Longitudinal association between fasting blood glucose concentrations and first stroke in hypertensive adults in China: effect of folic acid intervention[1–4]

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ABSTRACT

Background: Diabetes is a known risk factor for stroke, but data on its prospective association with first stroke are limited. Folic acid supplementation has been shown to protect against first stroke, but its role in preventing first stroke in diabetes is unknown.

Objectives: This post hoc analysis of the China Stroke Primary Prevention Trial tested the hypotheses that the fasting blood glucose (FBG) concentration is positively associated with first stroke risk and that folic acid treatment can reduce stroke risk associated with elevated fasting glucose concentrations.

Design: This analysis included 20,327 hypertensive adults without a history of stroke or myocardial infarction, who were randomly assigned to a double-blind daily treatment with 10 mg enalapril and 0.8 mg folic acid ($n = 10,160$) or 10 mg enalapril alone ($n = 10,167$). Kaplan-Meier survival analysis and Cox proportionate hazard models were used to test the hypotheses with adjustment for pertinent covariables.

Results: During a median treatment duration of 4.5 y, 616 participants developed a first stroke (497 ischemic strokes). A high FBG concentration (≥ 7.0 mmol/L) or diabetes, compared with a low FBG concentration (< 5.0 mmol/L), was associated with an increased risk of first stroke (6.0% compared with 2.6%, respectively; HR: 1.9; 95% CI: 1.3, 2.8; $P < 0.001$). Folic acid treatment reduced the risk of stroke across a wide range of FBG concentrations ≥ 5.0 mmol/L, but risk reduction was greatest in subjects with FBG concentrations ≥ 7.0 mmol/L or with diabetes (HR: 0.66; 95% CI: 0.46, 0.97; $P < 0.05$). There was a significant interactive effect of FBG and folic acid treatment on first stroke ($P = 0.01$).

Conclusions: In Chinese hypertensive adults, an FBG concentration ≥ 7.0 mmol/L or diabetes is associated with an increased risk of first stroke; this increased risk is reduced by 34% with folic acid treatment. These findings warrant additional investigation. This trial was registered at clinicaltrials.gov as NCT00794885. *Am J Clin Nutr* 2017;105:564–70.

INTRODUCTION

Stroke is the number one cause of death in China and the number 2 cause of death around the world (1). Approximately 77% of strokes are first events (2). The importance of the primary prevention of stroke was underscored in the latest American Heart Association/American Stroke Association guidelines (3).

Globally, there is an urgent need to identify major modifiable risk factors of first stroke and to develop safe, inexpensive, and effective primary prevention strategies to halt or reverse the rapidly rising trend of stroke in China and in many other developing countries (4).

Diabetes, which affects 415 million people worldwide (5), is a well-recognized risk factor for stroke (3). However, limited longitudinal data are available on the impact of diabetes on incident stroke, and even fewer studies exist on first stroke (6). Such information is important for the establishment of primary prevention programs for stroke.

Few studies have examined the relation between fasting blood glucose below the current diabetic threshold and first stroke. This issue is important because of the escalating prevalence of prediabetes, which is an intermediate state between normoglycemia and hyperglycemia (7), and the uncertainty regarding whether the proactive identification and management of prediabetes are warranted in stroke prevention (8).

There has been considerable interest in whether folic acid (which is a synthetic form of folate and an essential B vitamin) supplementation can reduce risk of stroke in individuals with elevated glucose concentrations or diabetes and particularly in populations who reside in low-folate regions and are without the mandatory folic acid fortification of grain products. Further interest in this topic has been increased by the main finding of the CSPPT (China Stroke Primary Prevention Trial)[18] (9), which showed that folic acid treatment could reduce risk of first stroke by 21% in the overall CSPPT participants.

The current study aimed to use data from the CSPPT (9) to address the following 2 questions: 1) what is the prospective association between fasting blood glucose concentrations and first stroke risk in Chinese hypertensive adults? We were particularly interested in assessing a wide range of blood glucose concentrations (from normal to prediabetes to diabetes) and first stroke risk; and 2) can folic acid treatment reduce risk of first stroke associated with elevated blood glucose concentrations? We hypothesized that elevated baseline fasting blood glucose concentrations can increase risk of first stroke and that folic acid treatment is effective in reducing risk of first stroke that is associated with elevated blood glucose concentrations.

METHODS

Participants

All participants were part of the CSPPT (clinicaltrials.gov; NCT00794885). The CSPPT was approved by the ethics committee of the Institute of Biomedicine, Anhui Medical University, Hefei, China (Federalwide Assurance number is 00001263). All participants provided written informed consent.

The methods and primary results of the CSPPT trial have been previously reported elsewhere (9). Briefly, the CSPPT was a multicommunity, randomized, double-blind controlled trial that was conducted from May 2008 to August 2013 in 32

communities in the Jiangsu and Anhui provinces (2 study centers) of China. Eligible participants were men and women aged 45–75 y old who had hypertension, which was defined as having a seated resting systolic blood pressure (SBP) $\geq$140 mm Hg or diastolic blood pressure (DBP) $\geq$90 mm Hg at both the screening and recruitment visits, or were taking an antihypertensive medication. The major exclusion criteria included a history of physician-diagnosed stroke, myocardial infarction, heart failure, post-coronary revascularization, or congenital heart disease.

Procedures

Eligible participants were first stratified according to 5,10-methylenetetrahydrofolate reductase (*MTHFR*) C677T genotypes (CC, CT, or TT). Then, within each genotype group, participants were randomly assigned, in a 1:1 ratio, to receive one of the following 2 treatments: a daily oral dose of 1 tablet containing 10 mg enalapril and 0.8 mg folic acid or a daily oral dose of 1 tablet containing 10 mg enalapril only. During the trial period, concomitant use of other antihypertensive drugs (mainly calcium channel blockers or diuretics) was allowed but not of B vitamins. Participants were scheduled for follow-up visits every 3 mo.

Laboratory assessment

Overnight fasting venous blood samples were collected at baseline. Laboratory tests were performed at the core laboratory of the National Clinical Research Center for Kidney Disease, Nanfang Hospital, Guangzhou, China, as previously described (9). Fasting glucose, fasting lipids (serum total cholesterol, LDL, HDL, and triglycerides), and serum homocysteine were measured with the use of automatic clinical analyzers (Beckman Coulter). An ABI Prism 7900HT sequence-detection system (Life Technologies) was used to detect *MTHFR* C677T polymorphisms. Serum folate and vitamin B-12 were measured at baseline by a commercial laboratory with the use of a chemiluminescent immunoassay (New Industrial).

Glucose-status classification

Type 2 diabetes mellitus was defined according to a previous physician diagnosis of diabetes (other than during pregnancy) or a fasting glucose concentration $\geq$7.0 mmol/L, which corresponds to the American Diabetes Association criterion for diabetes (10). In participants without a previous diagnosis of diabetes, baseline fasting glucose concentrations were grouped into the following categories: <5.0, $\geq$5.0 and <5.6, and $\geq$5.6 and <7.0 mmol/L. The category $\geq$5.6 and <7.0 mmol/L corresponds to the ADA criterion for impaired fasting glucose or prediabetes (10, 11). Participants with normal glycemia (<5.6 mmol/L) were grouped into <5.0 and $\geq$5.0 and <5.6 mmol/L categories to further explore the dose-response relation.

Outcomes

As detailed in a previous report (9), the primary outcome was a first nonfatal or fatal stroke (ischemic or hemorrhagic) that occurred between baseline and follow-up (a median of 4.5 y) with the exclusion of a subarachnoid hemorrhage and silent stroke. All stroke cases were adjudicated by experts on the Endpoint Adjudication Committee with the use of predefined criteria.

Statistical analyses

Data are presented as means ± SDs for continuous variables and as frequencies (percentages) for categorical variables according to baseline fasting glucose categories. The effects of baseline fasting glucose categories on first stroke were evaluated with the use of Kaplan-Meier curves (log-rank test). HRs and 95% CIs for risk of a primary outcome that was associated with elevated blood glucose concentrations were estimated with the use of Cox proportional hazards models with adjustment for age, sex, study centers, *MTHFR* C677T genotypes, baseline SBP and DBP, BMI (in kg/m²), homocysteine, triglycerides, HDL, total cholesterol, smoking, alcohol drinking; and mean SBP and DBP over the treatment period. Similarly, HRs and 95% CIs of first stroke in response to folic acid supplementation across baseline fasting glucose categories were estimated, and their interactions were tested. A 2-tailed $P < 0.05$ was considered to be statistically significant in all analyses. Data were analyzed with the use of the statistical packages R (The R Foundation; http://www.r-project.org; version 3.1.2 2014–10-31) and Empower (R) (www.empowerstats.com; X&Y Solutions Inc.).

RESULTS

Study participants and baseline characteristics

This analysis used the data from the CSPPT. Of the total sample of 20,702, a total of 375 participants (1.8%) with missing baseline glucose measurements were excluded; thus, the final analysis included 20,327 hypertensive adults without a history of stroke or myocardial infarction (**Supplemental Figure 1**). At baseline, 5353 participants (26.3%) had glucose concentrations <5.0 mmol/L, 6164 participants (30.3%) had glucose concentrations ≥5.0 and <5.6 mmol/L, 6553 participants (32.2%) had glucose concentrations ≥5.6 and <7.0 mmol/L, and 2257 participants (11.1%) had glucose concentrations ≥7.0 mmol/L or had diabetes.

Table 1 presents the population characteristics stratified according to the categories of baseline fasting glucose concentrations. There were differences in baseline characteristics between participants across the 4 glucose-concentration categories. However, an approximately equal number of participants were in the enalapril and enalapril–folic acid groups, and baseline characteristics were comparable between the 2 treatment groups (Supplemental Figure 1, **Supplemental Table 1**).

Effects of baseline glucose concentrations on first stroke

During a median treatment duration of 4.5 y, 616 participants developed first strokes (of which 497 were ischemic strokes). The Kaplan-Meier curve of the cumulative event rate of first stroke within each baseline glucose strata is shown in **Figure 1**. High fasting glucose concentrations (≥7.0 mmol/L) or diabetes compared with low fasting glucose concentrations (<5.0 mmol/L) was an independent predictor of first stroke (6.0% compared with 2.6%, respectively; HR: 1.9; 95% CI: 1.3, 2.8; $P < 0.001$) (**Table 2**) after adjustment for age, sex, study center, *MTHFR* C677T genotypes, baseline SBP and DBP, BMI, homocysteine, triglycerides, HDL, smoking, alcohol drinking, and mean SBP and DBP during treatment. These findings were mainly observed for ischemic stroke. Impaired fasting glucose (either defined by the 1997 ADA criterion of ≥6.1 and <7.0 mmol/L or by the 2003

ADA criterion of ≥5.6 and <7.0 mmol/L) was associated with a slightly increased risk of stroke, but the association was not statistically significant. In individuals with normal fasting glucose concentrations, subjects with glucose concentrations <5.0 mmol/L had the lowest risk of stroke compared with that of all other glucose categories.

Impact of folic acid treatment on risk of first stroke associated with hyperglycemia or diabetes

We examined the degree to which folic acid supplementation can reduce risk of first stroke in various glucose strata ranging from normal to elevated glucose concentrations and diabetes. As shown in **Supplemental Figure 2** and Table 2, we first observed a differential association between fasting glucose concentrations and risk of first stroke between the 2 treatment groups. Compared with the no–folic acid group, the association was considerably attenuated in the folic acid–treatment group (HR: 1.91 compared with 1.35, respectively, for fasting blood glucose concentrations ≥7.0 mmol/L or diabetes). Furthermore, as shown in **Table 3**, for a given glucose category, folic acid supplementation significantly reduced risk of stroke, which was observed across a wide range of elevated glucose concentrations except in subjects with glucose concentrations <5.0 mmol/L. Notably, risk reduction was the greatest in those with fasting blood glucose concentrations ≥7.0 mmol/L or diabetes (34%; HR: 0.66; 95% CI: 0.46, 0.97; $P < 0.05$), which was supported by our finding that there was a significant interactive effect of fasting plasma glucose concentrations and folic acid treatment on first stroke and ischemic stroke (P-interaction = 0.01).

DISCUSSION

Previous studies have shown a positive association between baseline diabetes or hyperglycemia with the risk of stroke during follow-up in Asian countries such as Korea and Japan (6, 12, 13). To our knowledge, our study, with the use of data from the CSPPT, is the first large-scale longitudinal study in Chinese hypertensive adults to examine the relation between baseline fasting blood glucose concentrations and the incidence of first stroke over a 4.5-y follow-up and to test whether folic acid treatment can reduce the incidence of first stroke across a range of fasting glucose concentrations from normal and prediabetes to ≥7.0 mmol/L or diabetes. To our knowledge, our study has contributed the following new information to the field.

Independent effect of fasting blood glucose concentrations on incidence of first stroke

Diabetes is a well-recognized risk factor for stroke (3). However, several important data gaps exist. First, the magnitude of risk varies widely between studies (14–19), which may have been due to multiple reasons including differences in population characteristics, the diagnostic criterion for glucose concentrations, and definitions of stroke endpoints. Although 77% of all strokes are first events, limited data are available on fasting blood glucose and first stroke. In our study, we showed that diabetes or a fasting blood glucose concentration ≥7.0 mmol/L was associated with significantly increased risk of first stroke with an HR of 1.9 even after adjustment for major covariables. This observed association is consistent with the findings from a large-scale prospective study in a Japanese population that consisted of 13,129 men and 22,528

TABLE 1
Baseline and follow-up characteristics of study participants for total samples and subgroups according to baseline fasting glucose categories[1]

Characteristic	Total	Baseline fasting glucose category, mmol/L			
		<5.0	≥5.0, <5.6	≥5.6, <7.0	≥7.0 or diabetes
Participants, n	20,327	5353	6164	6553	2257
Women, n (%)	12,015 (59.1)	2946 (55.0)	3707 (60.1)	3941 (60.1)	1421 (63.0)
Age, y	60.0 ± 7.5[2]	60.1 ± 7.7	59.8 ± 7.4	60.1 ± 7.5	60.2 ± 7.4
BMI, kg/m^2	24.9 ± 3.7	23.9 ± 3.6	24.9 ± 3.6	25.4 ± 3.7	26.2 ± 3.6
MTHFR C677T genotypes, n (%)					
CC	5567 (27.4)	1704 (31.8)	1666 (27.0)	1653 (25.2)	544 (24.1)
CT	9983 (49.1)	2576 (48.1)	3052 (49.5)	3275 (50.0)	1080 (47.9)
TT	4777 (23.5)	1073 (20.0)	1446 (23.5)	1625 (24.8)	633 (28.0)
Smoking, n (%)					
Never	14,028 (69.1)	3564 (66.6)	4355 (70.7)	4498 (68.7)	1611 (71.4)
Former	1428 (7.0)	434 (8.1)	404 (6.6)	423 (6.5)	167 (7.4)
Current	4859 (23.9)	1351 (25.3)	1401 (22.7)	1629 (24.9)	478 (21.2)
Alcohol drinking, n (%)					
Never	14,028 (69.1)	3564 (66.6)	4355 (70.7)	4498 (68.7)	1611 (71.4)
Former	1428 (7.0)	434 (8.1)	404 (6.6)	423 (6.5)	167 (7.4)
Current	4859 (23.9)	1351 (25.3)	1401 (22.7)	1629 (24.9)	478 (21.2)
Baseline laboratory results					
Fasting glucose, mmol/L	5.8 ± 1.7	4.6 ± 0.4	5.3 ± 0.2	6.1 ± 0.4	9.2 ± 3.0
Total cholesterol, mmol/L	5.5 ± 1.2	5.2 ± 1.1	5.5 ± 1.1	5.7 ± 1.2	6.0 ± 1.4
Triglycerides, mmol/L	1.7 ± 1.2	1.5 ± 0.8	1.6 ± 1.5	1.7 ± 1.0	2.0 ± 1.2
HDL, mmol/L	1.3 ± 0.4	1.4 ± 0.4	1.3 ± 0.4	1.3 ± 0.4	1.3 ± 0.4
Creatinine, μmol/L	66.0 ± 19.3	66.6 ± 18.2	65.9 ± 20.6	65.9 ± 15.1	64.9 ± 26.9
eGFR, mL · min^{-1} · 1.73 m^{-2}	93.5 ± 13.3	93.4 ± 13.6	93.7 ± 12.6	93.2 ± 12.7	93.9 ± 16.2
Homocysteine, μmol/L	14.5 ± 8.4	14.5 ± 8.2	14.3 ± 8.3	14.6 ± 8.8	14.2 ± 7.8
Vitamin B-12, pg/mL	412.3 ± 156.2	409.8 ± 145.0	406.2 ± 159.5	408.6 ± 157.0	445.8 ± 165.6
Folate, ng/mL	8.6 ± 3.9	9.2 ± 4.3	8.4 ± 3.8	8.3 ± 3.8	8.6 ± 3.5
SBP, mm Hg					
At baseline	166.9 ± 20.4	164.2 ± 19.8	166.7 ± 20.1	168.5 ± 20.7	169.3 ± 20.9
Over treatment period	139.4 ± 10.8	138.3 ± 10.5	138.9 ± 10.8	140.6 ± 11.0	141.1 ± 11.1
DBP, mm Hg					
At baseline	94.1 ± 11.9	93.2 ± 11.8	94.3 ± 11.9	94.8 ± 11.9	93.7 ± 12.1
Over treatment period	82.9 ± 7.4	82.7 ± 7.6	83.2 ± 7.4	83.3 ± 7.3	82.1 ± 7.2
Treatment group, n (%)					
Enalapril	10,167 (50.0)	2645 (49.4)	3086 (50.1)	3290 (50.2)	1146 (50.8)
Enalapril and folic acid	10,160 (50.0)	2708 (50.6)	3078 (49.9)	3263 (49.8)	1111 (49.2)

[1] DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; *MTHFR*, 5,10-methylenetetrahydrofolate reductase; SBP, systolic blood pressure.
[2] Mean ± SD (all such values).

women aged 40–69 y at baseline. During a median 12.0-y follow-up, diabetes was associated with 2–3 times higher risk of ischemic stroke for both sexes than that of individuals with normal glucose concentrations (6).

Uncertainty remains regarding the role of prediabetes in first stroke and whether the proactive identification and management of prediabetes are warranted in stroke prevention (8). A relatively recent study showed that, compared with normoglycemic individuals, international expert committee–defined prediabetes was associated with increased stroke risk in South Asians but not in Europeans (13). A more recent meta-analysis showed that impaired fasting glucose, as defined by the ADA, was associated with increased risk of stroke (RR: 1.06) (20).

Our study took the opportunity to examine the effect of the entire spectrum of baseline plasma glucose concentrations on first stroke in over 20,000 Chinese hypertensive adults. Our data showed a J-shaped curve; i.e., individuals with elevated glucose concentrations below the diabetes threshold had only slightly increased risk of first stroke (NS), whereas subjects with concentrations above the threshold had significantly increased risk of stroke. This J-shaped relation was also observed in a meta-analysis of 698,782 people from 102 prospective studies that examined the association between fasting blood glucose concentration and stroke (21). Our findings are also in line with a recent analysis of 294,998 participants (from 73 prospective studies) without a known history of diabetes mellitus or cardiovascular disease (CVD) at the baseline assessment. The study analysis provided a comparison of 4 glycemia measures (i.e., glycated hemoglobin concentrations and fasting, random, and postload plasma glucose concentrations) and observed approximately J-shaped associations between each of these glycemia measures and CVD risk (not specific to stroke) (22).
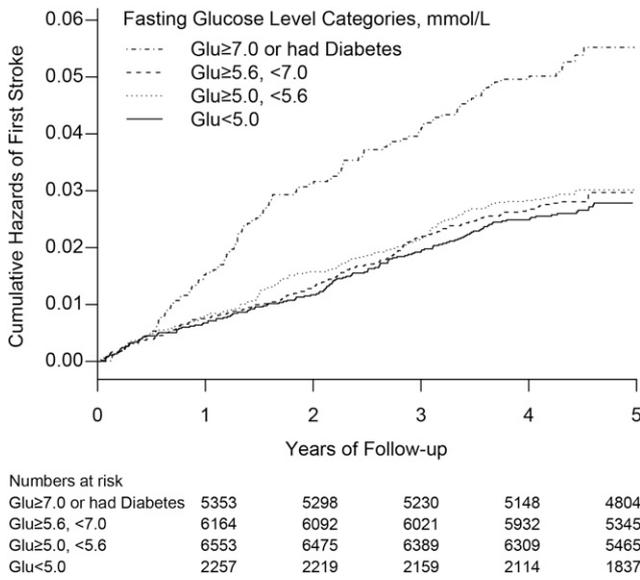
FIGURE 1 Kaplan-Meier curves of the cumulative event rate of first stroke stratified by the following baseline Glu categories: <5.0 mmol/L (n = 5353), ≥5.0 and <5.6 mmol/L (n = 6164), ≥5.6 and <7.0 mmol/L (n = 6553), and ≥7.0 mmol/L or diabetes (n = 2257)] in the China Stroke Primary Prevention Trial (2008–2013). Glu, fasting plasma glucose concentration.

Impact of folic acid treatment on risk of first stroke associated with hyperglycemia or diabetes

In the current study, we showed that folic acid treatment reduced risk of stroke across a wide range of glucose concentrations ≥5.0 mmol/L, but risk reduction was greatest (a 34% reduction) in subjects with concentrations ≥7.0 mmol/L or diabetes.

Furthermore, we showed that there was a significant interactive effect of fasting glucose and folic acid treatment on first stroke ($P = 0.01$). Our findings, if confirmed, suggest that hypertensive adults with hyperglycemia or diabetes may particularly benefit from folic acid treatment to prevent first stroke.

The biological mechanism by which folic acid supplementation can prevent first stroke in hypertensive patients, especially in individuals with hyperglycemia or diabetes, remains to be determined. We speculate that the beneficial effect of folate may stem from its multifaceted biological pathways. For example, folic acid supplementation is known to be effective in correcting folate deficiency, lowering homocysteine concentrations, and overcoming the low-enzyme function that is secondary to an *MTHFR* C677T mutation, all of which are known to affect cardiovascular outcomes (23, 24) including stroke (9). Folic acid promotes the conversion of methionine to *S*-adenosylmethionine, which is the major donor for the methylation of lipids, DNA, and histones (25), that affects a wide range of cellular functions such as gene expression and repair and plays an essential role in DNA synthesis via de novo purine and thymidine biosyntheses (26). Folate may also act as an antioxidant or have direct interactions with endothelial nitric oxide synthase (27), which may partially counteract the adverse effect of hyperglycemia on the vascular system.

Limitations

We note several limitations of the current study. Our study was underpowered for the assessment of hemorrhagic stroke. The generalizability of our findings to other populations with different demographic and clinical characteristics requires caution. Our study did not perform oral-glucose-tolerance tests, and thus, we were unable to examine the effect of 2-h postload plasma glucose

TABLE 2
Effect of baseline fasting plasma glucose concentrations on first stroke (overall and subtypes) in the enalapril group (n = 10,167)

Glucose category	n	With outcome, n (%)	Model 1		Model 2	
			HR (95% CI)	P	HR (95% CI)	P
First stroke						
<5.0 mmol/L	2645	68 (2.6)	1.0	—	1.0	—
≥5.0 and <5.6 mmol/L	3086	101 (3.3)	1.11 (0.81, 1.53)	0.5021	1.09 (0.79, 1.50)	0.5961
≥5.6 and <7.0 mmol/L	3290	108 (3.3)	1.05 (0.76, 1.45)	0.7554	1.02 (0.74, 1.41)	0.9023
≥7.0 mmol/L or diabetes	1146	69 (6.0)	1.95 (1.37, 2.78)	0.0002	1.91 (1.32, 2.77)	0.0006
P-trend	—	—	0.0001	—	0.0002	—
Ischemic stroke						
<5.0 mmol/L	2645	46 (1.7)	1.0	—	1.0	—
≥5.0 and <5.6 mmol/L	3086	79 (2.6)	1.22 (0.84, 1.77)	0.2989	1.17 (0.80, 1.70)	0.4029
≥5.6 and <7.0 mmol/L	3290	97 (2.9)	1.30 (0.90, 1.88)	0.1687	1.22 (0.84, 1.77)	0.3004
≥7.0 mmol/L or diabetes	1146	63 (5.5)	2.43 (1.63, 3.62)	<0.0001	2.17 (1.43, 3.30)	0.0003
P-trend	—	—	<0.0001	—	0.0001	—
Hemorrhagic stroke						
<5.0 mmol/L	2645	21 (0.8)	1.0	—	1.0	—
≥5.0 and <5.6 mmol/L	3086	22 (0.7)	0.98 (0.52, 1.82)	0.9398	1.02 (0.54, 1.90)	0.9580
≥5.6 and <7.0 mmol/L	3290	11 (0.3)	0.47 (0.22, 1.01)	0.0539	0.53 (0.24, 1.15)	0.1059
≥7.0 mmol/L or diabetes	1146	6 (0.5)	0.76 (0.29, 1.96)	0.5644	1.19 (0.44, 3.19)	0.7292
P-trend	—	—	0.3086	—	0.8593	—

[1] Model 1 was a Cox proportional hazards model that was adjusted for age, sex, and study center. Model 2 was a Cox proportional hazards model adjusted as for model 1 and for baseline systolic blood pressure and diastolic blood pressure, BMI, 5,10-methylenetetrahydrofolate reductase C677T polymorphisms, homocysteine, HDL, triglycerides, total cholesterol, smoking, alcohol drinking, and mean systolic blood pressure and diastolic blood pressure over the treatment period.

TABLE 3
Effect of folic acid treatment on first stroke (overall and subtypes) in participants with elevated fasting plasma glucose concentrations

Glucose concentration category	Enalapril		Enalapril and folic acid		Effect of folic acid[1]	
	n	Stroke, n (%)	n	Stroke, n (%)	HR (95% CI)	P
First stroke						
Total	10,167	346 (3.4)	10,160	270 (2.7)	0.78 (0.67, 0.92)	0.0028
<5.0 mmol/L	2645	68 (2.6)	2708	73 (2.7)	1.03 (0.74, 1.43)	0.8719
≥5.0 and <5.6 mmol/L	3086	101 (3.3)	3078	71 (2.3)	0.74 (0.55, 1.00)	0.0537
≥5.6 and <7.0 mmol/L	3290	108 (3.3)	3263	80 (2.5)	0.75 (0.56, 1.00)	0.0500
≥7.0 mmol/L or diabetes	1146	69 (6.0)	1111	46 (4.1)	0.66 (0.46, 0.97)	0.0330
Test for interaction[2]	—	—	—	—	—	0.0125
Ischemic stroke						
Total	10,167	285 (2.8)	10,160	212 (2.1)	0.75 (0.63, 0.89)	0.0014
<5.0 mmol/L	2645	46 (1.7)	2708	50 (1.8)	1.02 (0.68, 1.53)	0.9239
≥5.0 and <5.6 mmol/L	3086	79 (2.6)	3078	54 (1.8)	0.73 (0.51, 1.03)	0.0733
≥5.6 and <7.0 mmol/L	1883	97 (2.9)	3263	69 (2.1)	0.72 (0.53, 0.98)	0.0362
≥7.0 mmol/L or diabetes	1146	63 (5.5)	1111	39 (3.5)	0.62 (0.42, 0.93)	0.0202
Test for interaction[2]	—	—	—	—	—	0.0131
Hemorrhagic stroke						
Total	10,167	60 (0.6)	10,160	57 (0.6)	0.95 (0.66, 1.37)	0.7921
<5.0 mmol/L	2645	21 (0.8)	2708	23 (0.8)	1.08 (0.59, 1.96)	0.8027
≥5.0 and <5.6 mmol/L	3086	22 (0.7)	3078	17 (0.6)	0.80 (0.43, 1.52)	0.5008
≥5.6 and <7.0 mmol/L	1883	11 (0.3)	3263	10 (0.3)	0.95 (0.40, 2.26)	0.9109
≥7.0 mmol/L or diabetes	1146	6 (0.5)	1111	7 (0.6)	1.03 (0.34, 3.17)	0.9550
Test for interaction[2]	—	—	—	—	—	0.5708

[1] Cox proportional hazards model with the treatment group as the primary exposure and adjusted for age, sex, study center, 5,10-methylenetetrahydrofolate reductase C677T polymorphisms, baseline systolic blood pressure and diastolic blood pressure, BMI, homocysteine, HDL, triglycerides, total cholesterol, smoking, alcohol drinking, and mean systolic blood pressure and diastolic blood pressure over the treatment period.

[2] Test for interaction between baseline fasting plasma glucose concentration (continuous) and folic acid treatment (yes or no) on stroke.

(2hPG) concentrations on risk of first stroke. A study of 9 Finnish and Swedish cohorts, which included 3743 men and 3916 women aged 25–90 y who had fasting plasma glucose concentrations <6.1 mmol/L and 2hPG concentrations <7.8 mmol/L and were free of CVD at enrollment, showed that, during a median follow-up of 16.4 y, individuals with glucose concentrations in the normoglycemic range but whose 2hPG concentrations did not return to their fasting plasma glucose concentrations during an oral-glucose-tolerance test had increased risk of ischemic stroke (28). Note that there is an inherit limitation of a post hoc analysis; we could not exclude the possibility of residual confounding despite our control of important epidemiologic and clinical covariables in the analyses. Our findings cannot be regarded as causal. Caution is needed in interpreting the results.

Summary and clinical and public health implications

In conclusion, in Chinese hypertensive patients without a history of myocardial infarction or stroke, we show that having a baseline fasting blood glucose concentration ≥7.0 mmol/L or diabetes is a significant and independent predictor of first stroke. We further show that folic acid therapy can reduce risk of first stroke and ischemic stroke that are associated with elevated blood glucose concentrations (>5.0 mmol/L) and that the greatest benefit is seen in participants with fasting blood glucose concentrations ≥7.0 mmol/L or clinical diabetes.

In the current American Heart Association/American Stroke Association guidelines on the primary prevention of stroke, there is no definite recommendation on the use of folic acid in the primary prevention of stroke in general or in diabetes patients in particular (3). In contrast with Western populations, China has not implemented the mandatory folic acid fortification of grain products, and the Chinese population has relatively low dietary and supplemental folate intakes. Should our study findings be replicated in another low-folate region of the world, folic acid could be considered to be a simple strategy to further reduce risk of first stroke in hypertensive patients with elevated blood glucose concentrations and, in particular, in individuals with blood glucose concentrations that exceed the diabetes threshold. In light of the global epidemic of type 2 diabetes and because >1 billion people have hypertension and many regions of the world live without folic acid fortification, our findings merit further investigation.

REFERENCES

1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2095–128.
2. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C, et al. Heart disease and stroke statistics–2010 update: a report from the American Heart Association. Circulation 2010;121:e46–215.
3. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, Creager MA, Eckel RH, Elkind MS, Fornage M, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:3754–832.
4. Yang G, Wang Y, Zeng Y, Gao GF, Liang X, Zhou M, Wan X, Yu S, Jiang Y, Naghavi M, et al. Rapid health transition in China, 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet 2013; 381:1987–2015.
5. International Diabetes Federation. IDF diabetes atlas. 7th ed. Brussels (Belgium): International Diabetes Federation; 2015.
6. Cui R, Iso H, Yamagishi K, Saito I, Kokubo Y, Inoue M, Tsugane S. Diabetes mellitus and risk of stroke and its subtypes among Japanese: the Japan public health center study. Stroke 2011;42:2611–4.
7. Selvin E, Parrinello CM, Sacks DB, Coresh J. Trends in prevalence and control of diabetes in the United States, 1988-1994 and 1999-2010. Ann Intern Med 2014;160:517–25.
8. Yudkin JS, Montori VM. The epidemic of pre-diabetes: the medicine and the politics. BMJ 2014;349:g4485.
9. Huo Y, Li J, Qin X, Huang Y, Wang X, Gottesman RF, Tang G, Wang B, Chen D, He M, et al. Efficacy of folic acid therapy in primary prevention of stroke among adults with hypertension in China: the CSPPT randomized clinical trial. JAMA 2015;313: 1325–35.
10. Qin X, Li J, Zhang Y, Chen D, Wang B, He M, Fu J, Tang G, Cai Y, Shi X, et al. Effect of folic acid supplementation on risk of new-onset diabetes in adults with hypertension in China: findings from the China stroke primary prevention trial (CSPPT). J Diabetes 2016;8: 286–94.
11. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33(Suppl 1):S62–9.
12. Sung J, Song YM, Ebrahim S, Lawlor DA. Fasting blood glucose and the risk of stroke and myocardial infarction. Circulation 2009;119:812–9.

13. Eastwood SV, Tillin T, Sattar N, Forouhi NG, Hughes AD, Chaturvedi N. Associations between prediabetes, by three different diagnostic criteria, and incident CVD differ in South Asians and Europeans. Diabetes Care 2015;38:2325–32.
14. Rodriguez BL, D'Agostino R, Abbott RD, Kagan A, Burchfiel CM, Yano K, Ross GW, Silbershatz H, Higgins MW, Popper J, et al. Risk of hospitalized stroke in men enrolled in the Honolulu Heart Program and the Framingham Study: a comparison of incidence and risk factor effects. Stroke 2002;33:230–6.
15. Tuomilehto J, Rastenyte D, Jousilahti P, Sarti C, Vartiainen E. Diabetes mellitus as a risk factor for death from stroke. Prospective study of the middle-aged Finnish population. Stroke 1996;27:210–5.
16. Kuusisto J, Mykkanen L, Pyorala K, Laakso M. Non-insulin-dependent diabetes and its metabolic control are important predictors of stroke in elderly subjects. Stroke 1994;25:1157–64.
17. Jørgensen H, Nakayama H, Raaschou HO, Olsen TS. Stroke in patients with diabetes. The Copenhagen Stroke Study. Stroke 1994;25: 1977–84.
18. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the multiple risk factor intervention trial. Diabetes Care 1993;16:434–44.
19. Abbott RD, Donahue RP, MacMahon SW, Reed DM, Yano K. Diabetes and the risk of stroke. The Honolulu Heart Program. JAMA 1987;257: 949–52.
20. Huang Y, Cai X, Mai W, Li M, Hu Y. Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis. BMJ 2016;355:i5953.
21. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010;375:2215–22.
22. Di Angelantonio E, Gao P, Khan H, Butterworth AS, Wormser D, Kaptoge S, Kondapally Seshasai SR, Thompson A, Sarwar N, Willeit P, et al. Glycated hemoglobin measurement and prediction of cardiovascular disease. JAMA 2014;311:1225–33.
23. Ganguly P, Alam SF. Role of homocysteine in the development of cardiovascular disease. Nutr J 2015;14:6.
24. McCully KS. Homocysteine and the pathogenesis of atherosclerosis. Expert Rev Clin Pharmacol 2015;8:211–9.
25. McKay JA, Williams EA, Mathers JC. Folate and DNA methylation during in utero development and aging. Biochem Soc Trans 2004;32: 1006–7.
26. Bailey LB, Gregory JF 3rd. Folate metabolism and requirements. J Nutr 1999;129:779–82.
27. Verhaar MC, Stroes E, Rabelink TJ. Folates and cardiovascular disease. Arterioscler Thromb Vasc Biol 2002;22:6–13.
28. Ning F, Zhang L, Dekker JM, Onat A, Stehouwer CD, Yudkin JS, Laatikainen T, Tuomilehto J, Pyorala K, Qiao Q. Development of coronary heart disease and ischemic stroke in relation to fasting and 2-hour plasma glucose levels in the normal range. Cardiovasc Diabetol 2012;11:76.