Prospective Study of Fasting Blood Glucose and Intracerebral Hemorrhagic Risk

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Background and Purpose—Although diabetes mellitus is an established independent risk factor for ischemic stroke, the association between fasting blood glucose and intracerebral hemorrhage (ICH) is limited and inconsistent. The objective of the current study was to examine the potential impact of long-term fasting blood glucose concentration on subsequent risk of ICH.

Methods—This prospective study included 96 110 participants of the Kailuan study, living in Kailuan community, Tangshan city, China, who were free of cardiovascular diseases and cancer at baseline (2006). Fasting blood glucose concentration was measured in 2006, 2008, 2010, and 2012. Updated cumulative average fasting blood glucose concentration was used as primary exposure of the current study. Incident ICH from 2006 to 2015 was confirmed by review of medical records.

Results—During 817 531 person-years of follow-up, we identified 755 incident ICH cases. The nadir risk of ICH was observed at fasting blood glucose concentration of 5.3 mmol/L. The adjusted hazard ratios and their 95% confidence intervals (CIs) of ICH were 1.59 (95% CI, 1.26–2.02) for diabetes mellitus or fasting blood glucose ≥7.00 mmol/L, 1.31 (95% CI, 1.02–1.69) for impaired fasting blood glucose (fasting blood glucose, 6.10–6.99 mmol/L), 0.98 (95% CI, 0.78–1.22) for fasting blood glucose 5.60 to 6.09 mmol/L, and 2.04 (95% CI, 1.23–3.38) for hypoglycemia (fasting blood glucose, <4.00 mmol/L), comparing with normal fasting blood glucose 4.00 to 5.59 mmol/L. The results persisted after excluding individuals who used hypoglycemic, aspirin, antihypertensive agents, or anticoagulants, and those with intracerebral hemorrhagic cases occurred in the first 2 years of follow-up.

Conclusions—In this large community-based cohort, low (<4.0 mmol/L) and high (≥6.1 mmol/L) fasting blood glucose concentrations were associated with higher risk of incident ICH, relative to fasting blood glucose concentrations of 4.00 to 6.09 mmol/L. **(*Stroke*. 2018;49:27-33. DOI: 10.1161/STROKEAHA.117.019189.)**

Key Words: cerebral hemorrhage ■ diabetes mellitus ■ follow-up studies ■ humans ■ risk factors

Intracerebral hemorrhage (ICH) accounts for ≈10% to 15% of all strokes[1,2] and is disproportionately associated with higher mortality and worse functional outcomes than other forms of stroke.[3] There are no proven interventions to improve the clinical course and mortality rate when ICH occurs because ICH has remained unchanged in recent decades,[4] with an even increasing trend reported in some Asian, African, and South American countries.[5] Therefore, prevention of ICH through understanding and reduction of risk factors has significant implications for public health and clinical practice. This is particularly important for populations where prevalence of vascular risk factors and incidence of ICH are higher, such as eastern Asia, as well as blacks and Hispanics in the United States.[1,5,6]

Although diabetes mellitus is an established independent risk factor for ischemic stroke,[7] evidence on diabetes mellitus and ICH risk remains limited. Diabetes mellitus could be a potential risk factor for ICH because it leads to atherosclerotic aneurysm and small vessel disease[8–11] and coexists with hypertension—a well-known risk factor for ICH. However, previous epidemiological studies,[7,12–15] including 2 meta-analyses,[7,12] have generated mixed results on the associations between diabetes mellitus and ICH. These studies were limited by small number of incident ICH cases in each individual

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study,[7,12] retrospective study design,[15] and failure to confirm the ICH cases by review of medical records.[13,14] Further, low glucose concentrations could be also associated with higher ICH risk because it may be a marker of disease burden or frailty and because it may provoke a surge of sympathoadrenergic activity and subsequently increase risk for ICH. This notion is supported by the observations that individuals with hypoglycemia have a higher risk for cardiovascular events and death, relative to those with normal glucose status.[12,16,17] However, the potential impact of hypoglycemia on ICH risk remains unknown.

We, therefore, prospectively examined the potential impact of fasting blood glucose (FBG) levels on ICH risk in >96 000 adults. FBG concentrations were measured every 2 years starting in 2006 (ie, baseline) through 2012. To reduce within-subject variation and better represent long-term FBG status, we used the updated cumulative average FBG concentration as the primary exposure. Because the pathogenesis and risk factors of ICH may vary based on their location,[18] in secondary analyses, we examined the relationship between FBG and the ICH location. We also examined whether baseline and the most recent glucose concentration, respectively, were associated with risk of incident ICH.

Methods

Study Design and Population

The Kailuan study is a prospective study, including 101 510 participants (81 110 men and 20 400 women, aged 18–98 years), started in 2006.[19–21] All participants were followed biennially to update information on potential risk factor and newly diagnosed disease. In the current analyses, we excluded 1239 participants who missed baseline FBG data. We further excluded 4161 participants with a history of stroke, myocardial infarction, or cancer before baseline because a prior diagnosis of, or active treatment for, cancer and cardiovascular disease could influence current glycemic control, leaving 96 110 participants in the current analyses. The detailed information on study design and participants can be found in the online-only Data Supplement.

Assessment of Incident ICH

The outcome was the first occurrence of ICH, either nonfatal or ICH death. We linked all participants to the Municipal Social Insurance Institution and all of the discharge register of the 11 hospitals to retrieve incidence of ICH, according to the ninth and tenth versions of *International Classification of Diseases* (*Ninth Revision* code 431 and *Tenth Revision* code I61). We further searched the death certificates from provincial vital statistic offices to add the fatal ICHs out of the hospitals. Additionally, information on medical history of stroke was collected via questionnaire biennially since 2006 to identify the ICH cases that did not admit to the local hospitals. In the current analysis, we did not include traumatic intracranial hemorrhages and epidural, subdural, subarachnoid hematomas.

For all potential ICH cases identified by the ICD code, death certificates, and questionnaire, 2 physicians, including experienced neurologists, reviewed the medical records and judged the case annually, blinded to the FBG concentration. In case of disagreement, the third physician had been consulted and made the final consensus. Fatal ICH cases were confirmed by medical records, autopsy reports, or death certificates with ICH listed as the primary cause. A nonfatal ICH was defined as the sudden onset of a focal neurological deficit and demonstration of acute primary intraparenchymal hemorrhage on either brain computed tomography or magnetic resonance imaging, which was available for all suspected nonfatal ICH cases. ICH was diagnosed according to the World Health Organization criteria.

In 2015, an experienced radiologist examined available brain scan imagines and recorded the locations. ICH location was ascertained only when the report or review of the imaging clearly confirmed the location of ICH. As an example, if the radiologist only reported a left frontal hemorrhage and we did not have images to review, we did not include such a patient in the secondary analyses by hemorrhage location because this hemorrhage might have been in a deep or nondeep region of the frontal lobe. We included 425 of 755 patients with incident ICH with clear information on parenchymal location of hematomas in our secondary analysis. The hematomas were divided into 2 categories based on location: deep (ie, basal, ganglia, thalami, cerebellar, and brain stem) or nondeep hematomas (ie, lobar).

Assessment of FBG and Covariates

Fasting blood samples were collected in the morning after an 8- to 12-hour overnight fast and transfused into vacuum tubes containing EDTA. An auto analyzer (Hitachi 747; Hitachi, Tokyo) was used to measure FBG with the hexokinase/glucose-6-phosphate dehydrogenase method in 2006, 2008, 2010, and 2012.[21] The coefficient of variation using blind quality control specimens was <2.0%.

To represent long-term glucose patterns of individuals, we calculated updated cumulative average FBG concentration using all available FBG measurements from 2006 to the end of follow-up. For example, the incident ICH from 2008 to 2010 was related to the average concentration of FBG in 2006 and 2008. We divided the cohort into 5 categories using 4 FBG cutoff points, which were based on current definitions of hypoglycemia (<4.00 mmol/L[22]), normal FBG(4.00–5.59 mmol/L[23]), upper range of normal fasting glucose (5.60–6.09 mmol/L), impaired fasting glucose (6.10–6.99 mmol/L[24]), and diabetes mellitus (≥7.0 mmol/L). Participants with physician-diagnosed diabetes mellitus or use of hypoglycemic medications were assigned to the ≥7.00 mmol/L group. We also used baseline and the most recent FBG concentration, respectively, as secondary exposures.

Information on potential covariates was collected in 2006 and updated every 2 years thereafter[19,21] and can be found in the online-only Data Supplement.

Statistical Analysis

All analyses were conducted using SAS, version 9.3 (SAS Institute, Inc, Cary, NC). Two-sided $P<0.05$ was considered statistically significant. We selected potential confounders a priori based on available literature and assessment of a causal diagram. The Cox proportional hazards model was used to investigate the association between FBG and ICH risk, after adjustment for potential confounders, including baseline age, sex, smoking, alcohol intake, education, physical activity, sodium intake, and family income; updated information on use of antihypertensive, aspirin, and lipid-lowering medications during following up; and updated cumulative average of systolic blood pressure, diastolic blood pressure, body mass index (BMI), estimated glomerular filtration rate, and blood concentration of high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, and high-sensitivity C-reactive protein from baseline to the end of follow-up. The proportional assumption was satisfied. Continuous variables were divided into categories based on related clinical cut points or quintile. Missing data of each of these covariates were coded as extra category.

The dose–response relationship between FBG and ICH was also evaluated by restricted cubic spline,[25] with 5 knots defined at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of the FBG distribution.

We examined whether the potential impact of FBG on ICH varied according to the hematoma location (deep versus nondeep). Because of only a few non-deep ICH cases (n=61), we grouped participants into 3 FBG categories (hypoglycemic, <4.00; normal glycemic, 4.00–6.09; and hyperglycemic, ≥6.10 mmol/L) for this secondary analysis.

We used likelihood ratio tests to examine potential interactions between FBG concentration and the sex, age (<60 versus ≥60 years),

hypertension (yes/no), and BMI (<25, 25–29, or ≥30 kg/m^2) in relation to ICH risk, adjusting for aforementioned covariates.

Because altered fasting glucose concentration might be the consequence of impending ICH (ie, reverse causality), we conducted a 2-year lag analysis by excluding incident ICH cases from the first 2 years of follow-up. To explore whether the potential association between FBG and ICH risk was confounded by medications, we conducted sensitivity analyses by excluding the participants who used aspirin, antihypertensive, or hypoglycemic medications, separately. Because anticoagulants could increase the risk of ICH, we excluded participants with atrial fibrillation or flutter, deep venous thrombosis, pulmonary infarction, or heart valve disease, which are major indications for use of anticoagulants. We also restricted the analyses to 73 687 participants with complete data on all covariates, excluded 7 cases without autopsy or computed tomography/magnetic resonance imaging imaging, and further included 1536 participants with history of MI or cancer at baseline in sensitivity analyses.

Results

During 817 531 person-years (median, 9.0 years and interquartile range from 8.7–9.2 years) of follow-up, we identified 755 incident ICH cases. Higher FBG concentration was associated with higher prevalence of use of antihypertensive, aspirin, or lipid-lowering medications and higher levels of BMI, blood pressure, and lipids. Individuals with FBG <4.0 mmol/L (n=687) were more likely to be older, have lower education, BMI, and low-density lipoprotein cholesterol and higher high-sensitivity C-reactive protein concentration, relative to those with normal FBG (Table 1).

We observed a U-shaped relation between FBG concentration and ICH risk, with the lowest risk at an FBG of 5.3 mmol/L (Figure 1; Table 2). Similar results were observed in the sensitivity analysis by excluding those who used hypoglycemic, aspirin, or antihypertensive medications at the baseline or during follow-up, excluding ICH onset during the first 2 years of follow-up, excluding participants who may use anticoagulants (Table 2), excluding participants with any missing data on the covariates, excluding cases without autopsy or computed tomography/magnetic resonance imaging imaging, or further including participants with history of MI or cancer at baseline (Table I in the online-only Data Supplement).

In a secondary analysis, we found that FBG <4.0 mmol/L tended to have higher risk of both deep and nondeep location of ICH. Interestingly, hyperglycemia was associated with higher risk of ICH with deep hematoma (adjusted hazard ratio, 1.43; 95% confidence interval, 1.08–1.88) but not with nondeep ICH (adjusted hazard ratio, 0.99; 95% confidence interval, 0.58–1.68; Table II in the online-only Data Supplement).

We observed that relationships between FBG and ICH were modified by sex, and hypertension (*P* interaction <0.05 for both), but not by age and BMI. The association between hyperglycemia and ICH risk was more pronounced in women, relative to men (Figure 2). Participants without hypertension and FBG <4.0 mmol/L had a >2-fold increased risk of ICH, and a strong gradient across elevated FBG categories, whereas the relationship was less convincing for those with hypertension (Figure 2).

When we used the baseline (2006) FBG as exposure, we found that FBG ≥5.60 mmol/L, but not FBG <4.00 mmol/L, was associated with increased ICH risk (Table III in the online-only Data Supplement), relative to FBG of 4.00 to 5.59

Table 1. Baseline (2006) Characteristics According to Updated Cumulative Average Fasting Blood Glucose Concentration, Among 96 110 Kailuan Participants

	<4.00 mmol/L	4.0–5.59 mmol/L	5.60–6.09 mmol/L	6.10–6.99 mmol/L	≥7.00 mmol/L
n	687	65 412	12 622	6331	11 058
FBG, mmol/L*	3.75	5.01	5.80	6.43	8.72
Age, y†	60.4	54.3	56.6	57.9	60.0
Women, %†	18.6	22.8	14.8	12.8	19.2
Smoking status, %†					
Current	33.6	32.6	37.3	37.3	30.7
Past	7.3	4.7	6.1	5.8	6.8
Never	52.3	60.0	54.6	54.6	59.1
Alcohol intake, %†					
Never	56.0	58.4	51.5	53.2	58.6
Past	6.3	2.9	3.3	3.6	4.9
Light‡	3.8	5.7	5.6	4.1	3.4
Moderate‡	6.1	3.9	4.2	3.8	3.7
Heavy‡	12.1	15.3	21.4	21.4	16.1
Physical activity, %†					
Never	6.4	8.1	10.7	10.2	6.9
1–2 times per wk	70.3	75.0	70.2	70.4	70.0
≥3 times per wk	15.4	13.4	16.2	16.0	18.2
Sodium intake, %†					
≥10 g/d	7.4	9.6	11.9	11.8	11.0
6–9 g/d	76.9	78.3	76.1	75.8	75.1
<6 g/d	7.7	8.6	9.1	9.0	9.1
Education, %†					
Illiteracy or elementary school	23.3	8.6	11.6	12.7	12.7
Middle school	64.2	80.2	80.7	80.0	78.7
College/ university	5.1	7.9	4.9	4.0	4.0
Average income, %†					
<500¥ per mo	23.7	26.4	32.0	31.9	27.0
500–2999¥ per mo	60.8	63.6	58.9	59.6	61.9
≥3000¥ per mo	8.0	6.6	6.1	5.1	6.4
Deep venous thrombosis or pulmonary infarction§	0.00	0.18	0.17	0.09	0.26
Heart valve disease§	0.15	0.21	0.15	0.16	0.35
Atrial fibrillation or flutter§‖	2.04	0.64	0.77	0.82	1.08
Use of antihypertensive agent, %§	14.6	15.3	21.5	23.7	36.2

(*Continued*)

Table 1. Continued

	<4.00 mmol/L	4.0–5.59 mmol/L	5.60–6.09 mmol/L	6.10–6.99 mmol/L	≥7.00 mmol/L
Use of lipid-lowering medications, %§	0.58	1.49	2.34	1.86	5.58
Use of hypoglycemic medications, %§	…	…	…	…	46.9
Use of aspirin§	1.02	0.90	1.20	1.03	2.18
hs-CRP, mg/L*	1.45	0.99	1.12	1.22	1.46
BMI, kg/m²*	23.7	24.6	25.5	25.8	26.1
LDL-C, mmol/L*	1.98	2.46	2.63	2.67	2.60
HDL-C, mmol/L*	1.58	1.52	1.52	1.52	1.48
TC, mmol/L*	4.65	4.92	5.14	5.25	5.24
TG, mmol/L*	1.39	1.54	1.79	2.00	2.15
SBP, mm Hg*	132	129	136	139	140
DBP, mm Hg*	82	83	86	88	87
eGFR, mL/min per 1.73 m²*	78.1	85.4	84.9	83.2	81.7

BMI indicates body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high sensitive C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; and TG, triglycerides.

*Updated cumulative average from baseline to the end of follow-up.

†Measured at baseline.

‡Light drinker, 0.1 to 0.4 serving per day for women and 0.1 to 0.9 serving per day for men; moderate, 0.5 to 1.5 servings per day for women and 1 to 2 serving per day for men; heavy, >1.5 servings per day for women and >2 serving per day for men; based on 15 g of alcohol per day.

§Updated during the follow-up.

‖Diagnosis of atrial fibrillation or flutter was based on 12-lead ECG and self-reported physician-diagnosis history and was updated by every survey from 2006.

mmol/L. However, the most recent FBG concentration was not significantly associated with altered short-term (0.1–1.9 years) ICH risk.

Discussion

In this large prospective study including 96 110 participants, we observed that FBG levels both in the hypoglycemic and hyperglycemic range are associated with increasd risk of incident ICH, after adjustment for potential confounders. These results obtained from a prospective observational study of an unprecedentedly large community-dwelling cohort have important implications for prevention of ICH.

We found that the risk for ICH increased in participants with FBG of ≥6.1 mmol/L. Our observations are consistent with a prior meta-analysis of diabetes mellitus and ICH[12] (pooled hazard ratio, 1.56). However, only 2 of 79 included studies in this meta-analysis had >100 ICH cases, and the small number of patients with ICH in these individual studies may preclude the accurate estimate of the association between diabetes mellitus and ICH. Nevertheless, this meta-analysis clearly reported the need for more powerful analyses to reliably characterize the strength of associations in ICH.

Our new finding that FBG of 6.1 to 6.9 mmol/L, which falls in the range of impaired fasting glucose,[26] was associated with higher ICH risk is consistent with previous observations on prediabetes and total stroke. A meta-analysis[27] of 5 prospective cohort studies found that individuals with FBG of 6.1 to 6.9 mmol/L had a 21% increased risk of total stroke; however, ICH was not separately analyzed in this study. Consistently, in a recent study conducted among Chinese adults without known diabetes mellitus, per 1-mmol/L higher usual random plasma glucose level was associated with 5% increased risk of ICH.[14] However, random plasma glucose is limited by its great intraindividual variation and might not accurately reflect an individual's long-term status.

Several biological mechanisms could explain the observed association between high FBG and ICH. Abnormal glucose metabolism could impair normal endothelial function[9] and subsequently lead to cerebral small vessel disease.[8] Degenerative changes in the walls of cerebral small vessels could cause ischemic lacunar infarcts, fibrinoid necrosis, microaneurysm formation, and ICH.[10] The 2 most common causes of ICH in elderly can be distinguished by the location of ICH in most cases, that is, deep ICH mostly caused by hypertensive small vessel disease, whereas lobar ICH mostly resulting from cerebral amyloid angiopathy, the latter caused by accumulation of amyloid beta in cortical and leptomeningeal vessel walls.[11] An important support to the view that FBG abnormalities can mechanistically contribute to the risk of ICH comes from our secondary analysis of ICH locations. The association between hyperglycemia and increased risk was found only for ICHs in deep locations. Small vessel disease driven by classical vascular risk factors, hypertension being the best known, is almost invariably the cause of such deep ICHs, and our results suggest that hyperglycemia might be a contributing factor. The number of incident lobar ICHs was relatively small, and it is impossible to prove or rule out a contribution from FBG disturbances on the risk of lobar ICH at this time.

Significant associations between high FBG and ICH risk were only observed when we used baseline or cumulative average, rather than the most recent FBG concentration (updated every 2 years), as the predictor. This finding suggests that chronic exposure, rather than short-term exposure, to hyperglycemia could result in unfavorable effects on ICH, supporting the potential causal association between high FBG and ICH risk. This finding also shows that any future study to confirm this association should include FBG assessments at multiple time points rather than relying on a single FBG measurement. Significant sex differences in the FBG–ICH relation observed in the current study are consistent with a systematic review,[7] in which the risk of total stroke associated with diabetes mellitus was significantly higher in women than in men. However, most of the included studies focused on the total stroke rather than ICH. Further studies are warranted to replicate our observations.

In the current study, low FBG concentration (<4.0 mmol/L) was also associated with higher risk for ICH, consistent with a previous study.[13] Low FBG could lead to activation of the sympathetic nervous system and adrenergic hormone release, which might induce vasoconstriction and hemodynamic

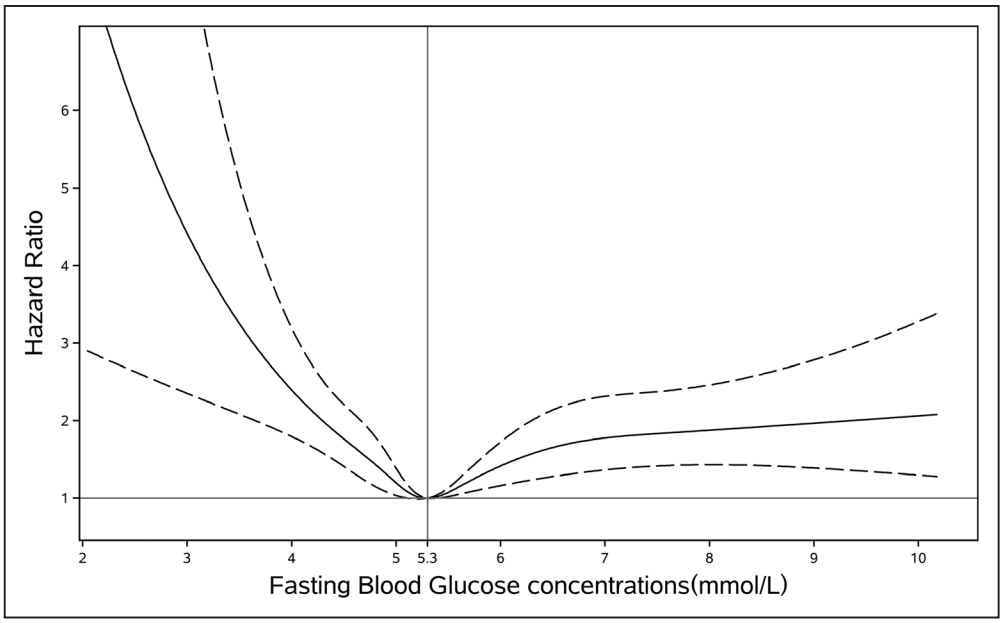

Figure 1. Adjusted hazard ratios of intracerebral hemorrhage according to updated cumulative average fasting blood glucose concentration. Model adjusted for age, sex, smoking, alcohol intake, education, physical activity, average monthly income of each family member, sodium intake, updated use of antihypertensive, aspirin, hypoglycemic, and lipid-lowering medications, and updated cumulative average body mass index, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, high sensitive C-reactive protein, systolic blood pressure, diastolic blood pressure, and estimated glomerular filtration rate. Data were fitted by a restricted cubic spline Cox proportional hazards model. The 95% confidence intervals are indicated by the dashed lines.

changes, resulting in several ICH-related physiological changes. Alternatively, hypoglycemia may be a marker of disease burden or frailty. In our study, hypoglycemia was associated with older age and lower levels of BMI and low-density lipoprotein, which were associated with higher ICH risk in previous studies.[28] Consistently, we found that the

Table 2. Adjusted Hazard Ratio of Intracerebral Hemorrhage, According to Updated Cumulative Average Fasting Blood Glucose Concentration

	<4.00 mmol/L	4.00–5.59 mmol/L	5.60–6.09 mmol/L	6.10–6.99 mmol/L	≥7.00 mmol/L
No. of cases/population	16/687	437/65 412	94/12 622	72/6331	136/11 058
Incidence rate, per 1000 person-years	3.04	0.78	0.88	1.35	1.47
Age- and sex-adjusted hazard ratio	2.95 (1.78–4.86)	1.00	1.05 (0.84–1.31)	1.55 (1.20–1.99)	1.69 (1.39–2.05)
Multivariate-adjusted hazard ratio 1*	2.81 (1.70–4.65)	1.00	1.07 (0.85–1.33)	1.56 (1.21–2.00)	1.68 (1.38–2.03)
Multivariate-adjusted hazard ratio 2†	2.04 (1.23–3.38)	1.00	0.98 (0.78–1.22)	1.31 (1.02–1.69)	1.59 (1.26–2.02)
Sensitivity analyses					
2-y lag analysis†‡	1.70 (0.84–3.46)	1.00	1.15 (0.88–1.49)	1.29 (0.94–1.78)	1.96 (1.49–2.58)
Excluding hypoglycemic users†	2.00 (1.20–3.31)	1.00	0.97 (0.77–1.21)	1.29 (1.00–1.66)	1.56 (1.23–1.98)
Excluding antihypertensive users†	2.32 (1.32–4.07)	1.00	1.16 (0.89–1.50)	1.47 (1.09–1.99)	1.77 (1.34–2.33)
Excluding aspirin users†	1.26 (0.76–2.10)	1.00	0.96 (0.77–1.21)	1.21 (0.94–1.56)	1.47 (1.16–1.86)
Excluding potential† anticoagulant users†§	1.19 (0.70–2.00)	1.00	0.93 (0.74–1.18)	1.20 (0.93–1.55)	1.44 (1.13–1.83)

ICH indicates intracerebral hemorrhage.

*Adjusted for age (year), sex, smoking (current, past, or never), alcohol intake (never, past, light, moderate, or heavy), education (illiteracy/elementary school, middle school, or college/university), physical activity (never, sometimes, or active), average monthly income of each family member (<500, 500–2999, or ≥3000¥), and sodium intake (≥10.0, 6.0–9.9, or <6.0 g/d).

†Included variables in model 1 and further adjusted for updated use of antihypertensive, aspirin, hypoglycemic, and lipid-lowering medications (yes/no for each), and updated cumulative average body mass index (≥30.0, 25.0–29.9, or <25.0 kg/m^2), triglycerides (quintile), high-density lipoprotein cholesterol (quintile), low-density lipoprotein cholesterol (quintile), high-sensitivity C-reactive protein (<1.00, 1.00–2.99, or ≥3.00 mg/L), systolic blood pressure (quintile), diastolic blood pressure (quintile), and estimated glomerular filtration rate (quintile).

‡Excluded person time and ICH events from the first 2 years of follow-up.

§Excluded participants with deep venous thrombosis, pulmonary infarction, heart valve disease, or atrial fibrillation or flutter.

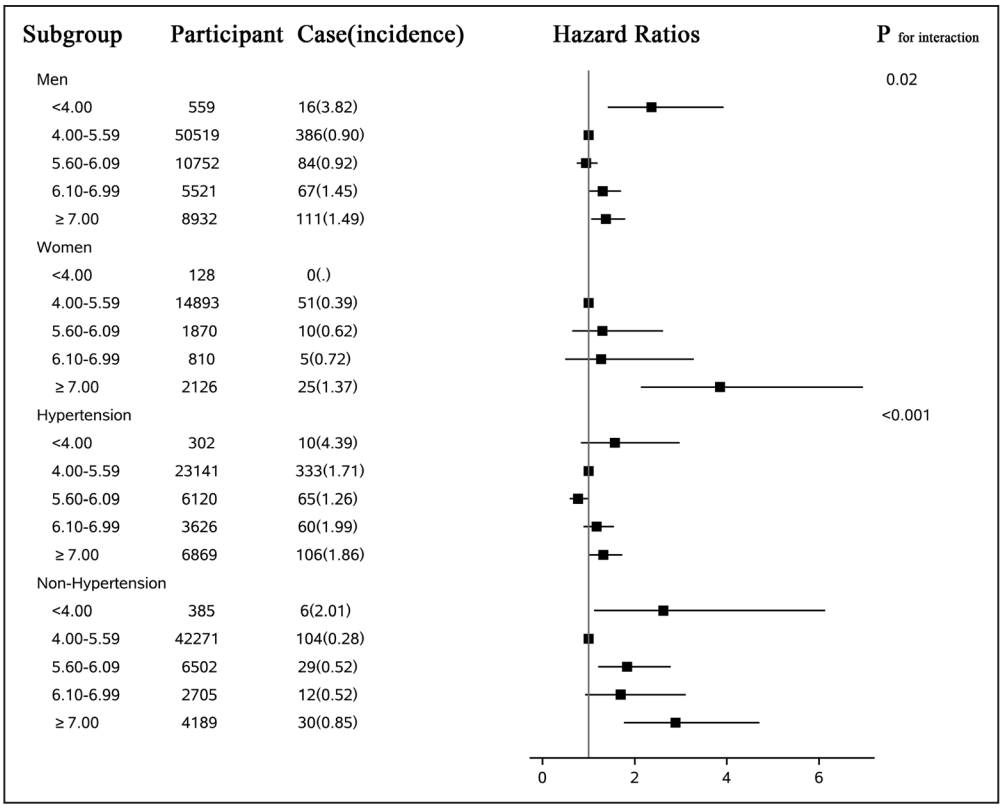

Figure 2. Adjusted hazard ratio of intracerebral hemorrhage by sex or hypertension, according to updated cumulative average fasting blood glucose concentration (mmol/L). *P* value is for interaction test. Model adjusted for age, sex, smoking, alcohol intake, education, physical activity, average monthly income of each family member, sodium intake, updated use of antihypertensive, aspirin, hypoglycemic, and lipid-lowering medications, and updated cumulative average body mass index, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, high-sensitivity C-reactive protein, systolic blood pressure, diastolic blood pressure, and estimated glomerular filtration rate. Hypertension was defined as a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg or use of antihypertensive agents.

association between low FBG and ICH was more pronounced among nonhypertensive participants. However, our results should be interpreted with caution because the significant association was only seen when we used cumulative average FBG as the exposure and only 687 participants (0.45% of the population) with FBG <4.0 mmol/L. Therefore, we cannot exclude the possibility of a chance finding. Another possible interpretation is that the hypoglycemia–ICH relationship could be partially because of use of aspirin[29] and anticoagulants,[30] which could lead to bleeding and hypoglycemia.[31] This is indicated by our sensitivity analyses in which excluding aspirin users and those who might use anticoagulants attenuated the association between hypoglycemia and ICH greatly.

Our study has several limitations. Oral glucose tolerance testing, casual random glucose, and HbA1C concentration were not available in the Kailuan study, and some cases of diabetes mellitus or prediabetes cases could, therefore, have been missed. However, repeated assessment of these indices in a large community-based cohort was unfeasible. Use of cumulative average of FBG in our study would reduce random errors greatly. We did not collect information on use of nonaspirin antithrombotic drugs. However, in the primary analysis, we excluded participants with a history of cardiovascular disease at baseline and further excluded the participants with atrial fibrillation or flutter, deep venous thrombosis, pulmonary infarction, or heart valve disease in the sensitivity analysis, which are major indications for anticoagulant use. The current study included only Chinese adults living in the Kailuan community who had higher incidence of ICH and the similar prevalence of diabetes mellitus comparing with whites.[32] Thus, it may not be generalizable to other populations. However, the biological effects of FBG on ICH in this cohort should be the same as those among men and women in general. Prior studies clearly showed a higher prevalence of ICH in eastern Asian populations, including China. It is, therefore, plausible that our cohort would be representative of a high ICH-risk population where knowledge of these findings would be most valuable. Another limitation is that we only included small number of women (n=19 827). However, in the subgroup analysis, we still observed significant association between high FBG and ICH risk. Further, for the ICH location analyses, we did not include ICH cases when specific location of deep or not deep was not clearly confirmed, which could underestimate the prevalence of lobar ICH. Because we started to document the ICH location in 2015 and we did not obtain the brain images for some cases. Only 1 experienced radiologist examined all these images; misclassification of outcome is thus inevitable. Because of these limitations, our findings on FBG and ICH location should be interpreted with caution.

Conclusions

Both low and high FBG concentrations were associated with higher future risk of ICH in this large community-based cohort. The lowest risk of ICH was observed among those in the normal FBG range (4.00–6.09 mmol/L). Replication of our findings in other ethnic populations with assessment of other markers of glycemic status, such as HbA1C, may strengthen the link between abnormal glycemic control and ICH risk.

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Disclosures

None.

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