of our study is that we did not have data on other obesity indicators, such as waist and hip circumferences. Third, our definition of stroke outcomes using ICD 9 codes is not as specific as ICD 10 codes are. Fourth, although our analyses adjusted for an extensive set of confounding factors, residual confounding due to the measurement error in the assessment of confounding factors, unmeasured factors such as carotid endarterectomy, physical activity, education, and dietary factors, cannot be excluded.

Conclusions

In summary, this large hospital-based cohort study demonstrated an inverse association between BMI and incident stroke among patients with type 2 diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics according to body mass index categories in African American and white patients with type 2 diabetes

	Body mass index (kg/m^2)					P value
	18.5–24.9	**25–29.9**	**30–34.9**	**35–39.9**	**≥40**	
No. of participants	3,121	6,658	7,425	5,606	6,744	-
Race, %						<0.001
African American	62.8	60.6	58.2	56.7	54.2	
White	37.2	39.4	41.8	43.3	45.8	
Male, %	48.3	43.5	38.4	31.2	23.9	<0.001
Age, y	53.0	53.3	52.2	50.7	48.1	<0.001
Annual income, $/family	18,601	18,968	18,871	18,976	18,617	0.902
SBP, mm Hg	139	142	144	146	148	<0.001
HbA1c, %	8.07	7.91	7.83	7.78	7.55	<0.001
LDL cholesterol, mg/dL	111	114	114	113	111	<0.001
eGFR (mL/min/1.73 m^2), %						<0.001
≥90	54.0	48.7	46.2	46.5	48.4	
60–89	33.3	38.0	40.8	41.2	40.6	
30–59	10.7	11.4	11.6	10.9	10.0	
15–29	1.2	1.2	1.1	1.1	0.8	
<15	0.9	0.8	0.4	0.3	0.3	
Smoking status, %						<0.001
Never smoking	49.0	62.3	66.5	70.9	74.3	
Past smoking	7.4	7.1	6.9	7.0	7.3	
Current smoking	43.6	30.6	26.7	22.1	18.4	
Type of insurance, %						<0.001
Free	72.7	76.0	78.3	80.5	83.2	
Self-pay	7.1	5.8	5.4	4.5	4.0	
Medicaid	6.7	4.8	4.3	5.2	5.1	
Medicare	11.7	11.2	9.7	7.3	5.6	
Commercial	1.9	2.3	2.2	2.5	2.2	
History of atrial fibrillation, %	0.38	0.26	0.32	0.32	0.12	0.12

	Body mass index (kg/m^2)					P value
	18.5–24.9	**25–29.9**	**30–34.9**	**35–39.9**	**≥40**	
Uses of medications, %						
Glucose-lowering medication	58.0	64.1	67.0	68.8	68.8	<0.001
Oral hypoglycemic agents	25.1	34.4	35.4	34.9	37.0	<0.001
Insulin	32.9	29.7	31.6	33.9	31.8	<0.001
Lipid-lowering medication	45.1	54.0	58.9	58.7	55.4	<0.001
Antihypertensive medication	63.5	70.5	74.5	75.6	76.0	<0.001

Values represent means or percentages. All continuous data adjusted for age, sex and race.

Table 2

HRs for total stroke according to different levels of body mass index at baseline, during follow-up and at last visit among patients with type 2 diabetes

	Body mass index (kg/m^2)					P_{trend}	Each 1 kg/m^2 increase
	18.5–24.9	**25.0–29.9**	**30–34.9**	**35–39.9**	**≥40**		
Baseline							
No. of participants	3,121	6,658	7,425	5,606	6,744	-	-
No. of cases	395	734	763	494	497	-	-
Person-years	25,162	55,474	62,195	46,764	56,527	-	-
HRs (95% CI)							
Model 1	1.00	0.84 (0.74–0.95)	0.81 (0.72–0.91)	0.74 (0.65–0.84)	0.68 (0.59–0.77)	<0.001	0.985 (0.980–0.990)
Model 2	1.00	0.86 (0.76–0.97)	0.83 (0.74–0.94)	0.76 (0.66–0.87)	0.70 (0.61–0.80)	<0.001	0.986 (0.981–0.991)
Model 3	1.00	0.81 (0.72–0.92)	0.77 (0.68–0.87)	0.70 (0.61–0.80)	0.64 (0.56–0.74)	<0.001	0.983 (0.978–0.988)
Follow-up							
No. of participants	2,959	6,774	7,656	5,617	6,548	-	-
No. of cases	363	792	774	482	472	-	-
Person-years	24,096	56,240	63,937	46,879	54,970	-	-
HRs (95% CI)							
Model 1	1.00	0.95 (0.84–1.08)	0.85 (0.75–0.96)	0.77 (0.67–0.88)	0.71 (0.62–0.81)	<0.001	0.983 (0.978–0.988)
Model 2	1.00	0.97 (0.85–1.10)	0.88 (0.77–0.99)	0.79 (0.69–0.91)	0.73 (0.63–0.84)	<0.001	0.984 (0.979–0.989)
Model 3	1.00	0.91 (0.81–1.04)	0.80 (0.71–0.91)	0.71 (0.62–0.82)	0.65 (0.56–0.75)	<0.001	0.980 (0.975–0.985)
Last visit							
No. of participants	3,466	6,825	7,373	5,405	6,485	-	-
No. of cases	464	767	729	451	472	-	-
Person-years	28,171	56,890	61,478	45,276	54,306	-	-
HRs (95% CI)							
Model 1	1.00	0.84 (0.75–0.95)	0.78 (0.69–0.87)	0.69 (0.61–0.79)	0.66 (0.58–0.75)	<0.001	0.983 (0.978–0.988)
Model 2	1.00	0.86 (0.76–0.96)	0.80 (0.71–0.90)	0.71 (0.63–0.81)	0.68 (0.60–0.78)	<0.001	0.984 (0.979–0.989)
Model 3	1.00	0.83 (0.74–0.93)	0.75 (0.67–0.85)	0.67 (0.58–0.76)	0.63 (0.55–0.72)	<0.001	0.981 (0.976–0.986)

Model 1, Adjusted for age, sex and race.

Model 2, additionally adjusted for types of insurance, income, and smoking.

Model 3, model 2 and also adjusted for LDL cholesterol, SBP, HbA1c, eGFR, history of atrial fibrillation, use of antihypertensive drugs, glucose-lowering agents, and cholesterol-lowering agent.

Table 3

HRs (95% CI) for stroke according to different levels of BMI at baseline among various subpopulations

	Body mass index (kg/m^2)					P_{trend}	$P_{interaction}$
	18.5–24.9	25.0–29.9	30–34.9	35–39.9	≥40		
Race							>0.10
African American	1.00	0.85 (0.72–0.99)	0.78 (0.67–0.92)	0.70 (0.58–0.83)	0.74 (0.62–0.89)	<0.001	
White	1.00	0.87 (0.72–1.06)	0.91 (0.76–1.10)	0.85 (0.70–1.05)	0.67 (0.54–0.82)	<0.001	
Sex							>0.25
Male	1.00	0.89 (0.75–1.07)	0.80 (0.67–0.97)	0.81 (0.65–1.00)	0.64 (0.50–0.81)	<0.001	
Female	1.00	0.82 (0.69–0.97)	0.84 (0.71–0.99)	0.73 (0.61–0.87)	0.70 (0.59–0.84)	<0.001	
Age groups, y							>0.50
<50	1.00	0.85 (0.68–1.07)	0.84 (0.67–1.04)	0.75 (0.59–0.95)	0.61 (0.48–0.76)	<0.001	
50–59	1.00	0.96 (0.78–1.18)	0.87 (0.71–1.07)	0.78 (0.63–0.98)	0.75 (0.60–0.94)	0.001	
60–94	1.00	0.72 (0.58–0.88)	0.73 (0.59–0.89)	0.67 (0.52–0.85)	0.64 (0.49–0.83)	<0.001	
Smoking status							>0.05
Never smoking	1.00	0.81 (0.68–0.98)	0.86 (0.72–1.03)	0.80 (0.66–0.97)	0.80 (0.66–0.97)	0.052	
Past smoking	1.00	1.15 (0.71–1.85)	1.07 (0.67–1.72)	0.86 (0.52–1.44)	0.58 (0.34–0.99)	0.015	
Current smoking	1.00	0.97 (0.77–1.23)	0.87 (0.69–1.11)	0.76 (0.57–1.00)	0.67 (0.49–0.90)	0.003	
HbA1c, %							<0.05
<7	1.00	0.91 (0.76–1.09)	0.86 (0.72–1.03)	0.75 (0.61–0.91)	0.68 (0.56–0.83)	<0.001	
≥7	1.00	0.82 (0.69–0.97)	0.83 (0.70–0.98)	0.78 (0.65–0.94)	0.75 (0.63–0.90)	0.003	
Using glucose-lowering agents							<0.025
No	1.00	0.87 (0.72–1.06)	0.78 (0.64–0.95)	0.63 (0.50–0.79)	0.68 (0.54–0.85)	<0.001	
Oral hypoglycemic agents	1.00	0.89 (0.70–1.15)	0.83 (0.65–1.07)	0.77 (0.59–1.02)	0.63 (0.47–0.84)	0.001	
Insulin	1.00	0.82 (0.67–1.01)	0.90 (0.73–1.09)	0.84 (0.68–1.04)	0.76 (0.61–0.94)	0.035	
Using antihypertensive drugs							>0.50
No	1.00	0.83 (0.60–1.14)	0.87 (0.63–1.22)	0.62 (0.41–0.93)	0.74 (0.50–1.09)	0.047	
Yes	1.00	0.85 (0.74–0.97)	0.82 (0.71–0.93)	0.77 (0.67–0.89)	0.69 (0.60–0.80)	<0.001	
Using cholesterol-lowering agent							>0.50
No	1.00	0.88 (0.73–1.06)	0.83 (0.68–1.00)	0.68 (0.54–0.84)	0.65 (0.52–0.81)	<0.001	
Yes	1.00	0.80 (0.68–0.94)	0.78 (0.67–0.92)	0.76 (0.64–0.90)	0.70 (0.59–0.84)	<0.001	

Adjusted for age, sex, race, income, type of insurance, and smoking status other than the variable for stratification.