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Association between fasting blood glucose levels and stroke events: a large-scale community-based cohort study from China

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Abstract

Objectives: Diabetes mellitus has been associated with stroke. However, the association between fasting blood glucose (FBG) and stroke risk in general population remains still not clear. The purpose of our study was to examine the FBG levels on subsequent stroke risk in a community-based cohort in China.

Design: Prospective cohort study, employing Cox proportional hazard model to analyze the association of FBG levels with stroke risk.

Setting: A community-based cohort study included adults participating a baseline survey conducted in 2013 in Changshu, eastern China.

Participants: 16,113 participants were recruited with a multi-stage sampling method, excluding participants with severe disability, severe cancer, severe psychiatric disturbance, or previous stroke before enrolment.

Primary and secondary outcome measures: FBG levels and stroke events.

Results: During a median follow-up of 5.5 years, 417 incident cases of stroke were identified. The adjusted HR for total and ischemic stroke for participants in the fourth quartile of FBG compared with the first quartile was 1.45 (95% CI: 1.06, 1.97) and 1.56 (95% CI: 1.09, 2.23), respectively. The risk associations were consistent if classifications of FBG levels following the American Diabetes Association and WHO criteria were used. In stratified analyses, risk associations existed in women (HR: 1.93, 95% CI: 1.22, 3.05) and among postmenopausal women (HR: 1.68, 95% CI: 1.06-2.68) for the fourth quartile vs. the first. More importantly, the meta-analysis observed a positive association between FBG levels and stroke risk [pooled HR: 1.70, 95% CI: 1.28, 2.24; n=7)].

Conclusions: Higher FBG level was independently associated with an increased risk of stroke in Chinese adults, especially significant in women.

Keywords: Stroke, Glucose, Risk, Cohort studies

Strengths and limitations of this study

- Large sample size, measurement of plasma FBG, and complete follow-up.
- This study provides the first meta-analysis studying the association between FBG levels and stroke risk in a general population.
- No data available on HbA1c measurements in this study.

Introduction

Stroke is one of the most important causes of human diseases and death[1]. According to the statistics of global disease burden in 2013, about 25.7 million stroke patients and 6.5 million stroke deaths worldwide[2]. There are 113 million disability-adjusted life years caused by stroke each year[3]. It poses a heavy psychological and economic burden to patients' families and society. Therefore, the primary prevention of stroke has now become a top priority for global public health. In China, it has become the leading cause of death[4] and one of the important reasons for disability in adults[5].

Studies have shown that diabetes mellitus can increase the risk of stroke[6,7]. A cohort study involving 510,000 people observed that diabetes significantly increased the risk of ischemic stroke and hematencephalon[7]. A meta-analysis of 58,160 patients with type 2 diabetes in China revealed that intensive blood glucose treatment could not reduce the incidence of stroke compared with conventional treatment[8]. A prospective study showed that insulin resistance or diagnosed diabetes can predict the first stroke[9]. However, these studies focus on diabetes status instead of continuous glucose levels as the study exposure, which limits the generalizability of the research findings. Since fasting blood glucose (FBG) is the least interfered by diet[10], the FBG levels are considered as a more reliable tool to measure blood glucose levels than random blood glucose levels[11]. FBG levels have a stronger predictive function for functional prognosis than random blood glucose levels. Although diabetes is closely related to cardiovascular disease (CVD), there is still insufficient data to support the evidence-based medicine proposal of strictly controlling FBG to prevent stroke.

Therefore, a further study focusing on the relationship between FBG levels and stroke is crucial, which can help us know whether people who are suffering from diabetes, impaired fasting glucose (IFG), insulin resistance, or other people with higher FBG levels should take prevention strategies against stoke. In this study, a community

population from China was followed up for 5.5 years to study the relationship between FBG levels and the incidence of stroke, aiming at providing suggestions and a basis for primary prevention of stroke among people with different FBG levels.

Methods

Study population

The baseline survey of the current cohort study was conducted in 2013. The source population was 20,343 participants aged 35-74 years in rural communities in Changshu, eastern China who participated in an earlier study on metabolic syndrome in 2008, in addition to a small proportion of new participants. A multi-stage sampling method was used to recruit participants. Individuals with severe disability, severe cancer, or a severe psychiatric disturbance were excluded. Of these, 16,457 subjects in total were included in the baseline survey. We excluded 137 patients with a previous stroke before enrolment. Participants with missing data on baseline health information (n=207) were also excluded, leaving 16,113 participants in total for final analyses.

Laboratory measurements

Blood samples were collected in the morning after overnight fasting and evaluated biochemical and clinical parameters on the same day. FBG was measured by an oxidase enzymatic method. The levels of high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and triglyceride (TG) were assessed enzymatically using commercial reagents with an automatic biochemistry analyzer (Hitachi Inc, Tokyo, Japan).

Follow-up and ascertainment of stroke

Follow-up began at the baseline and ended at the date of stroke diagnosis, death, or December 31, 2018, whichever came first. We classified total stroke into an ischemic stroke, and non-ischemic stroke (including hemorrhagic stroke, subarachnoid hemorrhage, and unexplained types of stroke). The primary outcome was

hospitalization or death due to stroke collected by ICD-10 codes (total stroke: I60-I61, I63-I64; ischemic stroke: 63 except I63.9). If a participant had more than 1 stroke event during the follow-up, only the first stroke was considered.

Assessments of covariates

Demographic characteristics, lifestyle factors, personal medical history [CVD, hyperlipidemia, hypertension, diabetes, chronic obstructive pulmonary disease (COPD), nephropathy, and cancer], and family history data for all participants were obtained using standard questionnaires administered by trained staff. After the subjects rested for 5 minutes, the trained observers used an electronic sphygmomanometer (Omron Hp1300, OMRON Corporation, China) to measure the blood pressure in the sitting position three times every 30 seconds. The criteria for judging hypertension are a continuous measurement of systolic blood pressure ≥ 140mmHg or diastolic blood pressure ≥ 90mmHg, diagnosis of hypertension, or antihypertensive medication. The body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters, among weight and height were measured by standard methods.

Meta-analysis

We conducted a meta-analysis combining the current study findings with previous observations on FBG and stroke risk. We searched the Medline and PubMed databases for related research articles published between January 01, 2000-September 10, 2020 using the keywords “stroke”, “cardiovascular disease” and “fasting blood glucose”, “blood glucose”, “fasting glucose”, “fasting plasma glucose”, “glucose”, in addition to “prospective study”, “cohort study”, or “follow-up”. The study subjects were restricted to apparently healthy adults in the community. Two authors extracted the data independently, and if they had disagreements, discussed it with the third

author. Finally, seven studies were included[12-17]. We extracted information about authors, sample size, the country where the study was implemented, time of follow-up, adjusted covariates, outcome (stroke events), and the effect size [hazard ratio (HR)]. We used a random-effect model to calculate the pooled risk estimation based on the assumption of study heterogeneity. The Begg and Egger tests were performed to detect potential publication bias.[18]

Statistical analysis

Baseline demographic characteristics for continuous variables were expressed as median (interquartile ranges), and categorical variables were presented as percentages. Log-transformation was used to all laboratory measures to normalize distributions.

Cox proportional hazard analyses were conducted to evaluate FBG levels and risk of stroke and results presented as HR and 95% confidence intervals (CI). FBG levels were included in the models as a categorical measure (quartiles and three categories by clinical criteria). Multivariable models included conventional risk factors at baseline: age (continuous), sex, BMI (continuous), current smoking (yes/no), family history of stroke (yes/no), hypertension (yes/no), HDL-C (mmol/L), TC (mmol/L), TG (mmol/L) and use of statins. IFG is defined as an FBG of 6.1-6.9 mmol/L by WHO[19] and an FBG of 5.6-6.9 mmol/L by the American Diabetes Association (ADA)[20]. We also used clinical classification (normal FBG, IFG, hyperglycemia) to classify FBG levels. In addition, we conducted stratified analyses by sex to check potential effect modification. Sensitivity analyses were conducted to determine the robustness of the primary analysis results. We limited the risk-association analyses to participants who didn't report their own medical history, including hypertension, hyperlipidemia, cancer, nephropathy, CVD, or COPD at baseline.

Statistical analyses were conducted with R (version 4.0.2, www.r-project.org). All

tests were 2-sided, and a P value less than 0.05 was considered statistically significant.

Patient and public involvement

Patients and the public were not involved this research.

Results

Characteristics of the study population

After a median follow-up of 5.5 years (range: 0.1-5.7 years), a total of 417 (192 men and 225 women) stroke events were identified, of which 323 (77.5%) were ischemic stroke. Table 1 shows the baseline characteristics of participants across the quartiles of FBG. Compared with the participants in the study with lower FBG, those with higher FBG levels were more likely to suffer from obesity, hypertension, and hyperlipidemia, had higher levels of TC and TG in the blood, and preferred to have a family history of stroke (P<0.001, Table 1).

FBG levels and risk of stroke

As shown in Table 2, we observed that higher FBG levels were significantly correlated with an increased risk of total and ischemic stroke in both the original models and models adjusted for age, sex, BMI, HDL-C, TC, TG, hypertension, smoking status, use of statins and family history of stroke. Compared to the lowest FBG quartile, the multivariable-adjusted HRs for the highest quartile were 1.45 (95% CI: 1.06-1.97, P=0.021) for total and 1.56 (95%CI: 1.09-2.23, P=0.016) for ischemic stroke. A positive association between FBG levels and non-ischemic stroke was observed in the crude model, but the risk association was rendered statistically nonsignificant in adjusted models. Further, we examined the association between clinical classifications of FBG levels and stroke risk, and the results are presented in Table 3. The multivariable-adjusted HR for total stroke was 1.68 (95%CI: 1.26-2.25, P=0.001) and 1.60 (95% CI: 1.21-2.12, P =0.002) for participants with hyperglycemia compared with those with normal blood glucose, following the ADA and WHO recommendations, respectively.

Results of sex-stratified analyses are shown in Table 4. We observed a positive correlation between the FBG levels and total stroke in men in the unadjusted model, but not in adjusted models. in original models, higher levels of FBG were significantly associated with an increased risk of total stroke in women. After adjustment covariate for age, BMI, and other variates, the risk association remained significant (HR: 1.93, 95%CI: 1.22-3.05, P=0.004) for the fourth level in female groups. Similar risk estimates were found in postmenopausal or oophorectomy women. But no significant association with stroke was observed for FBG levels in premenopausal women (supplemental appendix S1).

In sensitivity analyses, the study population was restricted to 15,404 subjects without a self-reported history of hyperlipidemia, CVD, cancer, nephropathy, and COPD yielded essentially no change in risk of total stroke (HR: 1.38, 95% CI: 1.01, 1.92) and ischemic stroke (HR: 1.55, 95% CI: 1.06, 2.26). Additional eliminated for participants with hypertension, the association in women was slightly raised for total stroke (HR: 2.50, 95% CI: 1.11, 5.60) and ischemic stroke (HR: 2.59, 95% CI: 1.03, 6.51) (data not shown).

Meta-analysis

Figure 1 shows the results of meta-analysis including six previously published prospective studies together with our current study. In a word, higher FBG levels were associated with an increased risk of stroke (pooled HR: 1.70, 95% CI: 1.27-2.29). The Begg and Egger tests didn't suggest existence of potential publication bias (P>0.1 for both tests).

Discussion

Principal findings

In our prospective community-based cohort, higher FBG levels were associated with an increased risk of total and ischemic stroke. The risk-association was prominent in women. After excluding the baseline of hypertension, hyperlipidemia, CVD, cancer, nephropathy, and COPD, these associations were still persisted in analyses of women. Our findings extend the previous knowledge on diabetes and stroke risk, suggesting an important role of routine glucose measurement in stroke prevention.

Associations of FBG with stroke risk

When analyzing stroke subtypes, there is no evidence that FBG is associated with non-ischemic stroke, but the association with ischemic stroke persists. This is consistent with the results of a prospective cohort study among Korean men[14]. It suggests that the correlation between FBG and stroke is mainly contributed by an ischemic stroke. A large-scale prospective study in China (including 96,110 participants) indicated that both hyperglycemia and hypoglycemia are associated with an increased risk of incident intracerebral hemorrhage, after adjustment for potential confounders[21].

Results based on the ADA and WHO criteria demonstrated that FBG levels of ≥7.0 mmol/L were a significant risk factor for stroke [HR (95% CI): 1.68 (1.26, 2.55) and 1.60 (1.21, 2.12) following the ADA and WHO criteria, respectively], whereas IFG was not. A large number of studies showed that people with diabetes are at increased risk of ischemic stroke[22, 23]. A meta-analysis including 698,782 participants reported that the risk of ischemic stroke in diabetic patients was 2.27 times higher than normal people[22]. A cohort study in Swedish also showed that poor blood glucose control in

patients with type 2 diabetes was associated with an increased risk of stroke and death[23]. Although diabetes is associated with stroke, the influence of prediabetes on future stroke risk has not been clear yet. In a meta-analysis including 15 cohort studies, more than half of the studies showed that after adjusting for cardiovascular risk factors, there was no significant association between pre-diabetes and stroke[24]. A cohort study investigated the sex-specific associations of pre-diabetes with major clinical outcomes reached the same conclusion[25]. Our findings on IFG and stroke also resemble the previously reported results.

Stratified analysis showed that the correlation between FBG levels and stroke risk only existed in women. According to the re-stratification of menopause, only postmenopausal women with the highest FBG level had a higher risk of stroke [HR (95% CI): 1.68 (1.06, 2.68)], no associations were found in premenopausal women. It probably due to the low number of stroke events in premenopausal women. Few published studies reported sex-stratified results. A sex-specific cohort study in the Middle East showed that only men with higher FBG levels showed an increased risk of stroke [HR: 2.15(1.26, 4.67) in FBG level of 6.1-6.9 mmol/L, HR: 2.38 (1.08, 5.25) in FBG level of >7.0 mmol/L][26]. Korean Heart Study showed that IFG was associated with an increased risk of ischemic stroke in men but not in women[27]. We suspect that the disparities in sex between studies could be due to different definitions of outcome (all stroke vs. ischemic stroke) and the variety in covariate adjustments. A meta-analysis including 64 cohort studies provides the clearest evidence yet for the sex difference of diabetes and stroke risk. The excess risk of diabetes-related stroke in women is significantly higher than that in men and independent of sex-difference in other cardiovascular risk factors[28]. Our results support the findings of this meta-analysis, indicating that the association between FBG levels and stroke cases in women, and the mechanism may be related to the protective effect of estrogen.

Possible mechanisms

Accumulating evidence suggests that FBG levels can be used to predict the risk of CVD[15, 22, 29]. As an adverse consequence of CVD, stroke is closely related to FBG levels[30, 31]. Its mechanism may be related to the dysfunction of cerebral microvasculature caused by hyperglycemia, insulin resistance, obesity, and hypertension[32]. The microvasculature is involved in the regulation of many brain processes. Once damaged, it's easy to cause cerebrovascular accidents[33]. The dysfunction is also obvious in the prediabetes population, which may suggest that IFG is the risk factor for stroke[34]. Besides, diabetic retinopathy was proved to be a sign of lacunar ischemic stroke, which had the same effects as cerebral microvascular dysfunction[35].

Compared with men, women with diabetes are at higher risk of stroke[28]. Previously, it was thought that the sex specificity of the severity of diabetes-related cardiovascular diseases was caused by the differences between men and women in treatment and chronic disease management. However, as the gradual equality of men and women, the risk of serious cardiovascular disease in postmenopausal women is still higher[28]. Sex hormones may explain the sex differences observed in human epidemiological studies[36-38], indicating the estrogen protection in women, preventing the progression of non-diabetic cardiovascular diseases at least before menopause. Animal experiments show that the decrease of estrogen levels in ovariectomized mice can lead to impaired glycemia, reduced glucose tolerance, hyperinsulinemia, and impaired insulin secretion, and then develop into hyperglycemia and atherosclerosis[39]. However, diabetes seemingly attenuates the protective effect of estrogen on women in the development of CVD[40].

Strengths and Limitations

The main strengths of this study include the large sample size, measurement of plasma FBG, and the complete follow-up. We followed up the cases by recording linkages with hospital discharge diagnoses and the Cause of Death Registry. We used

both quartiles and clinical classifications (normal FBG, IFG, hyperglycemia) to classify FBG levels, and obtained similar results. We considered different stroke subtypes as the study outcome. To our knowledge, this study provides the first meta-analysis investigating the association between FBG levels and stroke risk in the general population, therefore results are likely generalizable to all races.

Our study has several limitations. First, we do not have HbA_{1c} measurements in this study. Among indicators to assess glucose variability, HbA_{1c} is the gold standard for clinical evaluation of long-term blood glucose control[9], while FBG may overlook the potential effects of postprandial blood glucose levels and other meaningful factors[41]. Second, the levels of estradiol and testosterone in the study subjects were not measured, although we speculated that the sex difference was probably due to the protective effect of sex hormone. Third, due to a low number of stroke cases, the real risk association of the premenopausal population may be biased.

Conclusions

Our study indicates that higher FBG levels are associated with an increased stroke in the general population, and meta-analysis corroborated this finding. Further, we observed that the association was more prominent in women than in men. We also observed strong risk associations among postmenopausal or oophorectomy women. FBG levels as a routine and low-cost measurement could be used to identify individuals with higher stroke risk in the future.

Contributors

Conceptualization, YZ and HZ; methodology, YZ; software, YZ; validation, YZ; formal analysis, YZ; resources, SG, QZ, MY and ZZ; data curation, YZ; visualization, YZ; investigation, YZ, CW and DL; writing—original draft preparation, YZ; writing—review and editing, YZ and HZ; supervision, HZ; project administration, HZ; funding acquisition, HZ. All authors have agreed on the journal to which the article has been submitted and agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

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Competing interests

None declared.

Patient consent for publication

Not required.

Ethics approval

The study protocol conforms to the ethical guidelines of the Declaration of Helsinki. The baseline survey and record linkages with study outcomes were approved by the

Ethics Committee of Fuwai Cardiovascular Hospital, Beijing, China (No. 2012-399). After a detailed explanation of our study, we obtained a written informed consent form from each participant.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

The datasets generated and/or analyzed during the current study are not publicly available due to the restrictions of containing information that could compromise the privacy of research participants.

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Table 1. Baseline characteristics of study population by FBG levels and stroke risk: Cohort Changshu.

Characteristic	Total	Quartile of FBG Levels (mmol/L)				P Value
	n=16,113	Q1 (< 4.87) n=4097	Q2 (4.87-5.24) n=4027	Q3 (5.24-5.77) n=3979	Q4 (> 5.77) n=4010	
Age, yrs	55.7 (46.3, 64.4)	48.6 (41.4, 59.1)	53.8 (44.8,62.84)	57.8 (48.6, 65.9)	60.0 (51.4, 67.2)	<0.001
Men (%)	40.9	42.1	39.4	40.2	42.1	0.002
Premenopausal in women (%)	37.5	55.3	42.3	29.7	22.3	<0.001
Follow-up time, yrs	5.53 (5.49, 5.56)	5.52 (5.49, 5.54)	5.52 (5.49, 5.55)	5.53 (5.50, 5.57)	5.55 (5.50, 5.58)	<0.001
BMI (kg/m^2)	23.3 (21.2, 25.7)	22.6 (20.6, 24.9)	23.0 (21.0, 25.3)	23.6 (21.5, 25.9)	24.2 (22.0, 26.5)	<0.001
Current smoking (%)	23.6	26.9	23.5	21.9	21.9	<0.001
Family history of stroke (%)	5.8	3.8	5.4	6.5	7.6	<0.001
Hypertension (%)	22.8	13.9	18.6	24.9	34.0	<0.001
Fasting blood glucose, mmol/L	5.24 (4.87. 5.77)	4.66 (4.47, 4.77)	5.06 (4.97, 5.15)	5.47 (5.34, 5.60)	6.37 (6.01, 7.20)	<0.001
TC, mmol/L	4.70 (4.13, 5.36)	4.48 (3.95, 5.04)	4.62 (4.08, 5.23)	4.79 (4.22, 5.44)	4.99 (4.36, 5.70)	<0.001
TG, mmol/L	1.32 (0.96, 1.90)	1.20 (0.88, 1.68)	1.26 (0.93, 1.78)	1.33 (0.97, 1.91)	1.52 (1.08, 2.30)	<0.001
HDL-C, mmol/L	1.38 (1.14, 1.66)	1.36 (1.14, 1.62)	1.37 (1.14, 1.64)	1.40 (1.15, 2.68)	1.38 (1.14, 1.69)	<0.001
Use of statins (%)	0.4	0.1	0.3	0.3	0.7	<0.001

[1.] BMI, body mass index; HDL-C, high density lipoprotein cholesterol; Q, quartile; TC, total cholesterol; TG, triglyceride.

[2.]P Values were determined by Chi-square tests for categorical and Kruskal-Wallis tests for continuous variables.

Table 2. Hazard ratios (95% CI) for incident stroke by FBG quartiles

		Quartile of FBG Levels				P trend
		Q1	Q2	Q3	Q4	
		HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	
Total stroke	Cases/N	57/4097	89/4027	110/3979	161/4010	
	Model 1	1 (Ref.)	1.60 (1.15, 2.22)	2.00 (1.45, 2.75)	2.92 (2.16, 3.94)	<0.001
	Model 2	1 (Ref.)	1.21 (0.87, 1.69)	1.17 (0.85, 1.62)	1.46 (1.07, 1.98)	0.018
	Model 3	1 (Ref.)	1.20 (0.86, 1.68)	1.16 (0.84, 1.60)	1.45 (1.06, 1.97)	0.021
Ischemic stroke	Cases/N	42/4097	69/4027	83/3979	129/4010	
	Model 1	1 (Ref.)	1.68 (1.15, 2.47)	2.05 (1.41, 2.96)	3.17 (2.24, 4.49)	<0.001
	Model 2	1 (Ref.)	1.27 (0.87, 1.87)	1.19 (0.82, 1.73)	1.58 (1.11, 2.25)	0.013
	Model 3	1 (Ref.)	1.25 (0.85, 1.84)	1.17 (0.80, 1.71)	1.56 (1.09, 2.23)	0.016
Non-ischemic stroke	Cases/N	15/4097	20/4027	27/3979	32/4010	
	Model 1	1 (Ref.)	1.36 (0.70, 2.66)	1.86 (0.99, 3.50)	2.20 (1.19, 4.07)	0.006
	Model 2	1 (Ref.)	1.04 (0.53, 2.04)	1.13 (0.60, 2.14)	1.11 (0.59, 2.07)	0.713
	Model 3	1 (Ref.)	1.04 (0.53, 2.04)	1.13 (0.60, 2.13)	1.11 (0.69, 2.09)	0.844

Model 1: unadjusted model; Model 2: adjusted for age, sex and BMI; Model 3: further adjusted for HDL-C, TC, TG, hypertension, smoking status, use of statins and family history of stroke.

Table 3. Hazard ratios (95% CI) for incident stroke by clinical classifications of FBG levels

			Model 1	Model 2	Model 3
ADA definition	<5.6 mmol/L	Cases/N		220/11079	
		HR (95%CI)	1 (Ref.)	1 (Ref.)	1 (Ref.)
	5.6–6.9 mmol/L	Cases/N		136/3869	
		HR (95%CI)	1.78 (1.43, 2.20)	1.16 (0.94, 1.44)	1.18 (0.95, 1.47)
	≥7.0 mmol/L	Cases/N		61/1165	
		HR (95%CI)	2.69 (2.02, 3.57)	1.72 (1.29, 2.28)	1.68 (1.26,2.25)
	P trend		<0.001	0.001	0.001
WHO definition	<6.1 mmol/L	Cases/N		301/13422	
		HR (95%CI)	1 (Ref.)	1 (Ref.)	1 (Ref.)
	6.1–6.9 mmol/L	Cases/N		55/1526	
		HR (95%CI)	1.61 (1.21, 2.15)	1.08 (0.81, 1.45)	1.09 (0.82, 1.46)
	≥7.0 mmol/L	Cases/N		61/1165	
		HR (95%CI)	2.38 (1.81, 3.03)	1.64 (1.24, 2.17)	1.60 (1.21, 2.12)
	P trend		<0.001	0.001	0.002

ADA: American Diabetes Association; WHO: World Health Organization.

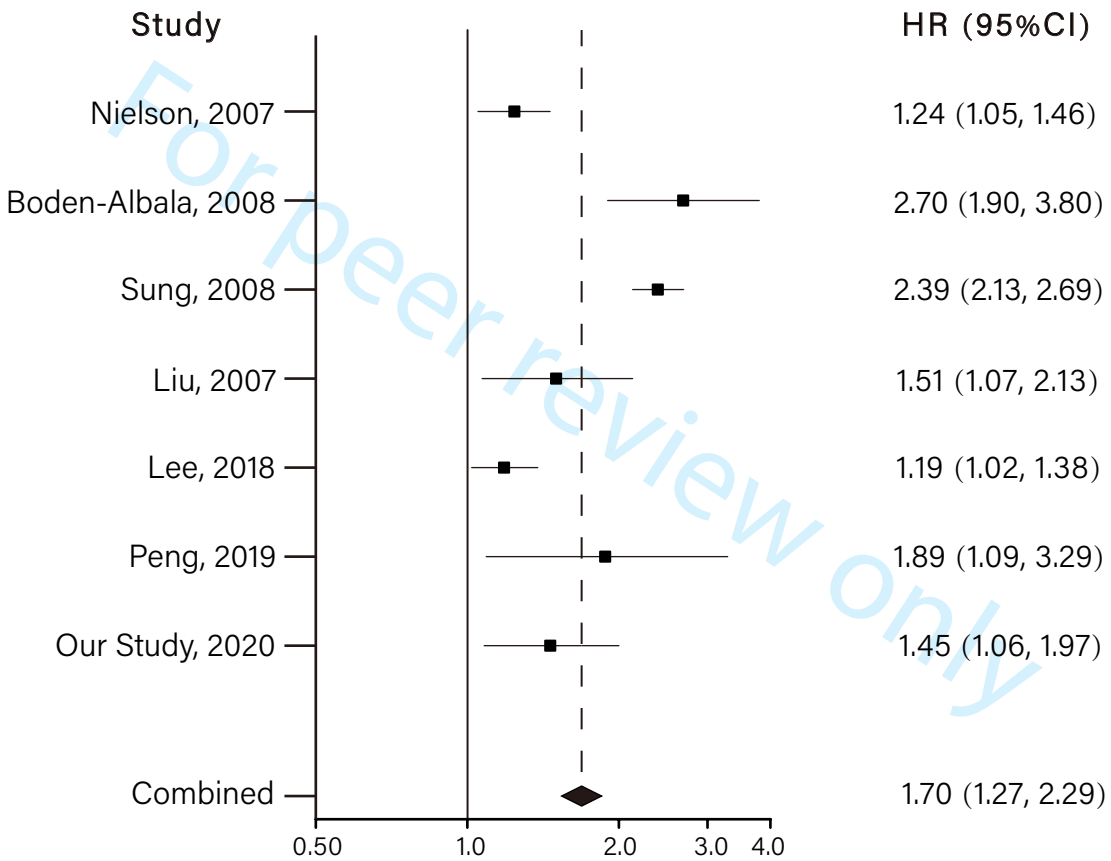
Model 1: unadjusted model; Model 2: adjusted for age, sex and BMI; Model 3: further adjusted for HDL-C, TC, TG, hypertension, smoking status, use of statins and family history of stroke.

Table 4. Hazard ratios (95% CI) for incident stroke by sex

		Quartile of FBG Levels				P trend
		Q1	Q2	Q3	Q4	
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Men	Cases/N	33/1725	42/1586	53/1599	64/1688	
	Model 1	1 (Ref.)	1.40 (0.89, 2.20)	1.74 (1.13, 2.69)	1.99 (1.31, 3.03)	0.001
	Model 2	1 (Ref.)	1.04 (0.66, 1.64)	1.16 (0.75, 1.80)	1.11 (0.73, 1.71)	0.560
	Model 3	1 (Ref.)	1.04 (0.66, 1.65)	1.15 (0.74, 1.79)	1.06 (0.69, 1.64)	0.741
Women	Cases/N	24/2372	47/2441	57/2380	97/2322	
	Model 1	1 (Ref.)	1.91 (1.21, 3.29)	2.38 (1.48, 3.84)	4.19 (2.68, 6.55)	<0.001
	Model 2	1 (Ref.)	1.45 (0.89, 2.37)	1.25 (0.78, 2.03)	1.90 (1.21, 2.99)	0.006
	Model 3	1 (Ref.)	1.43 (0.87, 2.34)	1.26 (0.78, 2.05)	1.93 (1.22, 3.05)	0.004

Model 1: unadjusted model; Model 2: adjusted for age, sex and BMI; Model 3: further adjusted for HDL-C, TC, TG, hypertension, smoking status, use of statins and family history of stroke.

Figure 1. Meta-analysis of fasting blood glucose at the highest vs lowest levels and the risk of developing stroke. The horizontal lines indicate the lower and upper limits of the 95% CI, and the grey squares reflects the HR of each study. HR: Hazard Ratio.



Appendix S1. Hazard ratios (95% CI) for incident stroke by menopausal status in women

			Model 1	Model 2	Model 3
Premenopausal	Q1	Cases/N		1/906	
		HR (95%CI)	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Q2	Cases/N		5/896	
		HR (95%CI)	5.07 (0.59, 43.37)	2.97 (0.34, 25.86)	2.54 (0.29, 22.48)
	Q3	Cases/N		7/883	
		HR (95%CI)	7.19 (0.89, 58.44)	3.88 (0.47, 31.97)	3.86 (0.47, 31.78)
	Q4	Cases/N		8/884	
		HR (95%CI)	8.18 (0.29, 22.48)	1.90 (0.22, 16.15)	1.80 (0.21, 15.30)
	P trend		0.013	0.850	0.916
Postmenopausal or oophorectomy	Q1	Cases/N		35/1489	
		HR (95%CI)	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Q2	Cases/N		42/1513	
		HR (95%CI)	1.18 (0.76, 1.85)	1.05 (0.67, 1.64)	1.06 (0.62, 1.79)
	Q3	Cases/N		49/1473	
		HR (95%CI)	1.42 (0.92, 2.19)	1.07 (0.69, 1.66)	1.14 (0.70, 1.87)
	Q4	Cases/N		78/1471	
		HR (95%CI)	2.28 (1.53, 3.40)	1.66 (1.11, 2.28)	1.68 (1.06, 2.68)
	P trend		<0.001	0.006	0.006

Model 1: unadjusted model; Model 2: Adjusted for age and BMI; Model 3: further adjusted for HDL-C, TC, TG, hypertension, use of statins and family history of stroke

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Association between fasting blood glucose levels and stroke events: a large-scale community-based cohort study from China

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Abstract

Objectives: Diabetes mellitus has been associated with stroke. However, the association between fasting blood glucose (FBG) and stroke risk in general population remains still not clear. The purpose of our study was to examine the FBG levels on subsequent stroke risk in a community-based cohort in China.

Design: Prospective cohort study, employing Cox proportional hazard model to analyze the association of FBG levels with stroke risk.

Setting: A community-based cohort study included adults participating a baseline survey conducted in 2013 in Changshu, eastern China.

Participants: 16,113 participants were recruited with a multi-stage sampling method, excluding participants with severe disability, severe cancer, severe psychiatric disturbance, or previous stroke before enrolment.

Primary outcome measures: Stroke events.

Results: During a median follow-up of 5.5 years, 417 incident cases of stroke were identified. The adjusted HR for total and ischemic stroke for participants in the fourth quartile of FBG compared with the first quartile was 1.44 (95% CI: 1.07, 1.94) and 1.57 (95% CI: 1.11, 2.21), respectively. FBG levels of ≥ 7.0 mmol/L was associated with an increased risk of stroke based on two clinical classifications [ADA: 1.68 (1.24, 2.27); WHO: 1.62 (1.21, 2.13)]. In stratified analyses, risk associations existed in women (HR: 1.92, 95% CI: 1.22, 3.01) and among postmenopausal women (HR: 1.68, 95% CI: 1.06-2.68) for the fourth quartile vs. the first. More importantly, the meta-analysis observed a positive association between FBG levels and stroke risk [pooled HR: 1.70, 95% CI: 1.27, 2.29; n=7)].

Conclusions: Higher FBG level was independently associated with an increased risk of stroke in Chinese adults, especially significant in women.

Keywords: Stroke, Glucose, Risk, Cohort studies

Strengths and limitations of this study

- Large sample size, measurement of plasma FBG, and complete follow-up.
- The meta-analysis based on 6 previously published studies and the current study further confirmed the association between fasting blood glucose levels and stroke risk.
- No data available on HbA1c measurements in our study.

Introduction

Stroke is one of the most important causes of human diseases and death[1]. According to the statistics of global disease burden in 2013, about 25.7 million stroke patients and 6.5 million stroke deaths worldwide[2]. There are 113 million disability-adjusted life years caused by stroke each year[3]. It poses a heavy psychological and economic burden to patients' families and society. Therefore, the primary prevention of stroke has now become a top priority for global public health. In China, it has become the leading cause of death[4] and one of the important reasons for disability in adults[5].

Studies have shown that diabetes mellitus can increase the risk of stroke[6 7]. A cohort study involving 510,000 people observed that diabetes significantly increased the risk of ischemic stroke and hematencephalon[7]. A prospective study showed that insulin resistance or diagnosed diabetes can predict the first stroke[8]. However, these studies focus on diabetes status instead of continuous glucose levels as the study exposure, which limits the generalizability of the research findings. Since fasting blood glucose (FBG) is the least interfered by diet[9], the FBG levels are considered as a more reliable tool to measure blood glucose levels than random blood glucose levels[10]. FBG levels have a stronger predictive function for functional prognosis than random blood glucose levels. Therefore, rather than focusing on random blood glucose, it is important to explore the association between FBG levels and the risk of stroke.

In this study, a community population from China was followed up for 5.5 years to study the relationship between FBG levels and the incidence of stroke, aiming at providing suggestions and a basis for primary prevention of stroke among people with different FBG levels.

Methods

Study population

The baseline survey of the current cohort study was conducted in 2013. The source population was 20,343 participants aged 35-74 years in rural communities in Changshu, eastern China who participated in an earlier study on metabolic syndrome in 2008, in addition to a small proportion of new participants. A multi-stage sampling method was used to recruit participants. Individuals with severe disability, severe cancer, or a severe psychiatric disturbance were excluded. Of these, 16,457 subjects in total were included in the baseline survey. We excluded 137 patients with a previous stroke before enrolment. Participants with missing data on baseline health information (n=207) were also excluded, leaving 16,113 participants in total for final analyses (supplemental appendix S1).

Laboratory measurements

Blood samples were collected in the morning after overnight fasting and evaluated biochemical and clinical parameters on the same day. FBG was measured by an oxidase enzymatic method. The levels of high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and triglyceride (TG) were assessed enzymatically using commercial reagents with an automatic biochemistry analyzer (Hitachi Inc, Tokyo, Japan). The levels of low-density lipoprotein cholesterol (LDL-C) were calculated by the Friedewald formula[11]. The estimated glomerular filtration rate (eGFR) was calculated on the basis of the chronic kidney disease-epidemiology creatinine equation[12].

Follow-up and ascertainment of stroke

Follow-up began at the baseline and ended at the date of stroke diagnosis, death, or December 31, 2018, whichever came first. We classified total stroke into an ischemic stroke, and non-ischemic stroke (including hemorrhagic stroke, subarachnoid hemorrhage, and unexplained types of stroke). The primary outcome was hospitalization or death due to stroke collected by ICD-10 codes (total stroke: I60-I61, I63-I64; ischemic stroke: 63 except I63.9). If a participant had more than 1 stroke event during the follow-up, only the first stroke was considered.

Assessments of covariates

Demographic characteristics, lifestyle factors, personal medical history [CVD, hyperlipidemia, hypertension, diabetes, chronic obstructive pulmonary disease (COPD), nephropathy, and cancer], and family history data for all participants were obtained using standard questionnaires administered by trained staff. After the subjects rested for 5 minutes, the trained observers used an electronic sphygmomanometer (Omron Hp1300, OMRON Corporation, China) to measure the blood pressure in the sitting position three times every 30 seconds. The criteria for defining hypertension were an average measurement of systolic blood pressure ≥ 140mmHg or diastolic blood pressure ≥ 90mmHg[13], diagnosis of hypertension, or antihypertensive medication. Impaired fasting glucose (IFG) is defined as an FBG of 6.1-6.9 mmol/L by WHO[14] and an FBG of 5.6-6.9 mmol/L by the American Diabetes Association (ADA)[15]. The body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters, among weight and height were measured by standard methods[16].

Meta-analysis

We conducted a meta-analysis combining the current study findings with previous observations on FBG and stroke risk. We searched PubMed, Web of Knowledge, medRxiv, and bioRxiv databases for related research articles published between

January 01, 2000-September 10, 2020 using the keywords “stroke”, “cardiovascular disease” and “fasting blood glucose”, “blood glucose”, “fasting glucose”, “fasting plasma glucose”, “glucose”, in addition to “prospective study”, “cohort study”, or “follow-up”. The study subjects were restricted to apparently healthy adults in the community. Two authors extracted the data independently, and if they had disagreements, discussed it with the third author. This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. Finally, seven studies were included[17-22]. We extracted information about authors, sample size, the country where the study was implemented, time of follow-up, adjusted covariates, outcome (stroke events), and the effect size [hazard ratio (HR)]. The measurement and definition of FBG levels were directly extracted from each literature. We used a random-effect model to calculate the pooled risk estimation based on the assumption of study heterogeneity. The Begg and Egger tests were performed to detect potential publication bias[23].

Statistical analysis

Baseline demographic characteristics for continuous variables were expressed as median (interquartile ranges), and categorical variables were presented as percentages. Log-transformation was used to all laboratory measures to normalize distributions.

Cox proportional hazard analyses were conducted to evaluate FBG levels and risk of stroke and results presented as HR and 95% confidence intervals (CI). FBG levels were included in the models as a categorical measure (quartiles and three categories by clinical criteria). Multivariable models included conventional risk factors at baseline: age (continuous), sex, BMI (continuous), current smoking (yes/no), family history of stroke (yes/no), hypertension (yes/no), eGFR(ml/min/1.73m²) LDL-C (mmol/L), HDL-C (mmol/L), TC (mmol/L), TG (mmol/L) and use of statins. We also used clinical classification (normal FBG, IFG, hyperglycemia) to classify FBG levels.

In addition, we conducted stratified analyses by sex to check potential effect modification. Sensitivity analyses were conducted to determine the robustness of the primary analysis results. We limited the risk-association analyses to participants who didn't report their own medical history, including hypertension, hyperlipidemia, cancer, nephropathy, CVD, or COPD at baseline.

Statistical analyses were conducted with R (version 4.0.2, www.r-project.org). All tests were 2-sided, and a P value less than 0.05 was considered statistically significant.

Patient and public involvement

Patients and the public were not involved in the design, conduct, or reporting of this study.

Results

Characteristics of the study population

After a median follow-up of 5.5 years (range: 0.1-5.7 years), a total of 417 (192 men and 225 women) stroke events were identified, of which 323 (77.5%) were ischemic stroke. Table 1 shows the baseline characteristics of participants across the quartiles of FBG. Compared with the participants in the study with lower FBG, those with higher FBG levels were more likely to suffer from obesity, hypertension, and hyperlipidemia, had lower levels of eGFR, and preferred to have a family history of stroke (P<0.001, Table 1).

FBG levels and risk of stroke

As shown in Table 2, we observed that higher FBG levels were significantly correlated with an increased risk of total and ischemic stroke in both the original models and models adjusted for age, sex, BMI, HDL-C, LDL-C, TC, TG, eGFR, hypertension, smoking status, use of statins and family history of stroke. Compared to the lowest FBG quartile, the multivariable-adjusted HRs for the highest quartile were 1.44 (95% CI: 1.07-1.94, P=0.021) for total and 1.57 (95%CI: 1.11-2.21, P=0.016) for ischemic stroke. A positive association between FBG levels and non-ischemic stroke was observed in the crude model, but the risk association was rendered statistically nonsignificant in adjusted models. Further, we examined the association between clinical classifications of FBG levels and stroke risk, and the results are presented in Table 3. The multivariable-adjusted HR for total stroke was 1.68 (95%CI: 1.24-2.27, P=0.001) and 1.62 (95% CI: 1.21-2.13, P =0.002) for participants with hyperglycemia compared with those with normal blood glucose, following the ADA and WHO recommendations, respectively.

Results of sex-stratified analyses are shown in Table 4. In original models, higher levels of FBG were significantly associated with an increased risk of total stroke only in women. After adjustment covariate for age, BMI, and other variates, the risk association remained significant (HR: 1.92, 95%CI: 1.22-3.01, P=0.004) for the fourth level in female groups. Similar risk estimates were found in postmenopausal or oophorectomy women. But no significant association with stroke was observed for FBG levels in premenopausal women (supplemental appendix S2).

In sensitivity analyses, the study population was restricted to 15,404 subjects without a self-reported history of hyperlipidemia, CVD, cancer, nephropathy, and COPD yielded essentially no change in risk of total stroke (HR: 1.38, 95% CI: 1.01, 1.92) and ischemic stroke (HR: 1.55, 95% CI: 1.06, 2.26). Additional eliminated for participants with hypertension, the association in women was slightly raised for total stroke (HR: 2.50, 95% CI: 1.11, 5.60) and ischemic stroke (HR: 2.59, 95% CI: 1.03, 6.51) (data not shown).

Meta-analysis

Figure 1 shows the results of meta-analysis including six previously published prospective studies together with our current study. In a word, higher FBG levels were associated with an increased risk of stroke (pooled HR: 1.70, 95% CI: 1.27-2.29). The Begg and Egger tests didn't suggest existence of potential publication bias (P>0.1 for both tests).

Discussion

Principal findings

In our prospective community-based cohort, higher FBG levels were associated with an increased risk of total and ischemic stroke. The risk-association was prominent in women. After excluding the baseline of hypertension, hyperlipidemia, CVD, cancer, nephropathy, and COPD, these associations were still persisted in analyses of women. Our findings extend the previous knowledge on diabetes and stroke risk, suggesting an important role of routine glucose measurement in stroke prevention.

Associations of FBG with stroke risk

When analyzing stroke subtypes, there is no evidence that FBG is associated with non-ischemic stroke, but the association with ischemic stroke persists. This is consistent with the results of a prospective cohort study among Korean men[14]. It suggests that the correlation between FBG and stroke is mainly contributed by an ischemic stroke. A large-scale prospective study in China (including 96,110 participants) indicated that both hyperglycemia and hypoglycemia are associated with an increased risk of incident intracerebral hemorrhage, after adjustment for potential confounders[24].

Results based on the ADA and WHO criteria demonstrated that FBG levels of ≥7.0 mmol/L were a significant risk factor for stroke [HR (95% CI): 1.68 (1.24, 2.27) and 1.62 (1.21, 2.13) following the ADA and WHO criteria, respectively], whereas the risk of stroke in patients with IFG had an increase trend but this trend was not statistically significant. A large number of studies showed that people with diabetes are at increased risk of ischemic stroke[25 26]. A meta-analysis including 698,782 participants reported that the risk of ischemic stroke in diabetic patients was 2.27

times higher than normal people[25]. A cohort study in Swedish also showed that poor blood glucose control in patients with type 2 diabetes was associated with an increased risk of stroke and death[26]. Although diabetes is associated with stroke, the influence of prediabetes on future stroke risk has not been clear yet. Some large sample meta-analyses reported prediabetes is associated with the risk of CVD[27 28] and heart failure[29]. But in another meta-analysis including 15 cohort studies, more than half of the studies showed that after adjusting for cardiovascular risk factors, there was no significant association between pre-diabetes and stroke[30]. A cohort study investigated the sex-specific associations of pre-diabetes with major clinical outcomes reached the same conclusion[31].

Stratified analysis showed that the correlation between FBG levels and stroke risk only existed in women. According to the re-stratification of menopause, only postmenopausal women with the highest FBG level had a higher risk of stroke [HR (95% CI): 1.68 (1.06, 2.68)], no associations were found in premenopausal women. It probably due to the low number of stroke events in premenopausal women. Few published studies reported sex-stratified results. A sex-specific cohort study in the Middle East showed that only men with higher FBG levels showed an increased risk of stroke [HR: 2.15(1.26, 4.67) in FBG level of 6.1-6.9 mmol/L, HR: 2.38 (1.08, 5.25) in FBG level of >7.0 mmol/L][32]. Korean Heart Study showed that IFG was associated with an increased risk of ischemic stroke in men but not in women[33]. We suspect that the disparities in sex between studies could be due to different definitions of outcome (all stroke vs. ischemic stroke) and the variety in covariate adjustments. A meta-analysis including 64 cohort studies provides the clearest evidence yet for the sex difference of diabetes and stroke risk. The excess risk of diabetes-related stroke in women is significantly higher than that in men and independent of sex-difference in other cardiovascular risk factors[34]. Our results support the findings of this meta-analysis, indicating that the association between FBG levels and stroke cases in women, and the mechanism may be related to the protective effect of estrogen.

Possible mechanisms

Accumulating evidence suggests that FBG levels can be used to predict the risk of CVD[20 25 35]. As an adverse consequence of CVD, stroke is closely related to FBG levels[36 37]. Its mechanism may be related to the dysfunction of cerebral microvasculature caused by hyperglycemia, insulin resistance, obesity, and hypertension[38]. The microvasculature is involved in the regulation of many brain processes. Once damaged, it's easy to cause cerebrovascular accidents[39]. The dysfunction is also obvious in the prediabetes population, which may suggest that IFG is the risk factor for stroke[40]. Besides, diabetic retinopathy was proved to be a sign of lacunar ischemic stroke, which had the same effects as cerebral microvascular dysfunction[41].

Compared with men, women with diabetes are at higher risk of stroke[34]. Previously, it was thought that the sex specificity of the severity of diabetes-related cardiovascular diseases was caused by the differences between men and women in treatment and chronic disease management. However, as the gradual equality of men and women, the risk of serious cardiovascular disease in postmenopausal women is still higher[34]. Sex hormones may explain the sex differences observed in human epidemiological studies[42-44], indicating the estrogen protection in women, preventing the progression of non-diabetic cardiovascular diseases at least before menopause. Animal experiments show that the decrease of estrogen levels in ovariectomized mice can lead to impaired glycemia, reduced glucose tolerance, hyperinsulinemia, and impaired insulin secretion, and then develop into hyperglycemia and atherosclerosis[45]. However, diabetes seemingly attenuates the protective effect of estrogen on women in the development of CVD[46].

Strengths and Limitations

The main strengths of this study include the large sample size, measurement of plasma FBG, and the complete follow-up. We followed up the cases by recording linkages with hospital discharge diagnoses and the Cause of Death Registry. We used both quartiles and clinical classifications (normal FBG, IFG, hyperglycemia) to classify FBG levels, and obtained similar results. We considered different stroke subtypes as the study outcome. To our knowledge, this study provides the first meta-analysis investigating the association between FBG levels and stroke risk in the general population, therefore results are likely generalizable to all races.

Our study has several limitations. First, we do not have HbA_{1c} measurements in this study. Among indicators to assess glucose variability, HbA_{1c} is the gold standard for clinical evaluation of long-term blood glucose control[8], while FBG may overlook the potential effects of postprandial blood glucose levels and other meaningful factors[47]. Reports revealed that HbA_{1c} played an important role in distinguishing people with high cardiovascular risk from those without diabetes[48 49]. Second, the levels of estradiol and testosterone in the study subjects were not measured, although we speculated that the sex difference was probably due to the protective effect of sex hormone. Third, due to a low number of stroke cases, the real risk association of the premenopausal population may be biased.

Conclusions

Our study indicates that higher FBG levels are associated with an increased stroke in the general population, and meta-analysis corroborated this finding. Further, we observed that the association was more prominent in women than in men. We also observed strong risk associations among postmenopausal or oophorectomy women. FBG levels as a routine and low-cost measurement could be used to identify individuals with higher stroke risk in the future.

Contributors

Conceptualization, YZ and HZ; methodology, YZ; software, YZ; validation, YZ; formal analysis, YZ; resources, SG, QZ, MY and ZZ; data curation, YZ; visualization, YZ; investigation, YZ, CW and DL; writing—original draft preparation, YZ and SG; writing—review and editing, YZ and HZ; supervision, HZ; project administration, HZ; funding acquisition, SG and HZ. All authors have agreed on the journal to which the article has been submitted and agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

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Competing interests

None declared.

Patient consent for publication

Not required.

Ethics approval

The study protocol conforms to the ethical guidelines of the Declaration of Helsinki. The baseline survey and record linkages with study outcomes were approved by the

Ethics Committee of Fuwai Cardiovascular Hospital, Beijing, China (No. 2012-399). After a detailed explanation of our study, we obtained a written informed consent form from each participant.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

The datasets generated and/or analyzed during the current study are not publicly available due to the restrictions of containing information that could compromise the privacy of research participants.

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Figure 1. Meta-analysis of fasting blood glucose at the highest vs lowest levels and the risk of developing stroke. The horizontal lines indicate the lower and upper limits of the 95% CI, and the grey squares reflects the HR of each study. HR: Hazard Ratio.

Table 1. Baseline characteristics of study population by FBG levels and stroke risk: Cohort Changshu.

Characteristic	Total	Quartile of FBG Levels (mmol/L)				P Value
	n=16,113	Q1 (< 4.87) n=4097	Q2 (4.87-5.24) n=4027	Q3 (5.24-5.77) n=3979	Q4 (> 5.77) n=4010	
Age, yrs	55.7 (46.3, 64.4)	48.6 (41.4, 59.1)	53.8 (44.8,62.84)	57.8 (48.6, 65.9)	60.0 (51.4, 67.2)	<0.001
Men (%)	40.9	42.1	39.4	40.2	42.1	0.002
Premenopausal in women (%)	37.5	55.3	42.3	29.7	22.3	<0.001
Follow-up time, yrs	5.53 (5.49, 5.56)	5.52 (5.49, 5.54)	5.52 (5.49, 5.55)	5.53 (5.50, 5.57)	5.55 (5.50, 5.58)	<0.001
BMI (kg/m^2)	23.3 (21.2, 25.7)	22.6 (20.6, 24.9)	23.0 (21.0, 25.3)	23.6 (21.5, 25.9)	24.2 (22.0, 26.5)	<0.001
Current smoking (%)	23.6	26.9	23.5	21.9	21.9	<0.001
Family history of stroke (%)	5.8	3.8	5.4	6.5	7.6	<0.001
Hypertension (%)	22.8	13.9	18.6	24.9	34.0	<0.001
Fasting blood glucose, mmol/L	5.24 (4.87. 5.77)	4.66 (4.47, 4.77)	5.06 (4.97, 5.15)	5.47 (5.34, 5.60)	6.37 (6.01, 7.20)	<0.001
impaired fasting glucose (%)	8.6	—	—	—	34.7	<0.001
Diabetes (%)	8.8	0.6	0.7	1.0	33.3	<0.001
TC, mmol/L	4.70 (4.13, 5.36)	4.48 (3.95, 5.04)	4.62 (4.08, 5.23)	4.79 (4.22, 5.44)	4.99 (4.36, 5.70)	<0.001
TG, mmol/L	1.32 (0.96, 1.90)	1.20 (0.88, 1.68)	1.26 (0.93, 1.78)	1.33 (0.97, 1.91)	1.52 (1.08, 2.30)	<0.001
HDL-C, mmol/L	1.38 (1.14, 1.66)	1.36 (1.14, 1.62)	1.37 (1.14, 1.64)	1.40 (1.15, 2.68)	1.38 (1.14, 1.69)	<0.001
LDL-C, mmol/L	2.57 (1.92, 3.27)	2.64 (2.03, 3.34)	2.62 (1.97, 3.30)	2.55 (1.89, 3.26)	2.47 (1.79, 3.17)	<0.001
eGFR (ml/min/1.73m^2)	95.59 (84.39, 105.42)	100.88 (89.80, 110.06)	96.744 (86.38, 106.50)	93.60 (83.12, 102.95)	91.65 (79.13, 101.17)	<0.001
Use of statins (%)	0.4	0.1	0.3	0.3	0.7	<0.001

[1.] BMI, body mass index; HDL-C, high density lipoprotein cholesterol; Q, quartile; TC, total cholesterol; TG, triglyceride.

[2.]P Values were determined by Chi-square tests for categorical and Kruskal-Wallis tests for continuous variables.

Table 2. Hazard ratios (95% CI) for incident stroke by FBG quartiles

		Quartile of FBG Levels				P trend
		Q1	Q2	Q3	Q4	
		HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	
Total stroke	Cases/N	57/4097	89/4027	110/3979	161/4010	
	Model 1	1 (Ref.)	1.60 (1.15, 2.22)	2.00 (1.45, 2.75)	2.92 (2.16, 3.94)	<0.001
	Model 2	1 (Ref.)	1.21 (0.87, 1.69)	1.17 (0.85, 1.62)	1.46 (1.07, 1.98)	0.018
	Model 3	1 (Ref.)	1.19 (0.86, 1.63)	1.16 (0.86, 1.62)	1.44 (1.07, 1.94)	0.021
Ischemic stroke	Cases/N	42/4097	69/4027	83/3979	129/4010	
	Model 1	1 (Ref.)	1.68 (1.15, 2.47)	2.05 (1.41, 2.96)	3.17 (2.24, 4.49)	<0.001
	Model 2	1 (Ref.)	1.27 (0.87, 1.87)	1.19 (0.82, 1.73)	1.58 (1.11, 2.25)	0.013
	Model 3	1 (Ref.)	1.25 (0.91, 1.86)	1.17 (0.81, 1.70)	1.57 (1.11, 2.21)	0.016
Non-ischemic stroke	Cases/N	15/4097	20/4027	27/3979	32/4010	
	Model 1	1 (Ref.)	1.36 (0.70, 2.66)	1.86 (0.99, 3.50)	2.20 (1.19, 4.07)	0.006
	Model 2	1 (Ref.)	1.04 (0.53, 2.04)	1.13 (0.60, 2.14)	1.11 (0.59, 2.07)	0.713
	Model 3	1 (Ref.)	1.10 (0.57, 2.14)	1.12 (0.64, 2.24)	1.07 (0.57, 1.99)	0.844

Model 1: unadjusted model; Model 2: adjusted for age, sex and BMI; Model 3: further adjusted for HDL-C, TC, TG, LDL-C, eGFR, hypertension, smoking status, use of statins and family history of stroke.

Table 3. Hazard ratios (95% CI) for incident stroke by clinical classifications of FBG levels

			Model 1	Model 2	Model 3
ADA definition	<5.6 mmol/L	Cases/N		220/11079	
		HR (95%CI)	1 (Ref.)	1 (Ref.)	1 (Ref.)
	5.6–6.9 mmol/L	Cases/N		136/3869	
		HR (95%CI)	1.78 (1.43, 2.20)	1.16 (0.94, 1.44)	1.17 (0.93, 1.42)
	≥7.0 mmol/L	Cases/N		61/1165	
		HR (95%CI)	2.69 (2.02, 3.57)	1.72 (1.29, 2.28)	1.68 (1.24, 2.27)
	P trend		<0.001	0.001	0.001
WHO definition	<6.1 mmol/L	Cases/N		301/13422	
		HR (95%CI)	1 (Ref.)	1 (Ref.)	1 (Ref.)
	6.1–6.9 mmol/L	Cases/N		55/1526	
		HR (95%CI)	1.61 (1.21, 2.15)	1.08 (0.81, 1.45)	1.11 (0.83, 1.47)
	≥7.0 mmol/L	Cases/N		61/1165	
		HR (95%CI)	2.38 (1.81, 3.03)	1.64 (1.24, 2.17)	1.62 (1.21, 2.13)
	P trend		<0.001	0.001	0.002

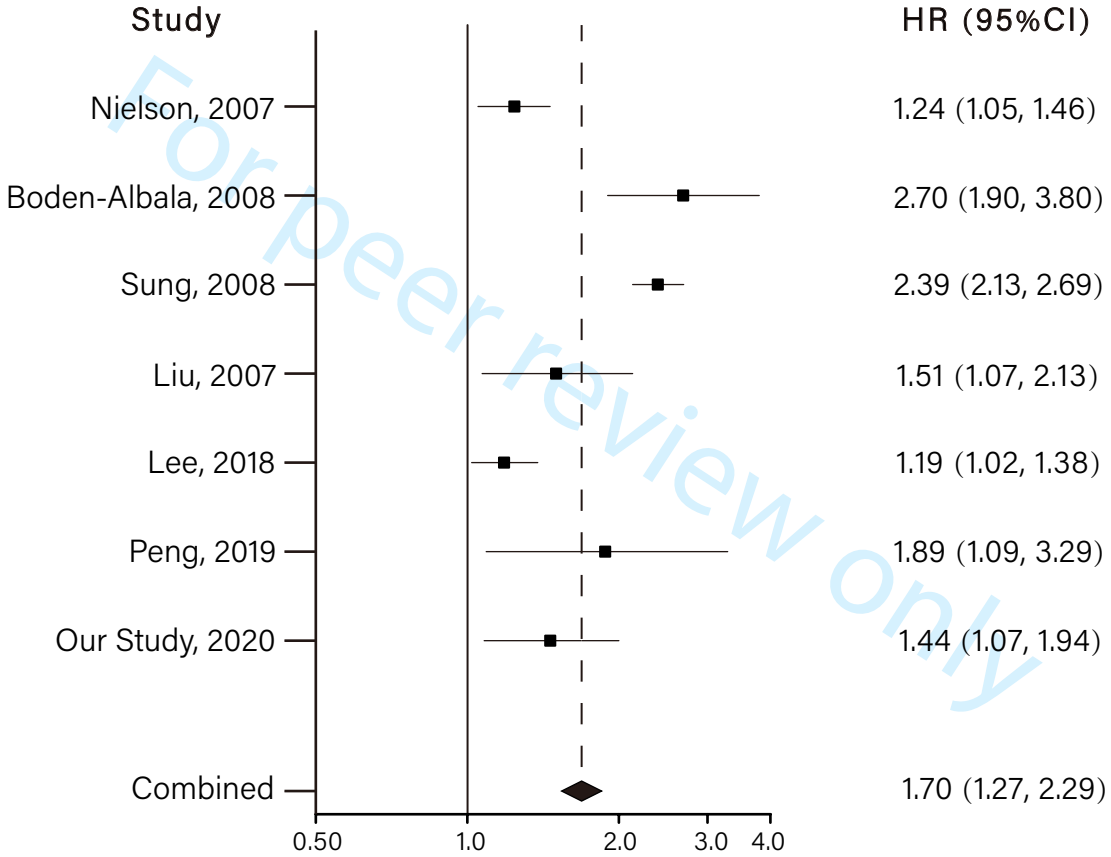
ADA: American Diabetes Association; WHO: World Health Organization.

Model 1: unadjusted model; Model 2: adjusted for age, sex and BMI; Model 3: further adjusted for HDL-C, TC, TG, LDL-C, eGFR, hypertension, smoking status, use of statins and family history of stroke.

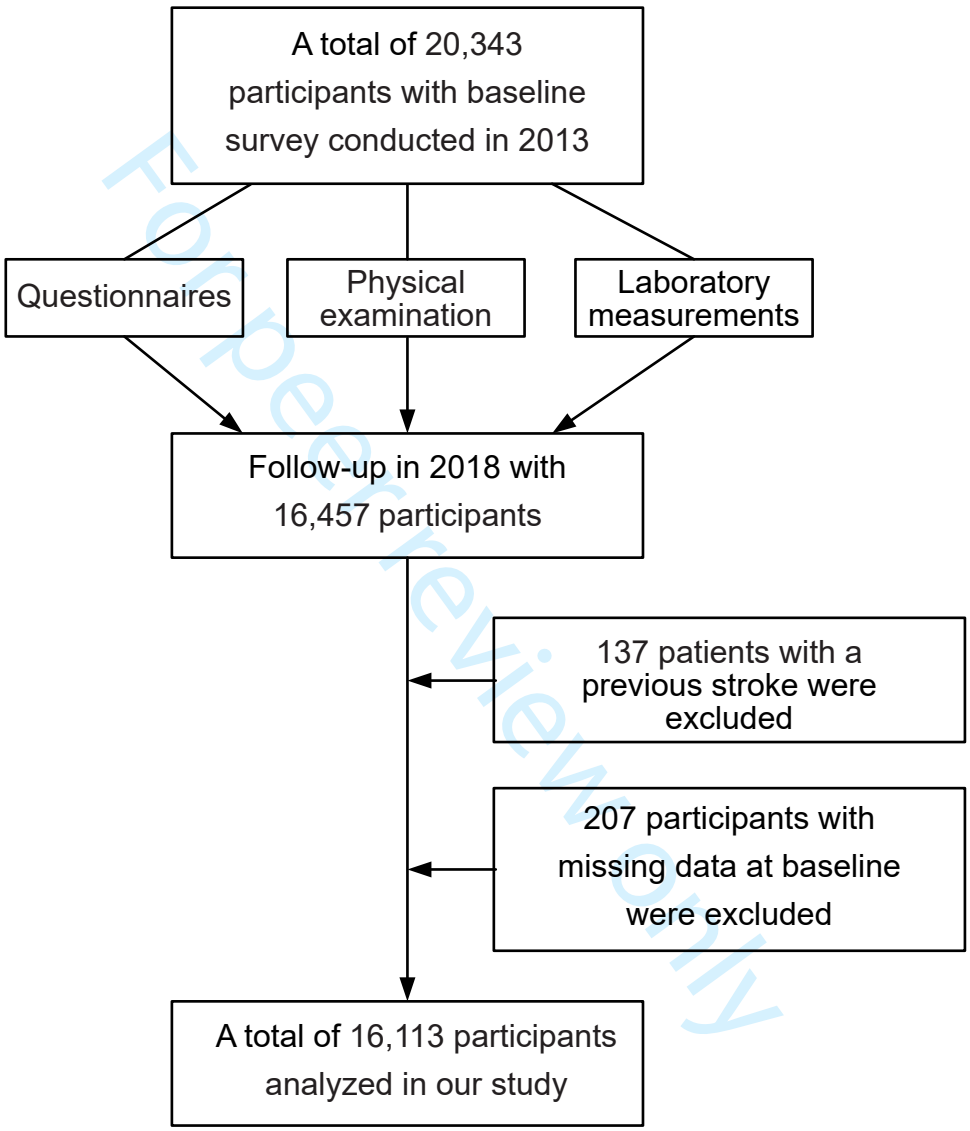
Table 4. Hazard ratios (95% CI) for incident stroke by sex

		Quartile of FBG Levels				P trend
		Q1	Q2	Q3	Q4	
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Men	Cases/N	33/1725	42/1586	53/1599	64/1688	
	Model 1	1 (Ref.)	1.40 (0.89, 2.20)	1.74 (1.13, 2.69)	1.99 (1.31, 3.03)	0.001
	Model 2	1 (Ref.)	1.04 (0.66, 1.64)	1.16 (0.75, 1.80)	1.11 (0.73, 1.71)	0.560
	Model 3	1 (Ref.)	1.05 (0.68, 1.69)	1.15 (0.74, 1.78)	1.04 (0.65, 1.62)	0.741
Women	Cases/N	24/2372	47/2441	57/2380	97/2322	
	Model 1	1 (Ref.)	1.91 (1.21, 3.29)	2.38 (1.48, 3.84)	4.19 (2.68, 6.55)	<0.001
	Model 2	1 (Ref.)	1.45 (0.89, 2.37)	1.25 (0.78, 2.03)	1.90 (1.21, 2.99)	0.006
	Model 3	1 (Ref.)	1.43 (0.87, 2.33)	1.30 (0.80, 2.09)	1.92 (1.22, 3.01)	0.004

Model 1: unadjusted model; Model 2: adjusted for age, sex and BMI; Model 3: further adjusted for HDL-C, TC, TG, LDL-C, eGFR, hypertension, smoking status, use of statins and family history of stroke.



Appendix S1. Flow chart



Appendix S2. Hazard ratios (95% CI) for incident stroke by menopausal status in women

			Model 1	Model 2	Model 3
Premenopausal	Q1	Cases/N		1/906	
		HR (95%CI)	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Q2	Cases/N		5/896	
		HR (95%CI)	5.07 (0.59, 43.37)	2.97 (0.34, 25.86)	2.54 (0.29, 22.48)
	Q3	Cases/N		7/883	
		HR (95%CI)	7.19 (0.89, 58.44)	3.88 (0.47, 31.97)	3.86 (0.47, 31.78)
	Q4	Cases/N		8/884	
		HR (95%CI)	8.18 (0.29, 22.48)	1.90 (0.22, 16.15)	1.80 (0.21, 15.30)
	P trend		0.013	0.850	0.916
Postmenopausal or oophorectomy	Q1	Cases/N		35/1489	
		HR (95%CI)	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Q2	Cases/N		42/1513	
		HR (95%CI)	1.18 (0.76, 1.85)	1.05 (0.67, 1.64)	1.06 (0.62, 1.79)
	Q3	Cases/N		49/1473	
		HR (95%CI)	1.42 (0.92, 2.19)	1.07 (0.69, 1.66)	1.14 (0.70, 1.87)
	Q4	Cases/N		78/1471	
		HR (95%CI)	2.28 (1.53, 3.40)	1.66 (1.11, 2.28)	1.68 (1.06, 2.68)
	P trend		<0.001	0.006	0.006

Model 1: unadjusted model; Model 2: Adjusted for age and BMI; Model 3: further adjusted for HDL-C, TC, TG, LDL-C, eGFR, hypertension, use of statins and family history of stroke.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2	Design
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	Results
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6	
Objectives	3	State specific objectives, including any prespecified hypotheses	5	
Methods				
Study design	4	Present key elements of study design early in the paper	7	Study population
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8	
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7	Study population
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	7	Study population
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8	
Bias	9	Describe any efforts to address potential sources of bias	7	Study population
Study size	10	Explain how the study size was arrived at	7	Study population
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9	Statistical analysis
		(*b*) Describe any methods used to examine subgroups and interactions	8-9	Statistical analysis
		(*c*) Explain how missing data were addressed	8-9	Statistical analysis
		(*d*) If applicable, explain how loss to follow-up was addressed	8-9	Statistical analysis
		(*e*) Describe any sensitivity analyses	8-9	Statistical analysis

Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11	Characteristics of the study population
		(b) Give reasons for non-participation at each stage	11	Characteristics of the study population
		(c) Consider use of a flow diagram		supplemental appendix S1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11	tables
		(b) Indicate number of participants with missing data for each variable of interest	11	Characteristics of the study population
		(c) Summarise follow-up time (eg, average and total amount)	11	tables
Outcome data	15*	Report numbers of outcome events or summary measures over time	11	tables
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12	tables and figures
		(*b*) Report category boundaries when continuous variables were categorized	11-12	tables and figures
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-12	tables and figures
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12	Meta-analysis
Discussion				
Key results	18	Summarise key results with reference to study objectives	13	Principal findings
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16	Strengths and Limitations
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15	Possible mechanisms
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14	
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if	18	Funding

	applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.