In utero exposure to the Great Chinese Famine and risk of intracerebral hemorrhage in midlife

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Abstract

Objective

To investigate whether in utero exposure to the Great Chinese Famine in 1959 to 1961 was associated with risk of intracerebral hemorrhage (ICH) in adulthood.

Methods

In this cohort analysis, we included 97,399 participants of the Kailuan Study who were free of cardiovascular disease and cancer at baseline (2006). Cases of incident ICH were confirmed by medical record review. We used the Cox proportional hazards model to calculate the hazard ratio (HR) and 95% confidence interval (CI) for ICH according to in utero famine exposure status.

Results

Among 97,399 participants in the current analyses, 6.3% ($n = 6,160$) had been prenatally exposed to the Great Chinese Famine. During a median 9.0 years of follow-up (2006–2015), we identified 724 cases of incident ICH. After adjustment for potential confounders, the HR of ICH was 1.99 (95% CI 1.39–2.85) for in utero famine-exposed individuals vs individuals who were not exposed to the famine. When exposure to famine and severity of famine were examined jointly, the adjusted HR was 2.99 (95% CI 1.21–7.39) for in utero exposure to severe famine and 1.94 (95% CI 1.32–2.84) for in utero exposure to less severe famine relative to those without exposure to famine.

Conclusions

Individuals with in utero exposure to famine, especially those exposed to severe famine, were more likely to have ICH in midlife, highlighting the role of nutritional factors in susceptibility to this severe cerebral condition.

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Glossary

CI = confidence interval; HR = hazard ratio; ICD-10 = International Classification of Diseases, 10th revision; ICH = intracerebral hemorrhage.

Intracerebral hemorrhage (ICH) is the second most common type of stroke. As a complex disease, multiple underlying risk factors contribute to the occurrence of ICH,^{1–4} and the exact mechanisms of ICH remain unclear. The understanding of such factors is key to prevention, the single most important approach to decrease the mortality and morbidity associated with ICH.

The developmental origins of health and disease hypothesis suggests that adversity in early life, particularly in utero, affects health status later in life.⁵ Previous studies have reported associations between prenatal exposure to malnutrition and maternal stress and increased risk of cardiovascular disease⁶ and odds of several ICH risk factors such as hypertension⁷ and type 2 diabetes mellitus^{8,9} in adult life. On the basis of these observations, we hypothesized that in utero exposure to unfavorable events might be associated with the risk of ICH in later life.

The Great Chinese Famine, one of the largest famines in human history, which occurred from Spring 1959 to the end of 1961, led to millions of excess deaths in China.¹⁰ In the current study, we examined in an ongoing cohort, the Kailuan study of ≈100,000 Chinese participants, whether in utero exposure to the Great Chinese Famine, an adversity characterized by malnutrition and stress, was associated with increased risk of ICH in midlife.

Methods

Study population

The Kailuan study is an ongoing prospective cohort study to explore risk factors for cardiovascular diseases. All 155,418 employees (including the retired) ≥18 years of age (133,551 men and 21,867 women) of the Kailuan Group were invited to participate in 2006. A total of 101,510 participants (age 18–98 years, 81,110 men and 20,400 women) agreed to participate and completed the baseline survey between June 2006 and October 2007 (referred as the 2006 survey here).^{11–13} As detailed elsewhere,^{11,13} there were no demographic differences between study participants and nonparticipants except for a small difference by sex (79.9% of men participated vs 85.9% men in the Kailuan community). All participants responded to the questionnaire (including demographic characteristics, lifestyle factors, medical comorbid conditions, and use of medications) and had physical examinations and laboratory tests biennially; adverse events were recorded annually.

In the current study, we excluded 4,111 participants with a history of stroke, myocardial infarction, or cancer before

2006 (study baseline), leaving 97,399 participants (19,859 women and 77,540 men; mean age 51.4 years) in the analysis.

Standard protocol approvals, registrations, and patient consents

This study protocol was approved by the ethics committee of the Kailuan Medical Group, Kailuan Company. All participants provided their written informed consent.

Famine exposure and severity

Consistent with previous Chinese famine studies,^{8,10} birth year was the basis for classification to famine exposure. Those born between 1959 and 1961 were classified as the in utero famine-exposed group (45–47 years of age in 2006)¹⁴; others were classified into 3 non-prenatal-exposed groups (born before 1953, born 1953–1955, or born 1956–1958) and 1 nonexposed group (born after 1961, used as the reference group in the current analyses).

The Great Chinese Famine affected all provinces of China; however, the severity varied by province.¹⁵ We classified severity of famine by the rate of excess mortality at the level of the province.⁸ Specifically, we calculated the percentage change in the mortality rate from the average level in 1956 to 1958 to the highest value over the period of 1959 to 1961.¹⁵ Provinces with an excess mortality rate of ≥50% were classified as severely affected areas; the remaining provinces were classified as less severely affected area, as analyzed previously.⁸

Assessment of incident ICH

The outcome of the current study was the first occurrence of ICH, either nonfatal or ICH-related death. Assessments of ICH incidence were conducted once a year during the follow-up period from 2006 to 2015, as detailed elsewhere.^{16,17} Potential ICH incidence was ascertained from 4 complementary sources: (1) Municipal Social Insurance Institution, which covered all study participants; (2) Hospital Discharge Register centers; (3) death certificates; and (4) questionnaire survey (biennially since 2006). Potential cases of ICH included those who were identified by the ICD-10 based on the first 3 sources or those who self-reported as having ICH in the questionnaire survey. Three neurologists reviewed the medical records to confirm the ICH diagnosis, which was based on the World Health Organization criteria combined with a brain CT or MRI scan. Nonfatal ICH was defined as the sudden onset of a focal neurologic deficit and demonstration of acute primary intraparenchymal hemorrhage on brain imaging. Cases of fatal ICH were confirmed by medical records, autopsy reports, or death certificates with ICH as the underlying cause of death. In the current study, we did not include traumatic intracranial hemorrhages and epidural, subdural, and subarachnoid hematomas.

An experienced radiologist examined and recorded the parenchymal location of hematomas on the basis of a clear report or review of the CT/MRI imaging, as described elsewhere.¹⁶ In the secondary analysis of prenatal famine exposure and hematoma location, we included 423 cases of ICH with clear location information available from 724 patients in total. On the basis of the location of the hematomas, cases were categorized as deep (e.g., basal, ganglia, thalami, cerebellar, and brainstem) or nondeep (e.g., lobar) ICH.

Assessment of covariates

Data on age, sex, birthplace, smoking, alcohol intake, salt intake, physical activity, education level, monthly income, and medical history (e.g., hypertension, diabetes mellitus, and active treatments such as hypoglycemic, antihypertensive and lipid-lowering medications) were collected on a self-reported questionnaire; height, weight, and blood pressure were assessed by trained nurses during the surveys, as detailed previously.¹⁸ Body mass index was calculated as weight in kilograms divided by height in meters squared.

Information on aspirin use was collected with a self-reported questionnaire and updated biennially since 2006. We did not collect information on anticoagulant use. We thus considered those with atrial fibrillation or flutter, deep venous thrombosis, pulmonary infarction, or heart valve disease as anticoagulant users because these conditions are major indications for anticoagulant use.

Blood samples were collected in the morning of the survey after at least a 12-hour fast and transfused into vacuum tubes containing ethylene diamine tetra acetic acid. Plasma glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, creatinine, and high-sensitivity C-reactive protein were measured by auto-analyzer (Hitachi 747; Hitachi, Tokyo, Japan) at the central laboratory of the Kailuan general hospital. Estimated glomerular filtration rate was calculated by the Chronic Kidney Disease Epidemiology Collaboration creatinine equation.

Statistical analysis

All analyses were conducted with SAS, version 9.3 (SAS Institute, Inc, Cary, NC). Two-sided values of $p < 0.05$ were considered statistically significant.

The person-year of follow-up for each participant was determined from the last day of the 2006 survey to the date of ICH onset, death, loss to follow-up ($n = 5,316$, 5.5%), or end of follow-up (December 31, 2015), whichever came first. We censored participants with onset of cancer, myocardial infarction, or cerebral infarction during the follow-up at the date of diagnosis of these diseases.

We used the Cox proportional-hazards model to predict the incidence of ICH and to investigate the association between in utero exposure to famine and ICH risk after adjusting for potential cofounders, including sex, systolic blood pressure

(≤ 120 , 121–139, or ≥ 140 mm Hg), diastolic blood pressure (≤ 80 , 81–89, or ≥ 90 mm Hg), 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/mL), fasting blood glucose (< 5.6 , 5.6–6.0, 6.1–6.9, or ≥ 7.0 mmol/L), estimated glomerular filtration rate (≤ 30 , 31–59, 60–89, or ≥ 90 mL/min/1.73 m²), body mass index (≥ 30.0 , 25.0–29.9, or < 25.0 kg/m²), and use of aspirin, anticoagulant, antihypertensive, hypoglycemic, and lipid-lowering medications (yes/no for each). We used the nonexposed group (born after 1961) as the reference group. The proportional-hazards assumption was satisfied. The percentage of missing data for a single variable ranged from 0% (e.g., age and sex) to 4.3% (physical activity). We thus coded the missing data of the covariates as an extra category. We also conducted a sensitivity analysis in which we restricted participants to those with complete data on all covariates.

Because use of aspirin and anticoagulants might increase the risk of ICH,¹⁹ we conducted a sensitivity analysis by excluding the participants who used these medicines.

To explore whether the association between prenatal exposure to famine and ICH risk was modified by sex, overweight (as indicated by body mass index > 25 kg/m²), or hypertension in later life, we tested the multiplicative interaction by comparing the -2 log likelihood of the multivariate-adjusted models with and without the cross-product interaction term of in utero famine exposure with the studied factors. We also conducted subgroup analyses stratified by these factors.

To evaluate whether the associations between famine and ICH risk were in dose-dependent manner, we classified participants according to the joint categories of in utero exposure to famine and the severity of famine.

Data availability

Deidentified data are available to researchers on request by contacting with Dr. Wu or Dr. Gao.

Results

Among 97,399 participants in the current analyses, 6.3% ($n = 6,160$) had been prenatally exposed to the Great Chinese Famine. Compared with the reference group (individuals born after 1961), those with the in utero exposure to famine were more likely to be smokers and nondrinkers and had higher body mass index, systolic and diastolic blood pressures, fasting blood glucose, and prevalence of using antihypertensives, aspirin, hypoglycemics, or lipid-lowering medications, as well as lower physical activity (table 1).

During a median of 9.0 years (interquartile range 8.7–9.2 years) of follow-up, we identified 724 cases of incident ICH. As expected, the subgroup of those not exposed in utero born

Table 1 Baseline characteristics in 2006 by prenatal exposure to the Great Chinese Famine among 97,399 Kailuan participants

	Non exposed (born after 1961, reference)	In utero exposed (born between 1959 and 1961)	Not in utero exposed (born between 1956 and 1958)	Not in utero exposed (born between 1953 and 1955)	Not in utero exposed (born before 1953)	<i>p</i> Value
No.	29,229	6,160	10,719	11,600	39,691	<0.001
Women, %	26.2	26.4	20.9	16.5	16.2	<0.001
Age (mean in 2006), y	36.9 ± 6.5	46.6 ± 0.9	49.5 ± 1.0	52.3 ± 0.9	62.9 ± 7.6	<0.001
Smoking status, yes/no, %	39.7/60.3	40.3/59.7	42.4/57.6	42.9/57.1	37.5/62.5	<0.001
Alcohol intake, yes/no, %	35.5/64.5	30.8/69.2	31.0/69.0	31.5/68.5	24.8/75.2	<0.001
Physical activity, <3/≥3 times/wk, %	6.8/93.2	7.5/92.5	10.6/89.4	10.9/89.1	5.1/94.9	<0.001
Body mass index, kg/m ²	24.8 ± 3.7	25.1 ± 3.4	25.1 ± 3.3	25.2 ± 3.2	25.1 ± 3.5	<0.001
LDL-C, mmol/L	2.37 ± 0.77	2.39 ± 0.79	2.37 ± 0.88	2.37 ± 0.89	2.33 ± 1.00	<0.001
HDL-C, mmol/L	1.49 ± 0.36	1.54 ± 0.37	1.54 ± 0.38	1.54 ± 0.40	1.59 ± 0.44	<0.001
Total cholesterol, mmol/L	4.78 ± 1.11	5.02 ± 1.11	5.02 ± 1.13	5.03 ± 1.11	5.00 ± 1.18	<0.001
Triglycerides, ^a mmol/L	1.21 (1.07)	1.27 (1.08)	1.30 (1.08)	1.29 (1.05)	1.29 (0.99)	<0.001
Fasting blood glucose, mmol/L	5.23 ± 1.24	5.53 ± 1.72	5.53 ± 1.65	5.58 ± 1.69	5.59 ± 1.88	<0.001
Systolic blood pressure, mm Hg	121.8 ± 17.3	127.6 ± 19.1	129.6 ± 19.6	131.5 ± 20.1	137.6 ± 21.6	<0.001
Diastolic blood pressure, mm Hg	80.6 ± 11.5	83.7 ± 11.8	84.3 ± 11.8	84.9 ± 11.9	84.7 ± 11.5	<0.001
hs-CRP, ^a mg/mL	0.60 (1.28)	0.60 (1.35)	0.70 (1.63)	0.79 (1.84)	1.09 (2.71)	<0.001
Use of antihypertensive agent, %	3.5	6.6	8.1	10.2	15.0	<0.001
Use of lipid-lowering medications, %	0.3	0.4	0.5	0.6	1.1	<0.001
Use of hypoglycemic medications, %	0.6	1.4	1.6	2.0	3.5	<0.001
Use of aspirin, ^b %	1.1	1.9	2.2	2.4	3.2	<0.001
Use of anticoagulant, ^c %	0.4	0.9	0.6	0.9	1.7	<0.001

Abbreviations: HDL-C = high-density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol.

^a Median (interquartile range).

^b Use of aspirin (yes/no for each) was updated by every survey from 2006.

^c Use of anticoagulant (yes/no for each) was estimated on the basis of heart valve disease, deep venous thrombosis or pulmonary infarction disease, and atrial fibrillation or flutter and was updated by every survey from 2006.

before 1953 (i.e., the oldest group) had the highest ICH incidence (figure 1). Participants born in 1959 or 1960, but not in 1961, had a higher incidence of ICH than those born in 1956 to 1958 or after 1961 (figure 1). When potential confounders were adjusted for, the hazard ratio (HR) of ICH was 1.99 (95% confidence interval [CI] 1.39–2.85) for individuals with in utero exposure to famine vs the nonexposed group (table 2). Similar results were observed in the sensitivity analyses by excluding participants <40 years of age at baseline, those who used aspirin or anticoagulant, or those with missing covariates (table 2). When we used individuals who were ≈3 years older than prenatal famine-exposed individuals as the

reference group (i.e., born between 1956 and 1958), the in utero exposed still had significantly higher ICH risk (adjusted HR 1.49, 95% CI 1.01–2.19). When the ICH location was studied, we observed a similar trend between in utero exposure to famine and higher risk of deep hematoma but not for nondeep hematoma after adjustment for confounders (table 3).

The association between in utero exposure to famine and ICH risk appeared to be modified by hypertension or overweight status in midlife ($P_{\text{interaction}} < 0.05$ for both, table 4). Specifically, the associations were stronger in those

Figure 1 Actual and predicted incidence of intracerebral hemorrhage by birth year (famine period is shaded)

Predicated rate was calculated from age; sex; use of antihypertensive, aspirin, anticoagulant, hypoglycemic, and lipid-lowering medications; smoking; alcohol intake; education; physical activity; sodium intake; family income; systolic blood pressure; diastolic blood pressure; body mass index; estimated glomerular filtration rate; and blood concentrations of high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, glucose, and C-reactive protein.

overweight relative to their counterparts who did not have hypertension or were normal weight. In contrast, we did not observe significant interaction between famine exposure and sex ($p_{\text{interaction}} = 0.19$).

We further classified the 60,079 participants exposed (including in utero and in early childhood) to famine according to the joint categories of exposure status and severity of famine. Compared with the non-famine exposure group, the

Table 2 Adjusted HR and 95% CI for risk of ICH by exposure to the Great Chinese Famine

	Not exposed (born after 1961, reference)	In utero exposed (born between 1959 and 1961)	Not in utero exposed (born between 1956 and 1958)	Not in utero exposed (born between 1953 and 1955)	Not in utero exposed (born before 1953)
Cases/participants, n	86/29,229	46/6,160	58/10,719	90/11,600	444/39,691
Incidence, per 10,000 person-y	3.5	9.0	6.5	9.3	13.9
Sex-adjusted HR	1.00	2.56 (1.79–3.67)	1.82 (1.31–2.54)	2.56 (1.90–3.44)	3.78 (3.00–4.76)
Multivariate-adjusted HR^a	1.00	2.37 (1.65–3.39)	1.66 (1.19–2.32)	2.30 (1.70–3.10)	3.18 (2.49–4.06)
Multivariate-adjusted HR^b	1.00	1.99 (1.39–2.85)	1.34 (0.96–1.87)	1.73 (1.28–2.34)	2.06 (1.60–2.67)
Sensitivity analyses					
Excluding 7,807 participants with missing data^b	1.00	1.88 (1.30–2.73)	1.25 (0.88–1.78)	1.81 (1.33–2.46)	2.11 (1.63–2.74)
Excluding 2,333 aspirin or anticoagulant users^c	1.00	1.96 (1.36–2.83)	1.32 (0.94–1.85)	1.81 (1.34–2.45)	2.20 (1.71–2.85)
Excluding 15,928 participants <40 y of age at baseline^b	1.00	1.51 (1.03–2.22)	1.02 (0.71–1.47)	1.32 (0.95–1.84)	1.58 (1.18–2.11)

Abbreviations: CI = confidence interval; HR = hazard ratio; ICH = intracerebral hemorrhage.

^a Adjusted for sex, smoking (never, former, or current), alcohol intake (never, former, light, moderate, or heavy; light: 0.1–0.4 servings/d for women and 0.1–0.9 serving/d for men; moderate: 0.5–1.5 servings/d for women and 1–2 serving/d for men; heavy: >1.5 servings/d for women and >2 serving/d for men; based on 15 g alcohol/d), education (illiteracy/elementary school, middle school, or college/university), physical activity (never, sometimes, or active), average monthly income of each family member (<¥500, ¥500–¥2,999, or ≥¥3,000), and sodium intake (≥10.0, 6.0–9.9, or <6.0 g/d).

^b Included variables in model 1 and further adjusted for systolic blood pressure (≤120, 121–139, or ≥140 mm Hg), diastolic blood pressure (≤80, 81–89, or ≥90 mm Hg), 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/mL), fasting blood glucose (<5.6, 5.6–6.0, 6.1–6.9, or ≥7.0 mmol/L), estimated glomerular filtration rate (≤30, 31–59, 60–89, or ≥90 mL/min/1.73 m²), body mass index (≥30.0, 25.0–29.9, or <25.0 kg/m²), and use of aspirin, anticoagulant, antihypertensive, hypoglycemic, and lipid-lowering medications (yes/no for each).

^c Adjusted for all variables in model b except the use of aspirin or anticoagulant.

Table 3 Adjusted HR and 95% CI for risk of deep and nondeep ICH^a by in utero exposure to the Great Chinese Famine

	Not exposed (born after 1961, reference)	In utero exposed (born between 1959 and 1961)	Not in utero exposed (born between 1956 and 1958)	Not in utero exposed (born between 1953 and 1955)	Not in utero exposed (born before 1953)
Deep					
Cases/participants, n	40/29,229	22/6,160	27/10,719	47/11,600	212/39,691
Incidence, per 10,000 person-y	1.6	4.3	3.0	4.9	6.6
Multivariate-adjusted HR ^b	1.00	2.00 (1.20–3.35)	1.43 (0.89–2.28)	1.89 (1.21–2.82)	1.90 (1.31–2.76)
Nondeep					
Cases/participants, n	3/29,229	3/6,160	5/10,719	6/11,600	41/39,691
Incidence, per 10,000 person-y	0.1	0.6	0.6	0.6	1.3
Multivariate-adjusted HR ^b	1.00	3.81 (0.76–18.9)	3.52 (0.83–14.8)	3.44 (0.85–13.9)	6.40 (1.87–21.9)

Abbreviations: CI = confidence interval; HR = hazard ratio; ICH = intracerebral hemorrhage.

^a Deep hematoma: basal, ganglia, thalami hematoma, cerebellar, and brainstem. Nondeep hematoma: lobar. Among 724 cases of ICH, 423 cases had the location of ICH, 6 cases with deep and nondeep hematoma at the same time.

^b Adjusted for sex, smoking (never, former, or current), alcohol intake (never, former, 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–¥2,999, or ≥¥3,000), sodium intake (≥10.0, 6.0–9.9, or <6.0 g/d), systolic blood pressure (≤120, 121–139, or ≥140 mm Hg), diastolic blood pressure (≤80, 81–89, or ≥90 mm Hg), 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/mL), fasting blood glucose (<5.6, 5.6–6.0, 6.1–6.9, or ≥7.0 mmol/L), estimated glomerular filtration rate (≤30, 31–59, 60–89, or ≥90 mL/min/1.73 m²), body mass index (≥30.0, 25.0–29.9, or <25.0 kg/m²), and use of antihypertensive, aspirin, anticoagulant, hypoglycemic, and lipid-lowering medications (yes/no for each).

adjusted HRs for those prenatally exposed to severe famine were greater than that for those prenatally exposed to less severe famine ($p_{\text{interaction}} = 0.08$; figure 2). A similar tendency between severity of famine and ICH risk was observed among participants who were exposed to famine during early childhood (1–6 years of age at the beginning of famine) but not among those with exposure when they were older (figure 2).

Discussion

In this large-scale community-based cohort, in utero exposure to the Great Chinese Famine was associated with higher risks of ICH in later life independently of known risk factors for ICH. As expected, exposure to famine by severity in utero and early childhood was also associated with higher ICH risk. This effect of in utero famine exposure was more pronounced among participants with hypertension or overweight in midlife. Our results provide further evidence to support the hypothesis of the developmental origins of health and disease, which contributes to our understanding of ICH etiology and pathogenesis. Our findings may have public health implications because the number of hungry and malnourished people is on the rise in the United States and globally^{20,21} due to the increased population,²¹ climate change,²² and air pollution.²² Our findings are important not only in emphasizing the importance of adequate nutrition in early life but also suggesting

a novel physiopathologic mechanism that might contribute to a higher risk of especially deep ICH, the subtype mostly related to vascular risk factors.

Although no published studies directly assess the relation between in utero exposure to adversity and risk of ICH, some studies found that in utero exposure to famine or maternal stress was associated with high risk of total stroke²³ and high blood pressure²⁴ in midlife, consistent with our observations. In contrast, in a study of 7,845 women exposed to the 1944 to 1945 Dutch famine when they were between 0 and 21 years of age, a nonsignificant trend between famine exposure and lower future stroke risk was observed after adjustment for cofounders.²⁵ Unlike the current analysis, this study did not examine in utero famine exposure and the results of ICH, which could be due to a relatively small sample size and wide range in age at exposure. Furthermore, differences in famine duration (≤6 months for the Dutch famine vs ≈3 years for the Great Chinese Famine) could be another reason for the discrepancy in results between the 2 studies.

The exact mechanisms by which in utero exposure to famine could increase the risk of ICH in adulthood remain unknown. Several pathways could be involved. First, animal experiments reveal that malnutrition in early life was associated with reconstruction of arterial wall and higher arterial stiffness and blood pressure in later life.^{26,27} Similarly, people with in utero

Table 4 Adjusted HR and 95% CI for incidence of ICH by in utero exposure to the Great Chinese Famine, body mass index, or blood pressure

	Not exposed (born after 1961, reference)	In utero exposed (born between 1959 and 1961)	Not in utero exposed (born between 1956 and 1958)	Not in utero exposed (born between 1953 and 1955)	Not in utero exposed (born before 1953)	<i>P</i> _{interaction} Value
Overweight^a						
Incidence, per 10,000 person-y	4.4	13.1	7.3	10.4	13.2	0.03
Multivariate-adjusted HR 1 ^b	1.00	2.62 (1.67–4.11)	1.43 (0.91–2.25)	1.92 (1.28–2.87)	2.08 (1.47–2.95)	
Nonoverweight						
Incidence, per 10,000 person-y	2.8	4.9	5.9	8.4	14.1	
Multivariate-adjusted HR 1 ^b	1.00	1.42 (0.75–2.67)	1.54 (0.93–2.56)	1.98 (1.25–3.13)	2.67 (1.81–3.93)	
Hypertension^c						
Incidence, per 10,000 person-y	8.4	17.4	11.3	15.4	18.5	0.04
Multivariate-adjusted HR 2 ^d	1.00	1.97 (1.28–3.04)	1.24 (0.83–1.87)	1.61 (1.12–2.32)	1.65 (1.20–2.26)	
Nonhypertension						
Incidence, per 10,000 person-y	1.8	4.0	3.2	4.4	8.4	
Multivariate-adjusted HR 2 ^d	1.00	1.98 (1.03–3.79)	1.51 (0.83–2.75)	1.98 (1.15–3.42)	3.26 (2.09–5.07)	

Abbreviations: CI = confidence interval; HR = hazard ratio; ICH = intracerebral hemorrhage.

^a Overweight was defined as body mass index ≥ 25 kg/m².

^b Adjusted for sex, smoking (never, former, or current), alcohol intake (never, former, light, moderate, or heavy), education (illiteracy/elementary school, middle school, or college/university), physical activity (never, sometimes, or active), sodium intake (≥ 10.0 , 6.0–9.9, or < 6.0 g/d), systolic blood pressure (≤ 120 , 121–139, ≥ 140 mm Hg), diastolic blood pressure (≤ 80 , 81–89, or ≥ 90 mm Hg), 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/mL), fasting blood glucose (< 5.6 , 5.6–6.0, 6.1–6.9, or ≥ 7.0 mmol/L), estimated glomerular filtration rate (≤ 30 , 31–59, 60–89, or ≥ 90 mL/min/1.73 m²), and use of antihypertensive, aspirin, anticoagulant, hypoglycemic, and lipid-lowering medications (yes/no for each).

^c Hypertension was defined as a systolic blood pressure ≥ 140 mm Hg, a diastolic blood pressure ≥ 90 mm Hg, or use antihypertensive agents.

^d Adjusted all variables in multivariate-adjusted HR 1 except systolic blood pressure and diastolic blood pressure; further adjusted for body mass index (≥ 30.0 , 25.0–29.9, or < 25.0 kg/m²).

exposure to famine were more likely to have hypertension,^{7,28} which is one of the most important risk factors for ICH.²⁹ Second, in utero exposure to famine was associated with hyperglycemia in adulthood,³⁰ which could be a potential risk factor for ICH because hyperglycemia might lead to atherosclerotic aneurysm formation and small vessel disease.³¹ Third, malnutrition during early life might result in renal dysfunction due to altered renal shape, reduced renal volume, and lower number of nephrons,³² which is a risk factor for ICH. In utero malnutrition usually was associated with short stature, which could lead to several ICH-related pathologic changes, including shortened return times for reflected waves, faster heart rates, and augmentation of the primary systolic pulses.³³ Furthermore, there could be a vicious cycle between in utero famine exposure and maternal stress, resulting in an increase in stress hormone secretion (e.g., cortisol).^{6,34,35}

We also observed that the association between in utero exposure to famine and ICH risk could be modified by being overweight

and having higher blood pressure. Particularly, in utero famine exposure was significantly associated with higher ICH risks among overweight participants compared to their counterparts. These results suggested that the potential adverse effects of in utero famine exposure could be alleviated by maintaining normal weight, which are modifiable factors. However, more studies are needed to replicate our findings and to understand the underlying mechanisms.

We found that the relationship between famine and ICH risk seems to be dose dependent on the basis of our joint analyses results. Compared with participants who were exposed to less severe famine, those exposed to severe famine in the prenatal period and early childhood had a higher future risk of ICH relative to those with less severe famine exposure. Consistently, previous studies reported that severe famine in early life was associated with a higher risk of hypertension prevalence,⁷ higher cholesterol level, higher prevalence of smoking,²⁵ and elevated peripheral resistance.³⁶

Figure 2 Joint analysis of in utero famine exposure and famine severity for risk of intracerebral hemorrhage^a

Exposure status	Severity of famine	No. of case/ participants	Incidence (/10,000 person years)	Hazard ratio (95% confidence interval) ^b
Not exposed (born after 1961)	Reference	86/29,229	3.5	1.00
Exposed in utero (born between 1959 and 1961)	Less severe	38/5,345	8.5	1.94 (1.32, 2.84)
	Severe	5/454	13.1	2.99 (1.21, 7.39)
Not exposed in utero (born between 1956 and 1958)	Less severe	40/9,312	5.2	1.08 (0.74, 1.58)
	Severe	7/655	12.9	2.89 (1.34, 6.26)
Not exposed in utero (born between 1953 and 1955)	Less severe	72/9,931	8.7	1.67 (1.21, 2.29)
	Severe	10/705	17.3	3.67 (1.90, 7.09)
Not exposed in utero (born before 1953)	Less severe	324/31,668	12.4	1.98 (1.52, 2.57)
	Severe	20/2,009	12.2	2.04 (1.24, 3.36)

^aExcluded 8,091 participants who lacked the data of severity of famine. ^bAdjusted for sex, smoking (never, former, or current), alcohol intake (never, former, 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–¥2,999, or ≥¥3,000), sodium intake (≥10.0, 6.0–9.9, or <6.0 g/d), systolic blood pressure (≤120, 121–139, or ≥140 mm Hg), diastolic blood pressure (≤80, 81–89, or ≥90 mm Hg), 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/mL), fasting blood glucose (<5.6, 5.6–6.0, 6.1–6.9, or ≥7.0 mmol/L), estimated glomerular filtration rate (≤30, 31–59, 60–89, or ≥90 mL/min/1.73 m²), body mass index (≥30.0, 25.0–29.9, or <25.0 kg/m²), and use of antihypertensive, aspirin, anticoagulant, hypoglycemic, and lipid-lowering medications (yes/no for each). The $p_{\text{interaction}}$ for exposure status to famine and severity of famine was 0.08.

We observed that participants born in the late period of famine (i.e., 1961) had a lower incidence of ICH compared with those born in the early famine period (i.e., 1959 or 1960). A previous study³⁷ reported that long-term exposure to famine could increase risks of miscarriage and stillbirth, leading to the selection of hardier infants with healthier growth potential.³⁸ In our study, only 1,280 participants were born in 1961, less than the numbers in 1960 (2,435 participants) or 1962 (2,608 participants). The participants born in 1961 were likely healthier than other participants due to natural selection. However, we could not exclude the possibility of chance because of small sample size of participants born in 1961.

The present study has several strengths, including a large sample size, neurologist-confirmed cases of ICH, and availability of ICH location. However, all participants were recruited from the Kailuan community, and most of the participants were men (79.9%); therefore, the observed results may not be generalizable. Furthermore, there were no exact start and end dates of the Great Chinese Famine, and detailed individual data on famine exposure were absent. Misclassification of exposure may exist, which could lead to underestimation of associations if the misclassification is nondifferential. Because the Chinese famine swept across all the areas in China, all the participants except those in the nonexposed group were exposed to the famine in different life periods, which could have different impacts on development

of primary vs secondary ICH. However, because of the lack of the etiology of ICH in the current study, these effects cannot be further investigated. A proportion of participants in the fetal-exposed group were also exposed to the famine in early childhood, which could result in a synergistic effect on ICH risk. Our study was also limited by lack of information on anticoagulant use. However, a sensitivity analysis to exclude participants with conditions that are major indications for anticoagulant use generated similar results. In this context, further studies with a large sample size of women and an age-comparable reference group can be helpful to confirm these associations.

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Disclosure

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Appendix Authors

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M. Edip Gurol MD	Massachusetts General Hospital and Harvard Medical School, Boston	Interpreted the data and critically revised the manuscript for the intellectual content
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Sheng Zhuang, MD	The Second Affiliated Hospital of Soochow University, Suzhou, China	Interpreted the data, and critically revised the manuscript for the intellectual content
Michele R. Forman, PhD	Department of Nutrition Science, Purdue University, West Lafayette, IN	Interpreted the data and critically revised the manuscript for the intellectual content
Shouling Wu, MD, PhD	Kailuan General Hospital, North China University of Science and Technology, Tangshan	Conceptualized and designed the study, collected and analyzed data, interpreted the data, performed statistical analysis, and critically revised the manuscript for the intellectual content
Xiang Gao, MD, PhD	Pennsylvania State University, State College	Conceptualized and designed the study, interpreted the data, and critically revised the manuscript for the intellectual content

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