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ARTICLE

Sex differences in the risk of stroke and HbA_{1c} among diabetic patients

Wenhui Zhao · Peter T. Katzmarzyk · Ronald Horswell · Yujie Wang · Jolene Johnson · Gang Hu

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Abstract
Aims/hypothesis Sex differences in macrovascular disease, especially in stroke, are observed across studies of epidemiology. We studied a large sample of patients with type 2 diabetes to better understand the relationship between glycaemic control and stroke risk.
Methods We prospectively investigated the sex-specific association between different levels of HbA_{1c} and incident stroke risk among 10,876 male and 19,278 female patients with type 2 diabetes.
Results During a mean follow-up of 6.7 years, 2,949 incident cases of stroke were identified. The multivariable-adjusted HRs of stroke associated with different levels of HbA_{1c} at baseline (HbA_{1c} <6.0% [<42 mmol/mol], 6.0–6.9% [42–52 mmol/mol] [reference group], 7.0–7.9% [53–63 mmol/mol], 8.0–8.9% [64–74 mmol/mol], 9.0–9.9% [75–85 mmol/mol] and ≥10.0% [≥86 mmol/mol]) were 0.96 (95% CI 0.80, 1.14), 1.00, 1.04 (0.85, 1.28), 1.11 (0.89, 1.39), 1.10 (0.86, 1.41) and 1.22 (0.92, 1.35) (p for trend=0.66) for men, and 1.03 (0.90, 1.18), 1.00, 1.09 (0.94, 1.26), 1.19 (1.00, 1.42), 1.32 (1.09, 1.59) and 1.42 (1.23, 1.65) (p for trend <0.001) for women, respectively. The graded association between HbA_{1c} during follow-up and stroke risk was observed among women (p for trend=0.066). When stratified by race, whether with or without glucose-lowering agents, this graded association of HbA_{1c} with stroke was still present among women. When stratified by age, the adjusted HRs were significantly higher in women older than 55 years compared with younger women.
Conclusions/interpretation The current study suggests a graded association between HbA_{1c} and the risk of stroke among women with type 2 diabetes. Poor control of blood sugar has a stronger effect in diabetic women older than 55 years.

Keywords Clinical diabetes · Epidemiology · Macrovascular disease

Abbreviations

eGFR	Estimated GFR
LSU HCSD	Louisiana State University Health Care Services Division
LSUHLS	Louisiana State University Hospital-Based Longitudinal Study
RCT	Randomised clinical trial

Introduction

Stroke is a leading cause of disability, cognitive impairment and death in the USA and accounts for 1.7% of national health expenditures [1]. In the USA, nearly 32,000 more women than men died of stroke in 2000, and this number is predicted to be 68,000 in 2050 [2]. Sex differences in stroke are observed across epidemiological studies, pathophysiology, treatments and outcomes. These sex differences have profound implications for the effective prevention and treatment of stroke. An increased knowledge of stroke risk factors in the population may lead to an improved prevention of stroke.

Epidemiological studies have reported that type 2 diabetes is an independent risk factor for stroke [3–7], but how much its effect varies by sex is uncertain. Some studies have shown that type 2 diabetes may have a stronger effect on stroke risk in women [3, 4, 8–10], but one study showed a greater effect in

W. Zhao · P. T. Katzmarzyk · R. Horswell · Y. Wang · G. Hu (✉)
Pennington Biomedical Research Center, 6400 Perkins Road, Baton Rouge, LA 70808, USA
e-mail: gang.hu@pbrc.edu

J. Johnson
LSU Health Baton Rouge, Baton Rouge, LA, USA

men [11]. Because randomised clinical trials (RCTs) and meta-analyses have failed to show the benefit of intensive glucose control on rates of stroke [12], and with the under-representation of females in RCTs [13], more observational data are needed to assess whether there is a sex-specific association between HbA_{1c} and the risk of stroke. The aim of the present study was to examine whether the associations between HbA_{1c} at baseline and during follow-up and the risk of incident stroke are different between men and women with type 2 diabetes in the Louisiana State University Hospital-Based Longitudinal Study (LSUHLS).

Methods

Study population LSU Health Care Services Division (LSU HCSD) operates seven public hospitals and affiliated clinics in Louisiana, which provide quality medical care regardless of the patient's income or insurance coverage [14–22]. Since 1997, administrative, anthropometric, laboratory, clinical diagnosis and medication data have been available in electronic form. The LSUHLS was established in 2010 by using these data [14]. Using ICD-9 (www.icd9data.com/2007/Volume1/240-279/250-259/250/default.htm) (code 250), we established a cohort of diabetic patients who used LSU HCSD hospitals from 1 January 1999 to 31 December 2009. All diabetic patients in the LSU HCSD hospitals were diagnosed using the American Diabetes Association (ADA) criteria: a fasting plasma glucose ≥7.0 mmol/l or 2 h glucose ≥11.1 mmol/l after a 75 g 2 h oral OGTT, or a patient with classic symptoms plus a random plasma glucose level of ≥11.1 mmol/l [23]. In the present study, we only included patients who had newly diagnosed diabetes. Before the diagnosis of diabetes, these patients had used the LSU HSCD system for a mean of 5.0 years (range 2–11 years). We have carried out a validated study for the diagnosis of diabetes in LSU HCSD hospitals [14], and 20,919 patients from a sample of 21,566 hospital discharge diagnoses based on ICD-9 codes also had physician-confirmed diabetes using the ADA diabetes criteria (the agreement being 97%) [23].

After excluding individuals with a history of stroke or CHD at baseline and patients with incomplete data on any of the required variables for analysis, the sample included 30,154 patients with type 2 diabetes (10,876 male and 19,278 female). Both the Pennington Biomedical Research Center and LSU Health Sciences Center Institutional Review Boards, LSU System, approved this study and analysis plan. Informed consent was not obtained from the participants involved in our study because we used pseudo-anonymised data compiled from electronic medical records.

Baseline and follow-up measurements The patients' characteristics, including demographic factors (age of diagnosis of diabetes, sex, race/ethnicity, family income, smoking status and types of health insurance), risk factors (body weight, height, BMI, blood pressure, HbA_{1c}, total cholesterol, HDL-cholesterol, LDL-cholesterol, triacylglycerols, estimated GFR [eGFR]) and information on medication (cholesterol-lowering, antihypertensive and glucose-lowering drugs) within a half year after the diagnosis of diabetes (baseline) and during follow-up after the diabetes diagnosis (follow-up) were extracted from the electronic medical records. The calculation of updated mean values of HbA_{1c}, LDL-cholesterol, BMI, blood pressure and eGFR were performed as previously described [24, 25]. The average number of HbA_{1c} measurements during the follow-up period was 7.7.

Prospective follow-up We obtained follow-up information on the clinical diagnosis (date of diagnosis, diagnosis code, priority assigned to diagnosis and ICD-9 code) from the LSUHLS inpatient and outpatient database by using the unique number assigned to every patient who visits the LSU HCSD hospitals. The ICD-9 codes were used to identify stroke (ICD-9 codes 430–436) from the LSU HCSD database for a routine clinical care visit. The stroke events occurring before or at the diagnosis of diabetes were identified from the LSU HCSD database retrospectively and were excluded from the analyses. Each cohort member was followed to 31 May 2012 for stroke diagnosis, the date of the last visit if the individual had stopped the use of LSU HCSD hospitals, or death (other than inpatient death from stroke), whichever occurred first [15, 21].

Statistical analyses The Cox proportional hazard model was used to estimate the association between HbA_{1c} level and risk of stroke. HbA_{1c} was evaluated in the following two ways: (1) as six categories (HbA_{1c} <6.0% [<42 mmol/mol], 6.0–6.9% [42–52 mmol/mol] [reference group], 7.0–7.9% [53–63 mmol/mol], 8.0–8.9% [64–74 mmol/mol], 9.0–9.9% [75–85 mmol/mol] and ≥10.0% [≥86 mmol/mol]), and (2) as a continuous variable. The significance of the trend over different categories of HbA_{1c} was tested in models with the median of each category as a continuous variable. All analyses were adjusted for age and race, and further for smoking, income, type of insurance, BMI, systolic blood pressure, LDL-cholesterol, eGFR, use of antihypertensive drugs, use of diabetes medications and use of cholesterol-lowering agents (multivariable model). We adjusted for updated means of BMI, LDL-cholesterol, systolic blood pressure and eGFR instead of these variables at baseline when we analysed the association between the updated means of HbA_{1c} and stroke risk. Because there was a significant interaction of sex and HbA_{1c} with stroke risk, men and women were analysed separately. To avoid the potential bias due to the presence of occult diseases at baseline, additional analyses were carried out excluding the participants who were diagnosed with stroke

Table 1 Baseline characteristics of male and female patients with diabetes

Characteristic	Male	Female	*p* values
No. of participants	10,876	19,278	
African-American, *n* (%)	6,106 (56.1)	11,403 (59.3)	<0.001
Age, mean (SD), years	50.90 (10.1)	51.48 (10.1)	<0.001
Income, mean annual (SD), $/family	20,989 (31,594)	20,617 (27,409)	<0.001
BMI (kg/m^2), mean (SD)	32.4 (8.0)	35.5 (8.7)	<0.001
Baseline blood pressure, mean (SD), mmHg			
Systolic	143 (23)	145 (24)	<0.001
Diastolic	82 (14)	79 (13)	<0.001
HbA_{1c}, mean, % (mmol/mol)[a]	8.1 (65)	7.6 (60)	<0.001
HbA_{1c} during follow-up, mean, % (mmol/mol)[a]	7.8 (62)	7.5 (58)	<0.001
LDL-cholesterol, mean (SD), mmol/l	2.80 (1.06)	3.00 (1.04)	<0.001
eGFR (ml min^{-1} [1.73 m]$^{-2}$), n (%)			<0.001
≥90	5,501 (50.7)	9,031 (46.9)	
60–89	4,096 (37.7)	7,717 (40.1)	
30–59	1,054 (9.7)	2,238 (11.6)	
15–29	135 (1.2)	184 (1.0)	
<15	72 (0.7)	74 (0.4)	
Current smoker, *n* (%)	4,629 (42.6)	5,746 (29.8)	<0.001
Type of insurance, *n* (%)			<0.001
Free	7,918 (72.8)	15,793 (81.9)	
Self-pay	832 (7.7)	817 (3.7)	
Medicaid	524 (4.8)	1,016 (5.3)	
Medicare	1,297 (11.9)	1,385 (7.2)	
Commercial	305 (2.8)	366 (1.9)	
Uses of medications, *n* (%)			
Lipid-lowering medication	6,470 (59.5)	12,530 (65.0)	<0.001
Antihypertensive medication	8,782 (80.3)	16,340 (84.8)	<0.001
Glucose-lowering medication	8,218 (75.6)	14,466 (75.0)	<0.001
Metformin	5,871 (54.0)	11,237 (58.3)	<0.001
Sulfonylurea	4,099 (37.7)	6,955 (36.1)	<0.001
Insulin	4,168 (38.3)	6,770 (35.1)	<0.001

Values represent means or percentages

[a] The SDs for HbA_{1c} are 2.7% and 2.3% for baseline and 2.0% and 1.8% for follow-up, for male and female participants respectively

during the first 2 years of follow-up. Statistical significance was considered to be $p<0.05$. All statistical analyses were performed with PASW for Windows, version 20.0 (IBM SPSS, Chicago, IL, USA).

Results

The general characteristics of the study population are presented by sex in Table 1. During a mean follow-up period of 6.7 years, 2,949 participants (1,093 male and 1,856 female) developed incident stroke (2,848 ischaemic and 115 haemorrhagic). The overall incidence of stroke was higher among men (16.0/1,000 person-years) than women (13.9/1,000 person-years). There was a significantly positive association of baseline HbA_{1c} with stroke risk among females but not males (Table 2). After further adjustment for other confounding factors (smoking, income, type of insurance, BMI, HbA_{1c}, LDL-cholesterol, eGFR, use of antihypertensive drugs, use of diabetes medications and use of cholesterol-lowering agents), this positive association remained significant among females (p for trend <0.001). Each 1% increase in baseline HbA_{1c} was associated with a 5% (95% CI 1.02, 1.07) increased risk of stroke in females and a 1% (95% CI 0.99, 1.04) increased risk of stroke in males. The risk of stroke associated with HbA_{1c} was higher in female than in male patient with diabetes ($\chi^2=7.85$, $df=1$, p for interaction= 0.005).

The interactions between age and HbA_{1c}, and between the use of glucose-lowering agents and HbA_{1c}, and stroke risk were significant ($p<0.005$ and $p<0.001$, respectively). This graded positive association of HbA_{1c} with stroke risk was confirmed among patients with diabetes whether or not they

Table 2 HR of stroke according to different levels of HbA_{1c} at baseline and during follow-up among male and female patients with diabetes

Variable	HbA_{1c} (%) (mmol/mol)						*p* for trend	Each 1% increase (continuous variable)
	<6.0 (42)	6.0–6.9 (42–52)	7.0–7.9 (53–63)	8.0–8.9 (64–74)	9.0–9.9 (75–85)	≥10.0 (86)		
Baseline								
Male	2,615	2,042	1,220	854	751	2,301		
No. of cases	276	255	153	113	85	211		
Person-years	16,583	14,732	8,960	6,538	5,606	15,945		
Age-adjusted HR (95% CI)	0.99 (0.83, 1.17)	1.00	1.07 (0.87, 1.30)	1.16 (0.93, 1.45)	1.12 (0.88, 1.44)	1.12 (0.92, 1.35)	0.60	1.01 (0.99, 1.04)
Multivariable-adjusted HR (95% CI)	0.96 (0.80, 1.14)	1.00	1.04 (0.85, 1.28)	1.11 (0.89, 1.39)	1.10 (0.86, 1.41)	1.12 (0.92, 1.35)	0.66	1.01 (0.99, 1.04)
Female	5,101	4,578	2,389	1,561	1,100	2,693		
No. of cases	456	464	289	186	138	323		
Person-years	34,320	34,659	20,011	13,299	9,298	22,057		
Age-adjusted HR (95% CI)	1.00 (0.87, 1.13)	1.00	1.13 (0.98, 1.31)	1.23 (1.04, 1.46)	1.36 (1.12, 1.65)	1.49 (1.29, 1.73)	<0.001	1.06 (1.04, 1.08)
Multivariable-adjusted HR (95% CI)	1.03 (0.90, 1.18)	1.00	1.09 (0.94, 1.26)	1.19 (1.00, 1.42)	1.32 (1.09, 1.59)	1.42 (1.23, 1.65)	<0.001	1.05 (1.02, 1.07)
Follow-up								
Male	2,103	2,213	1,782	1,286	947	1,452		
No. of cases	206	262	240	160	111	114		
Person-years	12,019	15,314	13,679	9,939	7,351	10,065		
Age-adjusted HR (95% CI)	1.05 (0.88, 1.26)	1.00	1.12 (0.94, 1.33)	1.20 (0.98, 1.46)	1.23 (0.98, 1.54)	1.08 (0.86, 1.36)	0.41	1.02 (0.98, 1.05)
Multivariable-adjusted HR (95% CI)	1.01 (0.83, 1.23)	1.00	1.09 (0.91, 1.30)	1.18 (0.96, 1.44)	1.30 (1.03, 1.63)	1.14 (0.90, 1.44)	0.28	1.03 (0.99, 1.07)
Female	4,090	4,865	3,240	2,000	1,365	1,862		
No. of cases	373	502	378	246	177	180		
Person-years	25,791	35,763	27,105	17,220	12,239	15,526		
Age-adjusted HR (95% CI)	1.06 (0.93, 1.21)	1.00	1.11 (0.97, 1.27)	1.30 (1.12, 1.52)	1.41 (1.19, 1.68)	1.33 (1.11, 1.59)	<0.001	1.06 (1.03, 1.09)
Multivariable-adjusted HR (95% CI)	1.12 (0.97, 1.30)	1.00	1.08 (0.95, 1.24)	1.21 (1.03, 1.42)	1.27 (1.06, 1.52)	1.19 (0.99, 1.43)	0.066	1.03 (1.00, 1.06)

Adjusted for age, race, type of insurance, income, smoking, BMI, LDL-cholesterol, systolic blood pressure, eGFR at baseline (in the baseline analyses) and during follow-up (in the follow-up analyses), and use of antihypertensive drugs, glucose-lowering agents and cholesterol-lowering agents

used glucose-lowering agents (all *p* for trend <0.05) (Table 3). When stratified by race, the positive association of baseline HbA_{1c} with stroke risk was present among both African-American and white patients with type 2 diabetes (all *p* for trend <0.01) (Table 3). When stratified by age, each 1% increase in baseline HbA_{1c} was associated with a 2% (95% CI 1.00, 1.05) increased risk of stroke in females aged <55 years and a 5% (95% CI 0.99, 1.04) increased risk of stroke in females aged ≥55 years. Compared with women with a baseline HbA_{1c} of 6.0–6.9% (42–52 mmol/mol), an increased risk of stroke was found among women with a baseline HbA_{1c} ≥10% (86 mmol/mol), who were ≥55 years (mean HR [95% CI]) (1.41 [1.11, 1.80]) and <55 years (1.24 [1.02, 1.50]) (Table 4).

When we carried out an additional analysis using an updated mean of HbA_{1c} during follow-up, each 1% increase in follow-up HbA_{1c} was associated with a 3% (95% CI 1.00, 1.06) increased risk of stroke in females and a 3% (95% CI 0.99, 1.07) increased risk of stroke in males. When HbA_{1c} was evaluated as categories, we found almost the same graded positive associations between HbA_{1c} and stroke risk among females with type 2 diabetes. There was a marked attenuation in the association between HbA_{1c} level and stroke risk in females after adjusting for confounders (*p* for trend >0.05) (Tables 2, 3 and 4).

We also compared the absolute sex risk of incident stroke by different HbA_{1c} levels (Table 5). The absolute sex differential for incident stroke appeared only among diabetic patients with an HbA_{1c} <7.0% (53 mmol/mol) at baseline and <8.0% (64 mmol/mol) during follow-up, and decreased or disappeared among diabetic patients with an HbA_{1c} >7.0% at baseline and >8.0% during follow-up.

Table 3 HR (95% CI) of stroke according to different levels of HbA_{1c} at baseline and during follow-up among various subpopulations

Variable	HbA_{1c} (%) (mmol/mol)						*p* for trend
	<6.0 (42)	6.0–6.9 (42–52)	7.0–7.9 (53–63)	8.0–8.9 (64–74)	9.0–9.9 (75–85)	≥10.0 (86)	
Baseline							
Male							
African-American	0.99 (0.77, 1.28)	1.00	1.06 (0.80, 1.40)	0.92 (0.66, 1.28)	1.13 (0.81, 1.57)	1.16 (0.90, 1.48)	0.72
White	0.91 (0.71, 1.17)	1.00	1.03 (0.77, 1.37)	1.35 (0.99, 1.83)	1.09 (0.75, 1.59)	1.07 (0.78, 1.46)	0.29
Female							
African-American	1.01 (0.83, 1.22)	1.00	1.03 (0.85, 1.26)	1.04 (0.83, 1.32)	1.24 (0.96, 1.61)	1.39 (1.15, 1.67)	0.007
White	1.05 (0.86, 1.27)	1.00	1.14 (0.91, 1.42)	1.38 (1.07, 1.78)	1.39 (1.04, 1.87)	1.36 (1.06, 1.75)	0.033
Follow-up							
Male							
African-American	1.20 (0.91, 1.58)	1.00	0.99 (0.77, 1.28)	1.13 (0.85, 1.49)	1.22 (0.89, 1.68)	1.17 (0.87, 1.58)	0.56
White	0.84 (0.63, 1.12)	1.00	1.22 (0.95, 1.56)	1.29 (0.96, 1.74)	1.42 (1.02, 1.98)	1.06 (0.71, 1.60)	0.049
Female							
African-American	1.16 (0.95, 1.42)	1.00	0.97 (0.80, 1.17)	1.06 (0.86, 1.31)	1.15 (0.91, 1.44)	1.06 (0.85, 1.33)	0.53
White	1.09 (0.88, 1.34)	1.00	1.24 (1.01, 1.51)	1.45 (1.14, 1.84)	1.42 (1.06, 1.90)	1.33 (0.96, 1.85)	0.03
Baseline							
Male							
Not using glucose-lowering agents	0.98 (0.74, 1.29)	1.00	0.92 (0.63, 1.33)	0.87 (0.56, 1.37)	0.92 (0.53, 1.58)	1.06 (0.74, 1.53)	0.97
Using glucose-lowering agents	0.93 (0.74, 1.17)	1.00	1.09 (0.86, 1.39)	1.20 (0.93, 1.56)	1.16 (0.87, 1.54)	1.15 (0.91, 1.44)	0.39
Female							
Not using glucose-lowering agents	0.99 (0.79, 1.23)	1.00	1.16 (0.88, 1.53)	1.08 (0.77, 1.53)	1.70 (1.17, 2.47)	1.74 (1.32, 2.31)	<0.001
Using glucose-lowering agents	1.07 (0.90, 1.27)	1.00	1.06 (0.89, 1.27)	1.23 (1.01, 1.51)	1.23 (0.98, 1.54)	1.35 (1.13, 1.60)	0.018
Follow-up							
Male							
Not using glucose-lowering agents	0.92 (0.69, 1.23)	1.00	1.10 (0.79, 1.54)	0.92 (0.61, 1.40)	1.11 (0.68, 1.80)	1.17(0.77, 1.79)	0.85
Using glucose-lowering agents	1.10 (0.84, 1.45)	1.00	1.10 (0.89, 1.36)	1.29 (1.02, 1.63)	1.38 (1.06, 1.80)	1.15 (0.87, 1.53)	0.18
Female							
Not using glucose-lowering agents	1.14 (0.92, 1.41)	1.00	1.10 (0.84, 1.45)	1.48 (1.09, 2.00)	1.16 (0.80, 1.69)	1.34 (0.94, 1.92)	0.19
Using glucose-lowering agents	1.12 (0.91, 1.36)	1.00	1.07 (0.91, 1.25)	1.12 (0.93, 1.35)	1.29 (1.05, 1.58)	1.13 (0.91, 1.40)	0.26

Adjusted for age, sex, race, type of insurance, income, smoking, BMI, LDL-cholesterol, systolic blood pressure, eGFR at baseline (in the baseline analyses) and during follow-up (in the follow-up analyses), and use of antihypertensive drugs, glucose-lowering agents and cholesterol- lowering agents, other than the variable for stratification

After excluding individuals who were diagnosed with stroke during the first 2 years of follow-up (n =866), the multivariable-adjusted HRs of stroke associated with different levels of HbA_{1c} did not change (data not shown).

When we performed another analysis by different types of stroke, the result of ischaemic stroke was similar to that for total stroke. For haemorrhagic stroke, a significantly increased risk of stroke (1.72 [CI 1.03, 2.87]) was observed among diabetic patients with HbA_{1c} <6.0% (42 mmol/mol) during follow-up (data not shown).

Discussion

Our study found a graded positive association between HbA_{1c} and risk of stroke among female patients with type 2 diabetes, and this graded positive association was more significant in women ≥55 years than in women <55 years of age. In addition, we found that this graded association was present in different race groups and among patients with diabetes who were using glucose-lowering agents and those who were not.

Table 4 HR (95% CI) of stroke according to different levels of HbA_{1c} at baseline and during follow-up among male and female patients of different ages

Variable	HbA_{1c} (%) (mmol/mol)						*p* for trend
	<6.0 (42)	6.0–6.9 (42–52)	7.0–7.9 (53–63)	8.0–8.9 (64–74)	9.0–9.9 (75–85)	≥10.0 (86)	
Baseline							
Male							
<55 years	0.85 (0.65, 1.12)	1.00	0.78 (0.57, 1.12)	0.89 (0.65, 1.22)	1.11 (0.82, 1.51)	0.89 (0.69, 1.14)	0.35
≥55 years	1.04 (0.83, 1.32)	1.00	1.25 (0.96, 1.62)	1.28 (0.93, 1.77)	0.78 (0.49, 1.24)	1.20 (0.88, 1.63)	0.72
Female							
<55 years	1.02 (0.82, 1.25)	1.00	1.02 (0.82, 1.27)	1.11 (0.87, 1.40)	1.20 (0.93, 1.55)	1.24 (1.02, 1.50)	0.23
≥55 years	1.04 (0.87, 1.24)	1.00	1.12 (0.91, 1.36)	1.20 (0.93, 1.54)	1.32 (0.98, 1.78)	1.41 (1.11, 1.80)	0.057
Follow-up							
Male							
<55 years	1.01 (0.77, 1.32)	1.00	0.99 (0.75, 1.32)	1.11 (0.82, 1.50)	0.94 (0.71, 1.26)	1.00 (1.00, 1.00)	0.91
≥55 years	1.05 (0.82, 1.35)	1.00	1.13 (0.89, 1.43)	1.27 (0.94, 1.71)	1.30 (0.89, 1.88)	0.98 (0.62, 1.56)	0.56
Female							
<55 years	0.98 (0.77, 1.24)	1.00	0.98 (0.81, 1.20)	1.00 (0.81, 1.24)	1.15 (0.92, 1.43)	0.90 (0.72, 1.12)	0.53
≥55 years	1.20 (1.00, 1.44)	1.00	1.13 (0.94, 1.36)	1.36 (1.07, 1.71)	1.09 (0.78, 1.51)	1.37 (0.96, 1.97)	0.09

Adjusted age, race, type of insurance, income, smoking, BMI, LDL-cholesterol, systolic blood pressure, eGFR at baseline (in the baseline analyses) and during follow-up (in the follow-up analyses), and use of antihypertensive drugs, glucose-lowering agents and cholesterol-lowering agents, other than the variable for stratification

Epidemiological studies have previously identified differences in stroke occurrence between women and men. Worldwide, stroke is more common among men, but women are more severely ill [26]. These sex differences have profound implications for the effective prevention and treatment of stroke. An increased knowledge of stroke risk factors in the population may lead to an improved prevention of stroke. Epidemiological studies have reported that type 2 diabetes is an independent risk factor for stroke [2–4]. Some studies have shown that diabetes may have a stronger effect on stroke risk in women than in men [3, 4, 8–10]. However, a sub-data analysis of the Diabetes Epidemiology: Collaborative analysis

Table 5 Hazard ratio (95% CI) of stroke according to different levels of HbA_{1c} with reference to the same female group

Variable	HbA_{1c} (%) (mmol/mol)					
	<6.0 (42)	6.0–6.9 (42–52)	7.0–7.9 (53–63)	8.0–8.9 (64–74)	9.0–9.9 (75–85)	≥10.0 (86)
Baseline						
Age adjustment						
Male	1.24 (1.07, 1.44)*	1.27 (1.09, 1.48)*	1.35 (1.12, 1.62)	1.48 (1.20, 1.81)	1.42 (1.13, 1.79)	1.42 (1.20, 1.68)
Female	1.00 (0.88, 1.14)	1.00	1.13 (0.98, 1.31)	1.23 (1.04, 1.46)	1.36 (1.12, 1.65)	1.49 (1.29, 1.72)
Multivariable adjustment						
Male	1.26 (1.08, 1.47)	1.28 (1.10, 1.49)*	1.35 (1.12, 1.62)	1.43 (1.16, 1.76)	1.42 (1.12, 1.79)	1.46 (1.23, 1.72)
Female	1.03 (0.90, 1.18)	1.00	1.10 (0.95, 1.27)	1.21 (1.02, 1.44)	1.35 (1.11, 1.63)	1.48 (1.28, 1.72)
Follow-up						
Age adjustment						
Male	1.26 (1.07, 1.49)*	1.22 (1.05, 1.42)*	1.37 (1.18, 1.60)*	1.47 (1.23, 1.75)	1.50 (1.22, 1.85)	1.33 (1.08, 1.64)
Female	1.06 (0.93, 1.21)	1.00	1.11 (0.97, 1.27)	1.30 (1.12, 1.52)	1.41 (1.19, 1.68)	1.32 (1.11, 1.58)
Multivariable adjustment						
Male	1.24 (1.05, 1.47)	1.18 (1.02, 1.37)	1.29 (1.10, 1.51)	1.35 (1.13, 1.62)	1.49 (1.21, 1.84)*	1.29 (1.04, 1.59)
Female	1.11 (0.96, 1.27)	1.00	1.10 (0.96, 1.26)	1.24 (1.06, 1.45)	1.32 (1.11, 1.57)	1.24 (1.04, 1.49)

Adjusted for age, race, type of insurance, income, smoking, BMI, LDL-cholesterol, systolic blood pressure, eGFR at baseline (in the baseline analyses) and during follow-up (in the follow-up analyses), and use of antihypertensive drugs, glucose-lowering agents and cholesterol-lowering agents, other than the variable for stratification

*Significant difference ($p<0.05$) between sexes in the same HbA_{1c} group

of Diagnostic criteria in Europe (DECODE) study showed that diabetes increased stroke risk more in men than in women [11]. There is thus considerable uncertainty, and the magnitude of the risk has not been described in sufficient detail from observational studies. On the other hand, RCTs and even meta-analyses of RCTs have failed to show the benefit of intensive glucose control on rates of stroke [12], and the under-representation of females in RCTs [13] has limited the power of RCTs to interpret why these sex differences exist.

In the present study, with a mean follow-up of 6.7 years, 2,949 incident cases (1,093 male and 1,856 female) of stroke were identified among 30,154 patients (10,876 male and 19,278 female) with type 2 diabetes. The overall incidence of stroke among men was higher than among women. We found a graded positive association by various HbA_{1c} intervals of clinical relevance or by using HbA_{1c} as a continuous variable at baseline and during follow-up with stroke risk among females but not males. The effect of the interaction between race and HbA_{1c} on stroke risk was not significant. In a previous paper, we described a graded positive association between HbA_{1c} and CHD in both male and female members of this cohort [22]. In addition, we found that this graded positive association was present in African-American and white female patients and in patients receiving and not receiving treatment with a glucose-lowering agent. There is some inconsistency between the findings for baseline and follow-up HbA_{1c}, which may suggest that relying on baseline HbA_{1c} levels alone may lead to biased results.

Several mechanisms could explain why diabetes has a greater adverse effect in women than in men. In the general population, the higher number of strokes occurring among women than men is at least partly attributed to the longer life expectancy of women [27]. Some studies have suggested that the sex difference in cardiovascular risk might come mainly from differences in the levels of cardiovascular risk factors; for example, women with diabetes have significantly higher blood pressure and lipid levels than men with diabetes [28]. Others have suggested that the greater risk associated with diabetes seen in women may reflect a treatment bias that favours men. Several recent studies have found that men with diabetes or cardiovascular disease are more likely than women to receive aspirin, statins or antihypertensive drugs [29]. In our study, after adjusting for systolic blood pressure, LDL-cholesterol and medication treatment, this graded association remained significant among females with type 2 diabetes.

When stratified by age, the adjusted HRs were more significantly increased in women ≥55 years than in women <55 years. This might suggest that poor blood glucose control is more harmful in elderly women than in younger ones. The possible explanation may point to a role for oestrogen. After the onset of menopause, when oestrogen levels decline, the incidence of cerebrovascular disease in women increases. Preclinical studies have indicated that oestrogen is neuroprotective and reduces the infarct volume of strokes [30], but clinical trials have failed to show this benefit [31–33]. There is a need for more research to clarify this association. In a geriatric population with considerable comorbidities, the competing risk of death is especially high. We described a graded positive association between HbA_{1c} and CHD in both male and female members in a previous paper [22]. There is a possibility that men with higher HbA_{1c} values die of CHD rather than having a stroke.

There are several strengths of and limitations to our study. The LSUHLS diabetic cohort is a hospital-based cohort with a large sample size of white and African-American patients with type 2 diabetes. The follow-up time is long, and has allowed for the accumulation of 2,949 incident cases of stroke during follow-up. The confounding influence of healthcare access and socioeconomic status may be minimised in our study samples between white and African-American patients. Since a large proportion of our population are from minority groups and are uninsured individuals with low socioeconomic status, the generalisability of our findings to a middle or high socioeconomic status population may be limited. However, LSU HCSD hospitals are public hospitals and cover over 1.6 million patients, most of whom are low-income persons living in Louisiana. Thus, the results of the current study will have wide applicability for the nearly 50 million Americans who met the poverty criteria in 2012. Second, the stroke diagnoses in our study were based on LSU HCSD hospital discharge registers and have not been confirmed by specialists. However, most American and European cohort studies, such as the Kaiser Permanente Medical Care Program [34, 35], the Atherosclerosis Risk in Communities Study [36], the Framingham Study [37] and the National FINRISK Survey [38], have used the same method to diagnose stroke. The agreement with the diagnosis of stroke by using hospital discharge registers in these cohort studies is 75–90% [35, 39]. Third, only fatal inpatient strokes were included in the outcome. We do not have access to the causes of outpatient death. Fourth, we cannot completely exclude the effects of residual confounding due to measurement errors in the assessment of confounding factors or some unmeasured factors.

Our study demonstrates a graded association between HbA_{1c} and the risk of stroke among females with type 2 diabetes even though the overall incidence of stroke was higher among men than women. This graded positive association was more significant in women ≥55 years than in women <55 years. This is important to keep in mind when studying blood sugar level and other CVD risk factors in the diabetic population and when planning a strategy to prevent CVD, especially for women with type 2 diabetes.

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Contribution statement WZ designed the study, acquired the data, performed the statistical analysis, interpreted the data, drafted the article and approved the final version to be published. GH designed the study, acquired the data, reviewed and critically revised the article and approved the final version to be published. PTK received tables of analysis output, suggested some reanalyses and helped to interpret these analyses in the writing of the results and discussion, reviewed and critically revised the article and approved the final version to be published. All other authors acquired the data, reviewed and critically revised the article, and approved the final version to be published. GH was responsible for the integrity of the work as a whole.

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