The effects of exposure to the Great Chinese Famine during the fetal stage and childhood on prevalence of hypertension in adulthood

Shui-jin Huang[1], Yu-qing Huang[2]*, Ying Wu[2]*

[1]Department of Geriatrics, National Key Clinic Specialty, Guangzhou First People's Hospital, South China University of Technology, Guangzhou, China
[2]Department of Cardiology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Southern Medical University, Guangzhou, China

Submitted: 4 February 2024; **Accepted:** 21 March 2024
Online publication: 16 December 2024

Arch Med Sci
DOI: https://doi.org/10.5114/aoms/186352

***Corresponding authors:**
Yu-qing Huang
Department of Cardiology
Guangdong Provincial
People's Hospital
Guangdong Academy
of Medical Sciences
Guangzhou 510080, China
E-mail: hyq513@126.com,
wy_wuying@163.com

Ying Wu
Department of Cardiology,
Guangdong Provincial
People's
Hospital,
Guangdong Academy of
Medical
Sciences,
Southern Medical University,
Guangzhou 510080, China
E-mail: wy_wuying@163.com

Abstract

Introduction: Many studies have found that famine exposure in early life was associated with higher prevalence of hypertension, but the results remain controversial. The aim was to examine the association of early life exposure to famine with hypertension in adulthood.

Material and methods: The cross-sectional study enrolled about 100,000 adults from Guangdong province, China, who were born between 1 October 1952 and 30 September 1964. Participants were classified as non-exposed, fetal exposed, early-childhood exposed, mid-childhood exposed, and late-childhood exposed group according to birth data. Multivariable logistic regression, subgroup analysis, and sensitivity analysis were used to estimate the odds ratios (ORs) and confidence intervals (CIs) for the association between famine exposure and hypertension.

Results: Among the 28,804 participants, the prevalence of hypertension in non-exposed, fetal, early-childhood, mid-childhood, and late-childhood exposed groups were 2686 (41.2%), 1777 (44.5%), 2998 (49.0%), 3196 (51.1%), 3192 (53.9%), respectively. Compared with the non-exposed group, the fully adjusted ORs of subjects exposed to the famine in the fetal, early-childhood, mid-childhood and late-childhood exposed groups were 1.10 (95% CI: 0.97–1.24, $p = 0.143$), 1.23 (95% CI: 1.10–1.37, $p < 0.001$), 1.39 (95% CI: 1.24–1.55, $p < 0.001$), and 1.55 (95% CI: 1.38–1.73, $p < 0.001$), respectively (p for trend < 0.001), and for the age-balanced group it was 1.37 (95% CI: 1.13–1.59, $p < 0.001$). Subgroup analyses showed that the effect of famine on hypertension was more pronounced in women and in the rural and overweight population.

Conclusions: Exposure to famine at any stage in childhood, but not in the fetal stage, was significantly associated with higher prevalence of hypertension in adults, especially in women and in the rural and overweight population.

Key words: fetal, childhood, famine exposure, adulthood, hypertension.

Introduction

Hypertension is one of the most common preventable and controllable chronic diseases and the major leading cause of cardiovascular diseases (CVDs) and death worldwide, especially in developing countries,

including China [1]. Despite numerous measures being implemented, the prevalence of hypertension in China is still gradually rising [2]. It has been found that a number of factors including obesity [3], chronic stress [4], insomnia [5], smoking [6], noise and air pollution exposure [7] may significantly increase the risk of hypertension, but the related risk factors of hypertension have not been fully elucidated. Although hypertension is a complex entity, it is now generally believed that hypertension is related to both environmental factors and genetics [8]. Importantly, studies have also demonstrated that dietary intake of sodium, potassium, and magnesium is associated with high blood pressure [9], as well as malnutrition [10].

Nutritional and dietary deficiencies are among the manifestations of famine. Numerous previous studies have demonstrated that famine exposure was closely related to the occurrence of a large number of CVDs, including hypertension [11, 12]. The Dutch famine provided evidence that nutritional deficiencies in the maternal diet during pregnancy were associated with the high prevalence of later hypertension among male but not female individuals [13]. The Biafran famine suggested that undernutrition in the fetal and infant stages was correlated with hypertension in adulthood [14]. The Great Chinese Famine (1959–1961) indicated that famine exposure at the fetal stage may be associated with an increased risk of hypertension in adults only among the female population [15]. Previous studies have also shown that there was no gender difference in the relationship between famine exposure during early life and high prevalence of hypertension in adulthood [16, 17]. In addition, a 22-year cohort study found in subjects with general or abdominal obesity that famine exposure was associated with a lower risk of hypertension [18]. The relationship between famine exposure in early life and hypertension in adulthood is still controversial.

Therefore, the aim of this study was to explore the relationship between famine exposure in fetuses and childhood and the development of hypertension in adulthood.

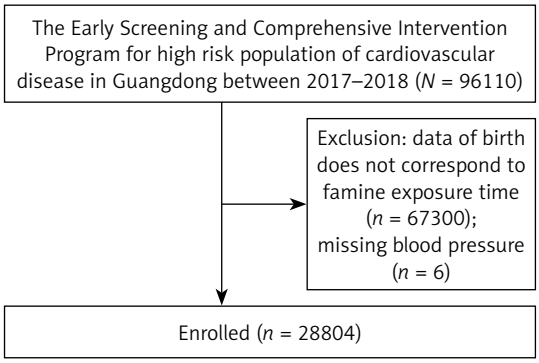

Figure 1. Research flow chart

Material and methods

Study design

Participants in the present study were from the Early Screening and Comprehensive Intervention Program for High Risk Population of CVD, an essential part of the China-PEACE (Patient Cantered Evaluative Assessment of Cardiac Events) Million Persons Project of Guangdong province between 1 January 2017 and 31 December 2018, China. The Early Screening and Comprehensive Intervention Program for High Risk Population of CVD was an ongoing prospective population-based national survey in China, details of which have been previously described [19, 20]. Briefly, a total of about 100,000 individuals were recruited from Guangdong province between 1 January 2017 and 31 December 2018 for the Early Screening and Comprehensive Intervention Program for High Risk Population of CVD. In the present study, individuals born between 1952/10/1 and 1964/9/30 and diagnosed with hypertension during the time of the survey were enrolled. Individuals without exposure to famine and missing blood pressure data were excluded. In addition, as the exact timing of the start and end of the famine in China was unclear, individuals who were born between 1958/10/1 to 1959/9/30 and 1961/10/1 to 1962/9/30 were also excluded to minimize misclassification. Finally, a total of 28,804 participants were enrolled for analysis (Figure 1). The research protocol was approved by the Ethics Committee of Guangdong Provincial People's Hospital (No. GDREC2016438H (R2)) and all participants signed informed consent.

Definition of famine exposure and grouping

Since China experienced the Great Famine for three years, from 1959 to 1961, most participants born in 1962 might have experienced the famine during fetal development [21]. Therefore, according to previous studies [16, 22], participants were categorized into five groups according to their date of birth: (1) no exposure group (1962/10/1–1964/9/30): n = 6517; (2) fetal exposure group (1959/10/1–1961/9/30): n = 3989; (3) early-childhood exposure group (1956/10/1–1958/9/30): n = 6123; (4) mid-childhood exposure group (1954/10/1–1956/9/30): n = 6252; (5) late-childhood exposure group (1952/10/1–1954/9/30): n = 5923.

Assessment of hypertension

According to our previously reported study [20], a face-to-face interviewer questionnaire was performed and blood pressure was measured twice for each participant in a seated position after

5 min of rest by using an electronic blood pressure monitor (Omron HEM-7430; Omron Corp) on the right upper arm, with a 1-minute delay between measurements. If 2 consecutive systolic blood pressure readings exceeded 10 mm Hg, a third measurement was required, and the average of the last 2 readings was used. Several affirmative questions were asked to determine whether the patient had a history of hypertension: "Have you ever been told by a doctor or other health care professional that you had hypertension, also called high blood pressure?" and "Are you now taking prescribed medication for high blood pressure?" The diagnostic criteria for hypertension must meet at least one of the following criteria: self-reported taking antihypertensive medication or being diagnosed with hypertension by a doctor or average systolic/diastolic blood pressure ≥ 140/90 mm Hg measured in a sitting position [23].

Assessment of covariates

A trained investigator collected relevant information on each participant by the face-to-face method. The demographic information mainly comprised gender, birth data, region, education and income level and marriage status. Histories of personal diseases including stroke, diabetes, hypertension and coronary heart disease were taken. Lifestyle behaviors including current smoking and drinking were recorded. Standing height and body weight were also measured by trained investigators. Body mass index (BMI) was calculated based on weight (kilograms) divided by height (meters squared), and BMI ≥ 25 kg/m^2 was defined as overweight [24]. In addition, morning fasting blood was used to detect blood sugar, blood lipids (total cholesterol, triglyceride, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol).

Statistical analysis

All continuous variables were presented as mean ± standard deviation, and categorical variables were presented as numbers or percentages. Comparison of baseline data between different famine-exposed groups was made using the analysis of variance for continuous variables, χ^2 tests for categorical variables, and the Wilcoxon rank sum test for ordinal variables as appropriate. Age adjustment did not improve the estimation between famine exposure and hypertension, as the dates of birth of the five famine-exposed groups did not overlap [25]. To control the effect of age difference on the relationship, we generated an age-balanced (the average age of famine exposure groups) control group for the fetal-exposed group by combining non-exposed, early-childhood exposed, mid-childhood exposed, and late-childhood exposed groups according to a previous study [26]. The hypertension risk was compared between the fetal-exposed group and age-balanced control group with a logistic model, and used the no exposure group as the reference. Crude and adjusted odds ratio (OR) and 95% confidence interval (CI) values were estimated to assess the relationships between famine exposure and hypertension. With the unexposed group as a control, univariable and multivariable logistic regression analyses were used to estimate the ORs and 95% CIs for the relationship between famine exposure and hypertension. In model I, no covariate was adjusted. In model II, age, gender, region, education, income, smoking, drinking, body mass index, low-density lipoprotein cholesterol, diabetes, stroke and coronary heart disease were all adjusted.

Subgroup analysis included gender (male or female), region (urban or rural) and BMI (≥ 25.0 kg/m^2 or < 25 kg/m^2). Interactions were used to assess the role of each subgroup in the relationship between famine exposure and hypertension. Sensitivity analysis was based on the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (the JNC 7 report) diagnostic criteria for hypertension: previously diagnosed by a specialist with hypertension or taking antihypertensive drugs in the past 2 weeks based on self-report, or systolic/diastolic blood pressure ≥ 130/80 mm Hg [27]. A two-sided $p < 0.05$ was considered statistically significant. All statistical analyses were performed using R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 19.0 (IBM, Armonk, NY, USA).

Results

Characteristics of participants by early life stage of exposure to the Chinese Great Famine

The baseline characteristics of the participants are summarized in Table I. A total of 28,804 subjects (11,025 male and 17,779 female) with a mean age of 59.63 ±3.75 years were included. Among all the 28,804 participants, the prevalence of hypertension in the non-exposed group, fetal exposed group, early-childhood exposed group, mid-childhood exposed group, late-childhood exposed and age-balanced group was 2686 (41.2%), 1777 (44.5%), 2998 (49.0%), 3196 (51.1%), 3192 (53.9%) and 1406(5.7%), respectively. We found that age, systolic blood pressure, BMI, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, gender composition, region, history of stroke and coronary heart disease, education level, income level, current smoking and

Table I. Baseline characteristics among different famine exposure groups

Parameter	Overall	No exposure	Fetal exposure	Early childhood	Mid childhood	Late childhood	*P*-value	Age balanced group
Number	28804	6517	3989	6123	6252	5923		24815
Age [years]	59.63 ±3.75	54.21 ±1.04	57.17 ±1.04	60.14 ±1.01	62.13 ±1.04	64.10 ±1.05	< 0.001	60.15 ±1.03
SBP [mm Hg]	133.72 ±18.81	130.65 ±18.24	132.45 ±18.94	134.29 ±18.83	134.95 ±18.73	136.07 ±18.89	< 0.001	134.15 ±18.65
DBP [mm Hg]	80.22 ±11.11	80.49 ±11.36	80.02 ±11.38	80.40 ±11.09	80.08 ±10.95	80.03 ±10.84	0.052	80.15 ±11.05
BMI [kg/m^2]	24.21 ±3.30	24.40 ±3.30	24.27 ±3.37	24.27 ±3.32	24.04 ±3.26	24.07 ±3.26	< 0.001	24.19 ±3.28
TC [mmol/l]	5.09 ±1.26	5.04 ±1.23	5.19 ±1.27	5.11 ±1.29	5.12 ±1.27	5.03 ±1.24	< 0.001	5.07 ±1.26
TG [mmol/l]	1.68 ±0.96	1.69 ±0.98)	1.70 ±1.00	1.68 ±0.96	1.67 ±0.94	1.67 ±0.95	0.313	1.68 ±0.96
HDL-C [mmol/l]	1.50 ±0.44	1.49 ±0.44)	1.52 ±0.45	1.51 ±0.45	1.51 ±0.44	1.49 ±0.43	0.003	1.50 ±0.44
LDL-C [mmol/l]	2.84 ±1.02	2.81 ±1.01)	2.91 ±1.03	2.84 ±1.02	2.88 ±1.04	2.80 ±1.02	< 0.001	2.83 ±1.02
FBG [mmol/l]	6.05 ±1.78	6.02 ±1.73)	6.08 ±1.87	6.06 ±1.78	6.03 ±1.72	6.05 ±1.84	0.491	6.04 ±1.77
Gender-female (%)	17779 (61.7)	4166 (63.9)	2660 (66.7)	3745 (61.2)	3784 (60.5)	3424 (57.8)	< 0.001	15119 (60.9)
Urban (%)	13187 (45.8)	2855 (43.8)	1874 (47.0)	2887 (47.2)	2835 (45.3)	2736 (46.2)	0.001	11313 (45.6)
Hypertension (≥ 140/90) (%)	13849 (48.1)	2686 (41.2)	1777 (44.5)	2998 (49.0)	3196 (51.1)	3192 (53.9)	< 0.001	12072 (48.6)
Hypertension (%) (≥ 130/80) (%)	19787 (68.7)	4133 (63.4)	2631 (66.0)	4240 (69.2)	4466 (71.4)	4317 (72.9)	< 0.001	17156 (69.1)
History of diabetes (%)	5697 (19.8)	1230 (18.9)	821 (20.6)	1245 (20.3)	1210 (19.4)	1191 (20.1)	0.119	4876 (19.6)
History of stroke (%)	215 (0.7)	30 (0.5)	22 (0.6)	46 (0.8)	60 (1.0)	57 (1.0)	0.002	193 (0.78)
History of coronary heart disease (%)	295 (1.0)	47 (0.7)	30 (0.8)	68 (1.1)	72 (1.2)	78 (1.3)	0.004	265 (1.07)
Education–high school or above (%)	6852 (23.8)	1788 (27.4)	1223 (30.7)	1548 (25.3)	1265 (20.2)	1028 (17.4)	< 0.001	5629 (22.7)
Income–more than 50k per year (%)	12648 (43.9)	2945 (45.2)	1805 (45.2)	2648 (43.2)	2758 (44.1)	2492 (42.1)	0.002	10843 (43.7)
Current smoking (%)	5342 (18.5)	1132 (17.4)	698 (17.5)	1125 (18.4)	1210 (19.4)	1177 (19.9)	0.001	4644 (18.7)
Current drinking (%)	1611 (5.6)	326 (5.0)	205 (5.1)	329 (5.4)	378 (6.0)	373 (6.3)	0.006	1406 (5.7)

Data are presented as mean ±standard deviation or percentage. P-values are for the comparison of the difference in famine exposure groups. Analyzed by analysis of variance. SBP – systolic blood pressure, DBP – diastolic blood pressure, FBG – fasting blood glucose, TC – total cholesterol, TG – triglyceride, LDL-C – low-density lipoprotein cholesterol, HDL-C – high-density lipoprotein cholesterol, BMI – body mass index.

drinking were significantly different among famine-exposed groups (all $p < 0.05$).

Association of famine exposure in early life stage with hypertension in adulthood

As shown in Table II, when the non-famine exposure group was used as the control, we found that in Model I with no confounding variables adjusted, the crude ORs for hypertension in adults from the fetal-exposed group, early-childhood exposed group, mid-childhood exposed group to late-childhood exposed group were 1.15 (95% CI: 1.06–1.24, $p = 0.001$), 1.37 (95% CI: 1.28–1.47, $p < 0.001$), 1.49 (95% CI: 1.39–1.60, $p < 0.001$),

Table II. Relationship between famine exposure and hypertension based on different definition of hypertension

Variable	Hypertension (≥ 140/90 mm Hg)		Hypertension (≥ 130/80 mm Hg)	
	Model I	Model II	Model I	Model II
	OR (95% CI), *p*-value	OR (95% CI), *p*-value	OR (95% CI), *p*-value	OR (95% CI), *p*-value
No exposure	Reference	Reference	Reference	Reference
Fetal exposure	1.15 (1.06–1.24) 0.001	1.10 (0.97–1.24) 0.143	1.12 (1.03–1.21) 0.008	1.07 (0.92–1.25) 0.394
Early childhood exposure	1.37 (1.28–1.47) < 0.001	1.23 (1.10–1.37) < 0.001	1.30 (1.21–1.40) < 0.001	1.17 (1.02–1.34) 0.027
Mid childhood exposure	1.49 (1.39–1.60) < 0.001	1.39 (1.24–1.55) < 0.001	1.44 (1.34–1.55) < 0.001	1.34 (1.17–1.54) < 0.001
Late childhood exposure	1.67 (1.55–1.79) < 0.001	1.55 (1.38–1.73) < 0.001	1.55 (1.44–1.67) < 0.001	1.45 (1.26–1.68) < 0.001
P for trend	< 0.001	< 0.001	< 0.001	< 0.001
No exposure	Reference	Reference	Reference	Reference
Age balanced group	1.40 (1.22–1.68) < 0.001	1.37 (1.13–1.59) < 0.001	1.37 (1.19–1.65) < 0.001	1.29 (1.15–1.50) < 0.001

Data are presented as the odds ratio (OR) and 95% confidence interval (CI). Model I with no variable adjusted. Model II with age, gender, region, education, income, smoking, drinking, body mass index, low-density lipoprotein cholesterol, diabetes, stroke and coronary heart disease adjusted.

and 1.67 (95% CI: 1.55–1.79, $p < 0.001$) (p for trend was $p < 0.001$), respectively, and for the age-balanced group the value was 1.40 (95% CI: 1.22–1.68, $p < 0.001$) compared to the non-famine exposure group. However, in Model II, when age, gender, region, education, income, smoking, drinking, body mass index, low-density lipoprotein cholesterol, diabetes, stroke and coronary heart disease were all adjusted, the fully adjusted ORs for hypertension from the fetal-exposed group, early-childhood exposed group, and mid-childhood exposed group were 1.10 (95% CI: 0.97–1.24, $p = 0.143$), 1.23 (95% CI: 1.10–1.37, $p < 0.001$), 1.39 (95% CI: 1.24–1.55, $p < 0.001$), and 1.55 (95% CI: 1.38–1.73, $p < 0.001$), respectively (p for trend < 0.001), and for the age-balanced group the value was 1.37 (95% CI: 1.13–1.59, $p < 0.001$).

Association of famine exposure with hypertension by subgroup and sensitivity analysis

To explore the independent effects of famine exposure on hypertension, subgroup analyses and sensitivity analyses were used. As shown in Table III, subgroup analysis revealed that famine exposure in the fetal period increased the risk of hypertension, but there was no statistically significant difference between the gender and BMI subgroups. However, the risk of hypertension from famine exposure was significantly higher in women than in men, regardless of whether it was in early, middle, or late childhood. Similar results were also found in the rural participants and overweight population. Interaction analysis showed there was no significant interaction of gender, region and BMI with famine exposure (all values of p-interaction > 0.05) (Table III). In addition, we performed a sensitivity analysis to explore whether the associations of famine exposure with hypertension were confounded by different definitions of hypertension. When using the JNC7 criteria definition of hypertension, it was still found that famine exposure in the fetal period had no significant effect on hypertension, while exposure during any stage of childhood significantly increased the prevalence of hypertension in adulthood, and similar results were found in the age-balanced group (Table II).

Discussion

In a large cross-sectional study of Chinese adults, we observed that the relationship between famine exposure in early life and adult hypertension occurred only with respect to childhood, not the fetal stage. This association was stronger among individuals who were female, living in rural areas and overweight.

In our study, we found that childhood exposure to famine might increase the risk of hypertension in adulthood among the Chinese population. Similar findings were also confirmed in famine populations in other countries, such as the Dutch famine of 1944–1945 [13, 28] and the Biafran famine of 1967–1970 [13, 28]. Furthermore, the present study found no significant association between exposure to famine in the fetal period and adult

Table III. Subgroup analysis on the association of famine exposure with hypertension

95% CI	No exposure	Fetal exposure			Early childhood			Mid childhood			Late childhood			Age balanced group			*P*-interaction
		OR	95% CI	*P*-value	OR	95% CI	*P*-value	OR	95% CI	*P*-value	OR	95% CI	*P*-value	OR	95% CI	*P*-value	
Gender																	0.215
Male (n = 11025)	Ref	1.05	0.85–1.30	0.640	1.16	0.97–1.39	0.096	1.28	1.07–1.53	0.006	1.41	1.18–1.69	< 0.001	1.25	1.02–1.50	< 0.001	
Female (n = 17779)	Ref	1.15	0.98–1.35	0.083	1.28	1.11–1.47	0.001	1.47	1.28–1.70	< 0.001	1.69	1.46–1.95	< 0.001	1.41	1.20–1.67	< 0.001	
Region																	0.147
Rural (n = 15617)	Ref	1.20	1.01–1.42	0.042	1.27	1.08–1.49	0.004	1.42	1.22–1.65	< 0.001	1.56	1.34–1.82	< 0.001	1.40	1.15–1.69	< 0.001	
Urban (n = 13187)	Ref	0.99	0.83–1.19	0.940	1.21	1.03–1.39	0.021	1.36	1.16–1.60	< 0.001	1.53	1.30–1.81	< 0.001	1.25	1.08–1.50	< 0.001	
BMI [kg/m^2]																	0.782
≥ 25 (n = 10902)	Ref	1.18	0.98–1.42	0.088	1.27	1.09–1.47	0.002	1.43	1.13–1.58	0.001	1.62	1.36–1.92	< 0.001	1.44	1.17–1.70	< 0.001	
< 25 (n = 17808)	Ref	1.02	0.86–1.21	0.820	1.15	0.97–1.35	0.110	1.37	1.18–1.58	< 0.001	1.46	1.26–1.69	< 0.001	1.25	1.06–1.46	< 0.001	

Data are presented as OR and 95% CI. P-values are for the comparison of the difference in subgroup condition. OR – odds ratio, CI – confidence interval, BMI – body mass index. When analyzing a subgroup, age, gender, region, education, income, smoking, drinking, body mass index, low-density lipoprotein cholesterol, diabetes, stroke and coronary heart disease were all adjusted except for the subgroup itself.

hypertension. This result was similar to those found in some previous studies [29–31]. However, other studies also demonstrated that exposure to famine during the gestation/fetal stage was linked with increased risk of hypertension in adults [29–31]. We speculated that the reasons for this disparate finding may be mainly due to differences in duration of exposure, ethnicity, living environment and dietary patterns. Therefore we adjusted for covariates including age. Importantly, a systematic review and meta-analysis found that uncontrolled age differences between famine and post-famine births may explain the association between the effects attributable to famine and later cardiovascular endpoints [32–34]. Additional analyses and reasonable controls for age were required for more reliable estimations of the long-term impact of famine in China.

In subgroup analyses, we found that the association of famine exposure in early life and adult hypertension was more pronounced in females. Stockwell HG and Guo HJ both found that exposure to famine during childhood has deleterious effects on adult hypertension, but the effects on females may be greater than that on males [35, 36]. The potential reasons for this phenomenon may be as follows: Firstly, the role of estrogenic effects has been demonstrated from animal studies suggesting that fetal malnutrition has a greater impact on the health of female animals [37]. Secondly, it was hypothesized that there is a gender difference in related mortality, with males tending to die earlier than females [38]. Thirdly, famine exposure may cause some epigenetic changes related to hypertension [39]. In addition, the traditional Chinese ideology of "preferring sons to daughters" may make women more vulnerable to famine exposure during early life. Finally, inconsistent results may be due to a family history of hypertension, or it may be that these participants carried hypertensive susceptibility genes.

We also found that exposure to the Chinese Famine in early life and the risk of hypertension in adulthood were more pronounced in individuals who lived in rural areas or were overweight as adults. Our findings are consistent with previous research [32, 40]. This may be because less food was available in rural areas, while being overweight in adulthood was itself a significant risk factor for hypertension [41]. However, a 22-year cohort study found that famine exposure in childhood was associated with a higher incidence of hypertension in both obese males and females, but famine exposure in mid- and late childhood was associated with a lower risk of hypertension only in males with normal weight [18]. At present, the specific mechanisms of the effect of BMI on the association of famine exposure with hypertension are still unclear.

Of course, the underlying reasons for the association of exposure to famine in early life with hypertension in adulthood are also not fully understood. On the one hand, studies have found that famine-exposed populations were more likely to "catch up with growth", thereby consuming more in the future and becoming overweight or obese [42]. On the other hand, malnutrition could lead to low body weight and some epigenetic change [43, 44]. Previous studies have shown that low body weight and some genetic changes were strongly associated with high blood pressure [45, 46]. Finally, famine in early life was also associated with hyperuricemia [47], obesity [48], and decreased kidney function [49] in adulthood. It has now been proved that high uric acid levels, obesity and decreased renal function could activate the sympathetic nervous system and the renin-angiotensin system, and may stimulate inflammatory responses and lead to endothelial dysfunction [50, 51]. Importantly, there is now unanimous agreement that inflammatory activation, endothelial dysfunction and activation of the renin-angiotensin system are important processes in the development of hypertension [52]. Nevertheless, more research is still needed to confirm the relationship between famine and hypertension in the future.

Study samples of sufficient size, adjusted for as many confounding variables as possible, and the application of sensitivity analysis were important advantages of this study. In addition, adjustment for age and generation of an age-balanced control group are further advantages. However, some shortcomings should also be noted. First, selection bias was important because only survivors were included in the analysis, whereas those who died of famine could not be assessed. Although there might be some selection bias and the samples were not representative of the Chinese adult population, this is still an important report and will surely add to a growing body of evidence in this field. Second, we defined famine by the time period alone, which did not guarantee that the individuals had experienced famine. The lack of birth weight data was another defect of concern. Third, data on famine severity, dietary intake and eating patterns of each participant were missing. The lack of data on diet and living habits, and the fact that the famine intensity at the prefecture or county level could not be assessed, also has a certain impact on the conclusions of this study. Fourth, the nutritional status, nutritional elements and nutritional scores in infants and childhood were not clear. Fifth, this was a cross-sectional study and could not draw causal conclusions. Sixth, the specific mechanism of the famine–hypertension relationship has not been further explored. Seventh, the lack of analysis and discussion of the effect of famine on blood pressure across generations was also an important shortcoming in this study. Previous studies have found that there were intergenerational effects of famine exposure during early life, and more research is needed to clarify the effect on the next generation of famine exposure in the future [53, 54]. In addition, although as many confounding variables as possible were adjusted in the present study, some specific variables related to hypertension including medication history, family history, mental status, sleep, and uric acid level were unavailable. Finally, some baseline variables were self-reported by participants and therefore may be underestimated or overestimated.

In conclusion, we found that exposure to famine in childhood, but not in fetuses, significantly increased the prevalence of hypertension in adulthood. The effects of famine exposure in early life on hypertension in adulthood differed according to gender, living region and overweight status, tending to occur more in the female, rural and overweight population. The specific mechanisms of famine exposure and hypertension are still unclear, and more research is needed in the future. The present study also suggests that the prevention of hypertension should start from childhood and more attention should be paid to nutritional status in early life.

Funding

This study was supported by initial funding of the National Natural Science Foundation-Youth Project (8210120459), and Guangdong Basic and Applied Basic Research Foundation-Provincial Enterprise Joint Fund (2022A1515220113), but they had no roles other than funding.

Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

References

1. Al-Makki A, DiPette D, Whelton PK, et al. Hypertension pharmacological treatment in adults: a world health organization guideline executive summary. Hypertension 2022; 79: 293-301.
2. Lu J, Lu Y, Wang X, et al. Prevalence, awareness, treatment, and control of hypertension in China: data from 1.7 million adults in a population-based screening study (China PEACE Million Persons Project). Lancet 2017; 390: 2549-58.
3. Natsis M, Antza C, Doundoulakis I, et al. Hypertension in obesity: novel insights. Curr Hypertens Rev 2020; 16: 30-6.
4. Liu MY, Li N, Li WA, Khan H. Association between psychosocial stress and hypertension: a systematic review and meta-analysis. Neurol Res 2017; 39: 573-80.

5. Jarrin DC, Alvaro PK, Bouchard MA, et al. Insomnia and hypertension: a systematic review. Sleep Med Rev 2018; 41: 3-38.
6. Gloria-Bottini F, Banci M, Neri A, Magrini A, Bottini E. Smoking and hypertension: effect of adenosine deaminase polymorphism. Clin Exp Hypertens 2019; 41: 548-51.
7. Mannucci PM, Ancona C. Noise and air pollution as triggers of hypertension. Eur Heart J 2021; 42: 2085-7.
8. Vallianou NG, Geladari E, Kounatidis D. Microbiome and hypertension: where are we now? J Cardiovasc Med (Hagerstown) 2020; 21: 83-8.
9. Appel LJ. The effects of dietary factors on blood pressure. Cardiol Clin 2017; 35: 197-212.
10. Azupogo F, Abizari AR, Aurino E, et al. Malnutrition, hypertension risk, and correlates: an analysis of the 2014 ghana demographic and health survey data for 15-19 years adolescent boys and girls. Nutrients 2020; 12: 2737.
11. Du R, Zheng R, Xu Y, et al. Early-life famine exposure and risk of cardiovascular diseases in later life: findings from the REACTION Study. J Am Heart Assoc 2020; 9: e14175.
12. Grey K, Gonzales GB, Abera M, et al. Severe malnutrition or famine exposure in childhood and cardiometabolic non-communicable disease later in life: a systematic review. BMJ Glob Health 2021; 6: e003161.
13. van Abeelen A, de Rooij SR, Osmond C, et al. The sex-specific effects of famine on the association between placental size and later hypertension. Placenta 2011; 32: 694-8.
14. Hult M, Tornhammar P, Ueda P, et al. Hypertension, diabetes and overweight: looming legacies of the Biafran famine. PLoS One 2010; 5: e13582
15. Liu L, Xu X, Zeng H, et al. Increase in the prevalence of hypertension among adults exposed to the Great Chinese Famine during early life. Environ Health Prev Med 2017; 22: 64.
16. Yu C, Wang J, Li Y, et al. Exposure to the Chinese famine in early life and hypertension prevalence risk in adults. J Hypertens 2017; 35: 63-8.
17. Zhang L, Yang L, Wang C, et al. Combined effect of famine exposure and obesity parameters on hypertension in the midaged and older adult: a population-based cross-sectional study. Biomed Res Int 2021; 2021: 5594718.
18. Wang Y, Jin J, Peng Y, Chen Y. Exposure to Chinese famine in the early life, adulthood obesity patterns, and the incidence of hypertension: a 22-year cohort study. Ann Nutr Metab 2021; 77: 109-15.
19. Lu J, Xuan S, Downing NS, et al. Protocol for the China PEACE (Patient-centered Evaluative Assessment of Cardiac Events) Million Persons Project pilot. Bmj Open 2016; 6: e10200.
20. Linderman GC, Lu J, Lu Y, et al. Association of body mass index with blood pressure among 1.7 million chinese adults. JAMA Netw Open 2018; 1: e181271.
21. Li C, Lumey LH. Exposure to the Chinese famine of 1959-61 in early life and long-term health conditions: a systematic review and meta-analysis. Int J Epidemiol 2017; 46: 1157-70.
22. Huang YQ, Liu L, Yu YL, et al. The relationship between famine exposure during early life and carotid plaque in adulthood. Eur J Clin Nutr 2021; 75: 546-54.
23. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2013; 34: 2159-219.
24. Janssen I, Heymsfield SB, Allison DB, Kotler DP, Ross R. Body mass index and waist circumference independently contribute to the prediction of nonabdominal, abdominal subcutaneous, and visceral fat. Am J Clin Nutr 2002; 75: 683-8.
25. Meng R, Lv J, Yu C, et al. Prenatal famine exposure, adulthood obesity patterns and risk of type 2 diabetes. Int J Epidemiol 2018; 47: 399-408.
26. Wang Z, Zou Z, Yang Z, et al. The association between fetal-stage exposure to the China famine and risk of diabetes mellitus in adulthood: results from the China health and retirement longitudinal study. Bmc Public Health 2018; 18: 1205.
27. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003; 289: 2560-72.
28. Stein AD, Zybert PA, van der Pal-de BK, Lumey LH. Exposure to famine during gestation, size at birth, and blood pressure at age 59 y: evidence from the Dutch Famine. Eur J Epidemiol 2006; 21: 759-65.
29. Roseboom TJ, van der Meulen JH, Ravelli AC, et al. Blood pressure in adults after prenatal exposure to famine. J Hypertens 1999; 17: 325-30.
30. Stanner SA, Bulmer K, Andres C, et al. Does malnutrition in utero determine diabetes and coronary heart disease in adulthood? Results from the Leningrad siege study, a cross sectional study. BMJ 1997; 315: 1342-8.
31. Wang Z, Li C, Yang Z, Zou Z, Ma J. Infant exposure to Chinese famine increased the risk of hypertension in adulthood: results from the China Health and Retirement Longitudinal Study. BMC Public Health 2016; 16: 435.
32. Yu C, Wang J, Li Y, et al. Exposure to the Chinese famine in early life and hypertension prevalence risk in adults. J Hypertens 2017; 35: 63-8.
33. Zhang L, Yang L, Wang C, et al. Individual and combined association analysis of famine exposure and serum uric acid with hypertension in the mid-aged and older adult: a population-based cross-sectional study. BMC Cardiovasc Disord 2021; 21: 420.
34. Li C, Lumey LH. Exposure to the Chinese famine of 1959-61 in early life and long-term health conditions: a systematic review and meta-analysis. Int J Epidemiol 2017; 46: 1157-70.
35. Chen H, Nembhard WN, Stockwell HG. Sex-specific effects of fetal exposure to the 1959-1961 Chinese famine on risk of adult hypertension. Matern Child Health J 2014; 18: 527-33.
36. Guo HJ, Ding X, Jiang W, et al. [Association analysis of famine exposure during early life and risk of hypertension in adulthood]. Zhonghua Yu Fang Yi Xue Za Zhi 2021; 55: 732-6.
37. Zambrano E, Martinez-Samayoa PM, Bautista CJ, et al. Sex differences in transgenerational alterations of growth and metabolism in progeny (F2) of female offspring (F1) of rats fed a low protein diet during pregnancy and lactation. J Physiol 2005; 566: 225-36.
38. Wu YT, Niubo AS, Daskalopoulou C, et al. Sex differences in mortality: results from a population-based study of 12 longitudinal cohorts. CMAJ 2021; 193: E361-70.
39. Edwards MJ. Genetic selection of embryos that later develop the metabolic syndrome. Med Hypotheses 2012; 78: 621-5.

40. Li Y, Jaddoe VW, Qi L, et al. Exposure to the Chinese famine in early life and the risk of hypertension in adulthood. J Hypertens 2011; 29: 1085-92.
41. Seravalle G, Grassi G. Obesity and hypertension. Pharmacol Res 2017; 122: 1-7.
42. Jiang X, Ma H, Wang Y, Liu Y. Early life factors and type 2 diabetes mellitus. J Diabetes Res 2013; 2013: 485082.
43. Heijmans BT, Tobi EW, Stein AD, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proc Natl Acad Sci USA 2008; 105: 17046-9.
44. Vaiserman A, Lushchak O. Prenatal famine exposure and adult health outcomes: an epigenetic link. Environ Epigenet 2021; 7: dvab013.
45. Ferreira VR, Jardim TV, Povoa TR, et al. Birth weight and its association with blood pressure and nutritional status in adolescents. J Pediatr (Rio J) 2018; 94: 184-91.
46. Syme C, Shin J, Richer L, et al. Epigenetic loci of blood pressure. Circ Genom Precis Med 2019; 12: e2341.
47. Wang Y, Weng P, Wan H, et al. Economic status moderates the association between early-life famine exposure and hyperuricemia in adulthood. J Clin Endocrinol Metab 2020; 105: dgaa523.
48. Song C, Wang M, Chen Z, et al. Fetal exposure to chinese famine increases obesity risk in adulthood. Int J Environ Res Public Health 2020; 17: 3649.
49. Abate KH, Abdulahi M, Abdulhay F, et al. Consequences of exposure to prenatal famine on estimated glomerular filtration rate and risk of chronic kidney disease among survivors of the great Ethiopian famine (1983-85): a historical cohort study. Nutr J 2021; 20: 19.
50. Yu MA, Sanchez-Lozada LG, Johnson RJ, Kang DH. Oxidative stress with an activation of the renin-angiotensin system in human vascular endothelial cells as a novel mechanism of uric acid-induced endothelial dysfunction. J Hypertens 2010; 28: 1234-42.
51. Iantorno M, Campia U, Di Daniele N, et al. Obesity, inflammation and endothelial dysfunction. J Biol Regul Homeost Agents 2014; 28: 169-76.
52. Saxena T, Ali AO, Saxena M. Pathophysiology of essential hypertension: an update. Expert Rev Cardiovasc Ther 2018; 16: 879-87.
53. Li C, Tobi EW, Heijmans BT, Lumey LH. The effect of the Chinese Famine on type 2 diabetes mellitus epidemics. Nat Rev Endocrinol 2019; 15: 313-4.
54. Li J, Yang Q, An R, et al. Famine and trajectories of body mass index, waist circumference, and blood pressure in two generations: results from the CHNS From 1993-2015. Hypertension 2022; 79: 518-31.